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REVIEW

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New frontiers in the treatment of colorectal cancer: Autophagy and the unfolded protein response as promising targets

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ABSTRACT

Colorectal cancer (CRC), despite numerous therapeutic and screening attempts, still remains a major life-threatening malignancy. CRC etiology entails both genetic and environmental factors. Macroautophagy/autophagy and the unfolded protein response (UPR) are fundamental mechanisms involved in the regulation of cellular responses to environmental and genetic stresses. Both pathways are interconnected and regulate cellular responses to apoptotic stimuli. In this review, we address the epidemiology and risk factors of CRC, including genetic mutations leading to the occurrence of the disease. Next, we discuss mutations of genes related to autophagy and the UPR in CRC. Then, we discuss how autophagy and the UPR are involved in the regulation of CRC and how they associate with obesity and inflammatory responses in CRC. Finally, we provide perspectives for the modulation of autophagy and the UPR as new therapeutic options for CRC treatment.

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Introduction and epidemiology

Colorectal cancer (CRC) is the second and third most common type of cancer in females and males, respectively, with 1.24 million new cases diagnosed in 2008 alone.[1] According to the Canadian Cancer Society, CRC has the third highest cancer incidence in both men and women.[2] Countries with the highest incidence include those in Europe, North America, and Oceania, while the lowest incidence is found in some South and Central Asian countries and in Africa.[3] In Saudi Arabia, CRC ranks first and third among males and females, respectively, of all cancers diagnosed in 2011.[4] According to the latest data by the Iran National Cancer Registry (INCR), the age-standardized incidence rate of Iranian CRC patients is 11.6 and 10.5 for men and women, respectively. The overall 5-year survival rate is 41%, and the proportion of CRC among the younger age group is higher than that of Western countries.[5] In developed countries, CRC occurrence is higher in nonsmokers of both males and females combined.[6] In Europe, CRC is the second leading cause of death among all cancer types in both men and women.[7] In the United States of America, CRC is the third leading cause of death and the 5-year overall survival (OS) of this disease is nearly 65%.

Seventy percent of CRC cases are sporadic with the presence of somatic mutations,[8] while about 20–30% of CRC are associated with a family history,[9,10] and 5–15% show hereditary diseases, including polyposis and nonpolyposis CRC (Fig 1). The common somatic mutations of CRC patients have been summarized in Table 1. There are several types of inherited CRC including hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), attenuated FAP, MUTYH-associated polyposis (MAP), hamartomatous polyps as the primary lesions in Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS), hyperplastic polyposis (HPP) and familial CRC (FCC) syndrome X.[11] The etiologies

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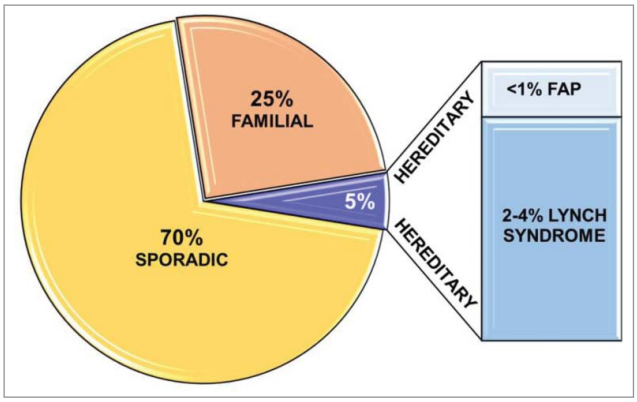

Figure 1. CRC distribution—relation to the genetic background. The graph shows percentages of sporadic, familial, and hereditary (familial adenomatous polyposis, FAP; Lynch syndrome) subtypes of CRC.

of the remaining familial CRCs, which are more common compared with the well-characterized inherited syndromes, are not completely understood. However, common single nucleotide polymorphism (SNP) in genes that regulate metabolic pathways or affecting genes regulated by environmental or other genetic factors influence the incidence of this type of CRC.[11]

Table 1. Common somatic mutations in colorectal cancer (data extracted from: https://civic.genome.wustl.edu/).

Genes	Variants	Evidence level	References
BRAF	V600E	Validated	320
		Clinical	321,322
		Clinical	323
		Clinical	324
		Preclinical	325
		Preclinical	326
	V600	Clinical	321, 327
KRAS	Exon 2 mutation	Validated	328,329
	G13D	Clinical	330
	G12D	Clinical	331
	G12C	Clinical	332
PIK3CA	E542K (exon9)	Inferential	332
	E545K (exon9)	Inferential	332
	H1047R	Inferential	328,329
	Exon10	Clinical	328,329
	Exon21	Clinical	333
ERBB3	Overexpression	Clinical	334
CDX2	Expression	Clinical	335
EGFR	S492R	Preclinical	335
	G465R	Case study	336
	G719S	Preclinical	336
	G724S	Preclinical	337
	Amplification	Clinical	335
	K467T	Preclinical	335
	R451C	Preclinical	338
APC	mutant	Preclinical	328,329
NRAS	Q61	Clinical	328,329
PTEN	Loss	Clinical	333
NT5E	Overexpression	Clinical	339
HRAS	G13D	Case study	340
PTP4A3	overexpression	Preclinical	341
FBXW7	mutant	Clinical	341
SMAD4	mutant	Clinical	342
HSPH1	T17 deletion intron repeat (MSI)	Clinical	343
NTRK1	NTRK1 3′ fusions (one *LMNA-NTRK1* and 2 *TPM3-NTRK1*)	Preclinical	
NOTCH1	Amplification	Preclinical	344
SLFN11	Expression	Preclinical	345
TOP1	Amplification	Clinical	346

Familial CRC is classified to familial adenomatous polyposis (FAP) and Lynch syndrome. FAP is an autosomal dominant hereditary disease that occurs in <1% of all CRC and is associated with a germline mutation in the tumor suppressor gene *APC* (APC, WNT signaling pathway regulator).[12] FAP is characterized by the presence of numerous adenomatous polyps (< 100) in the colon and rectum,[8] and is usually diagnosed between 20 and 30 y of age.[13] Lynch syndrome makes up approximately 2–4% of all CRC,[12] and is associated with autosomal dominant alterations in one of the DNA mismatch repair genes: *MLH1, PMS2, MSH2, or MSH6*.[14] This disease is characterized by early-onset CRC and an increased risk of other cancers, including skin, endometrium, stomach, ovary, upper urinary tract, pancreas, hepatobiliary tract, small bowel, and to a lesser extent, brain tumors.[15]

Development of sporadic CRC involves different molecular pathways that lead to the transformation of normal epithelium to adenoma and carcinoma with diverse phenotypes. The 3 major genetic pathways distinguished in CRC are the chromosomal instability (CIN) pathway, CPG island methylator phenotype (CIMP; the "serrated" pathway), and microsatellite instability (MSI) pathway.[15-17] In cases of sporadic CRC, epigenetic changes, including DNA methylation in gene promoters, leads to MSI because of inactivation of mismatch repair genes. Mutations in MMR genes can evoke similar genomic instability results.[14,17] Based on these alterations, sporadic CRC is classified into 4 groups including, hypermutated, non-hypermutated, CpG island methylator phenotype and elevated microsatellite alterations at tetranucleotide repeats with metastatic behavior.[17,18]

Etiology and risk factors

Presently, lifestyle and dietary patterns around the world are shifting toward the Western (high-fat) diet pattern.[19] Apart from age and sex, dietary patterns that include the high intake of red meat and/or processed meat, fatty meals, refined grains, and sweet foods increase the risk of CRC.[19,20] Diets with high intake of fiber, fruits, vegetables, whole grain cereals, fish, white meats, soy derivatives, vitamin D, calcium, and omega-3 fatty acids have the ability to favorably modulate the development of CRC.[19] A number of observational studies showed that regular physical exercise decreases the risk of CRC by 40%.[20] In addition, regular moderate exercise of 150 min per wk increases CRC survival rates by 28%.[21] Aside from lifestyle modifications, chemoprevention with aspirin is effective in reducing the incidence and mortality, without significant adverse systemic effects.[22]

Alcohol consumption has a positive dose-response correlation with the incidence of CRC; the higher the intake of alcohol, the higher the risk of CRC.[23] Cigarette smoking is associated with a wide variety of malignancies, and recently, has also been linked to CRC. Male smokers, especially those who smoke more than 20 cigarettes per d, are at the highest risk.[24] Another important risk factor is the presence of inflammatory bowel disease (IBD), a chronic inflammatory disorder of the gastrointestinal (GI) tract that includes Crohn disease and ulcerative colitis.[25] Patients with IBD are 6 times more susceptible to contracting CRC than the general population.[26] Regular colonoscopy is recommended after diagnosis.[27] Depending on their size, histology, and degree of dysplasia, the presence of GI tract

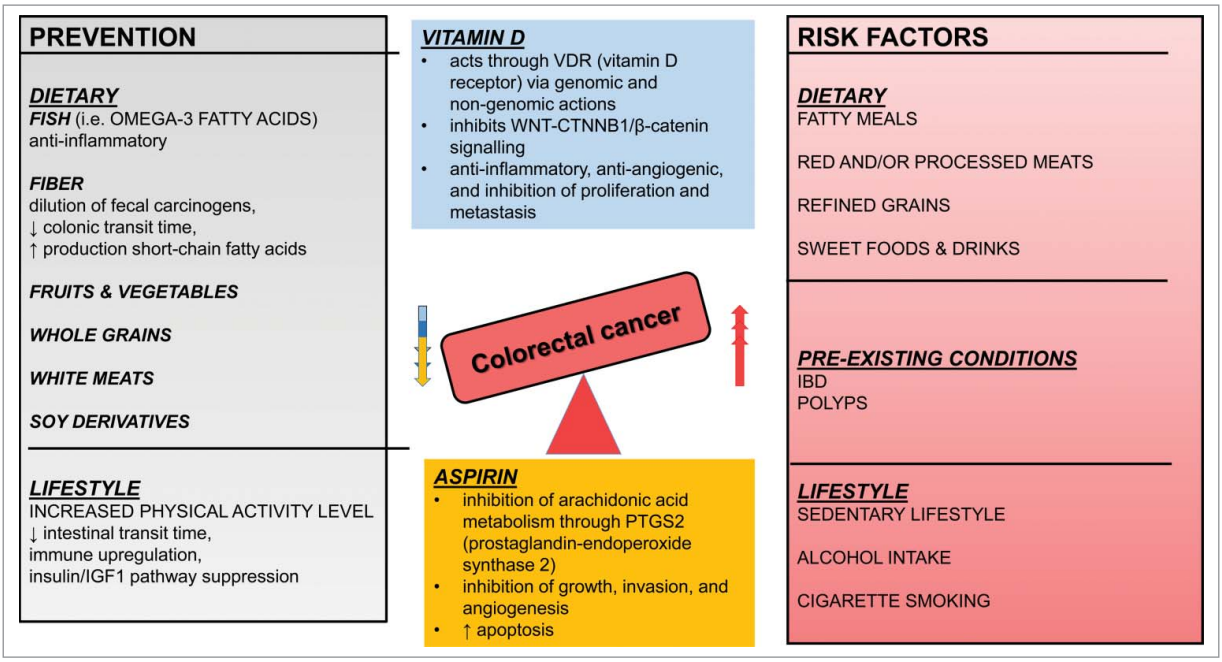

Figure 2. Schematic representation of factors that increase risk or prevent CRC. Both lifestyle and diet affect incidence of CRC as they can be both preventive and risk factors.

polyps, including hyperplastic polyps, tubular adenomas, tubule-villous and villous adenomas, adenoma with high-grade dysplasia, and malignant adenomas, increases the risk of CRC.[28] Figure 2 summarizes preventive and promoting factors affecting the risk of CRC.

Screening and treatment

CRC screening is an effective strategy, leading to early diagnosis and prevention of disease-associated death. Screening procedures include colonoscopy, stool occult blood testing, barium enema, and digital rectal examination. Colonoscopy is the most accurate method of screening,[29] and often recommended as a first-line screening approach.[30] Stool occult blood testing reduces CRC mortality,[31,32] and is currently the most widely used method of noninvasive screening for CRC. Advances in genomics, epigenetics, and proteomics will likely lead to the discovery of novel noninvasive biomarkers for the identification of CRC in the stool and/or blood.[33,34]

Early detection of CRC may result in CRC treatment with surgery alone, whereas late-stage advanced and/or metastasized CRC requires additional chemotherapy and radiotherapy. To ensure high quality treatment, a multidisciplinary team approach with radiologists, oncologists, surgeons, and pathologists is imperative. CRC treatment can be in the form of adjuvant therapy (AT) administered following primary tumor resection with the aim of reducing the risk of recurrence or as neo-adjuvant therapy (NAT) before tumor resection.[35] AT is highly recommended for CRC patients with stage III and 'high risk' stage II patients.[35] A study by Sauer et al. concluded that regardless of radiotherapy timing, NAT is favored over AT in terms of rates of local recurrences and toxic effects.[36] There are 2 possible NAT strategies. One approach is short-course radiotherapy without chemotherapy, followed by surgery within 1 wk.[37] Another approach is long-course pre-surgical chemotherapy and radiotherapy, while concurrently administrating 5-fluorouracil (5-FU)-based chemotherapy followed by surgery 8 to 12 wk later.[38] For the past 2 decades, standard chemotherapy for patients undergoing AT has been 5-FU in combination with levamisole and leucovorin.[39] Several treatment regimens have been developed since the millennium and include 5-FU in combination with leucovorin and oxaliplatin (FOLFOX), capecitabine in combination with oxaliplatin (CAPOX), and intravenous application of 5-FU and leucovorin in combination with irinotecan (FOLFIRI).[40] Administration of FOLFOX in 3-weekly cycles over 24 wk shows a 5–25% improvement in overall survival (OS).[41,42] Despite the ongoing development of new therapeutic regimens and the inclusion of novel antitumor agents, the primary treatment of patients with CRC continues to be systemic chemotherapy involving infusions of 5-FU and leucovorin.[40]

In stage IV CRC patients with unresectable metastatic lesions, a median OS of 6 mo was reported. After treatment with 5-FU and leucovorin, OS increased to 12 mo.[43] The GOLF regimen (gemcitabine, oxaliplatin, leucovorin, 5-FU) is another combination highly synergistic in inducing both growth inhibition and apoptosis of colon cancer cells.[44] Introduction of infusion regimens, such as FOLFIRI, has raised OS to a median of about 20 mo.[45] Regorafenib is a drug that targets and inhibits several tyrosine kinases involved in angiogenesis (FLT1/VEGFR1, KDR/VEGFR2, and FLT4/VEGFR3), oncogenesis (KIT, RET, RAF, BRAF), and the tumor microenvironment (PDGFR, FGFR), and it has been approved for use in patients that have relapsed or are refractory to all other systemic therapies.[46]

Personalized medicine involves the tailoring of medical treatment to an individual patient depending on the specific

Table 2. Summary of the chemotherapeutic drugs and their mechanism of action in CRC.

Drugs	Structure	Mechanism of Action	Function	Genes interaction	Cells fate effect	Ref
Fluorouracil (5-FU)	A pyrimidine analog	-TYMS (thymidylate synthetase) blocker[347-349] -Incorporation into and destabilization of the RNA and DNA[350]	Antimetabolite and anticancer[351,352]	*TP53*[353] *TYMS*[354] *DPYD*[355] *CASP3*[356] *CDKN1A*[357] *BCL2*[358] *CASP8*[359] *BAX*[360] *CASP9*[361] *FASN*[362]	Growth inhibition and apoptosis[165]	351,352 165,347- 349,353- 362
Levamisole	Synthetic imidazothiazole derivate[363]	-Antagonists of TSHR (thyroid stimulating sormone receptor)[421] -NFE2L2 activators -Inhibitors of GLS (glutaminase)[420] -Inhibition of ALPL (alkaline phosphatase, liver/ bone/kidney)[418,364]	-Increasing macrophage chemotaxis and T-lymphocyte function.[363,365,366] An antihelminthic and anti-parasite drug restoring the immune system	*ALPL*[367] *IFNG*[368] *RB1*[369] *ABTS1*[370] *ENPP1*[371] *IL4*[372] *PTGS2*[373] *TP53*[374] *BAK1*[375] *BCL2*[376]	Growth inhibition, autophagy and Inhibition of the unfolded protein response[373,377-379]	363-378,380- 383
Oxaliplatin	Platinum-based chemotherapy drug[384]	-Displacement of the labile oxalate ligand.[385] -Transient reactive species bind with macromolecules: monoaquo and diaquo DACH platinum.[386] -Binding preferentially to the guanine and cytosine moieties of DNA	Inhibiting DNA synthesis and nonspecific cell cycle cytotoxicity[387]	*TAC1*[388] *ITGA1*[388] *FOXC1*[388] *GMDS*[389] *PELO*[189] *XRCC1*[390] *ERCC2*[391]	Growth inhibition and autophagy[392]	189,384- 390,392
Irinotecan	A semisynthetic derivative of camptothecin[393]	TOP1 (topoisomerase [DNA] I) inhibitor[394] Relegation of the DNA strand prevention[394]	An antineoplastic drug Treatment of metastatic carcinoma of the colon or rectum[395]	*UGT1A1*[396] *ABCC4*[397] *PLCB1*[398] *EGFR*[399]	Growth inhibition and apoptosis[400]	394,397-400 395
Capecitabine	A deoxycytidine derivative. Active metabolites: 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP)[401]	TYMP (thymidine phosphorylase) activator[402] Nucleic acid synthesis inhibition Interfere with RNA processing and protein synthesis[401]	Cell cycle inhibitor	*DPYD*[403] *MTRR*[404] *SOX6*[404]	Autophagy[405]	401-405
Gemcitabine	Deoxycytidine analog Active metabolites: gemcitabine diphosphate and gemcitabine triphosphate[406]	TYMS inhibition DNA synthesis inhibition[407] RRM (ribonucleotide reductase) inhibition Competes with endogenous deoxynucleoside triphosphates for incorporation into DNA.[408]	An antineoplastic antimetabolite	*DCK*[409] *CACNA1C*[410] *DAPK1*[411] *IL17F*[412] *PRB2*[413]	Apoptosis[407]	406-413

genetic makeup of their cancer, taking into account different stages of care, which includes prevention, diagnosis, treatment, and followup. An example for this is temozolomide, which is used in pretreated patients with advanced CRC and *MGMT* promoter methylation. Patients with *KRAS*, *BRAF*, and *NRAS* wild-type (WT) CRC show significantly higher response when compared with CRC containing *KRAS* or *BRAF* mutations (44% versus 0%; P = 0.004).[17] Lists of chemotherapeutic drugs and regimens are presented in Table 2 and 3, respectively.

Table 3. Chemotherapeutic regimens (combination therapy) and their effect in CRC.

Chemotherapeutic regimen	Effect on cancer cells	References
FOLFOX (5-FU, Leucovorin and oxaliplatin)	Autophagy and apoptosis	287
FOLFIRI (5-FU, Leucovorin and Irinotecan)	Autophagy and apoptosis	212
GOLF (gemcitabine, oxaliplatin, leucovorin and 5-FU)	Growth inhibition and apoptosis	44
5-FU, levamisole and leucovorin	Growth inhibition, apoptosis, autophagy and Inhibition of the unfolded protein response	378,414,415
5-FU and Leucovorin	Growth inhibition, apoptosis and autophagy	414,415

General aspects of autophagy

New therapeutic strategies are being designed to target autophagy to improve treatment options of different diseases, including cancer. In the context of cancer, autophagy may prevent cellular transformation in normal tissue by decreasing reactive oxygen species (ROS) content of the cells. Conversely, it can also promote cancer progression depending on the stage of cancer.[47,48] Recent investigations revealed that autophagy has diverse functions in the development, maintenance, and progression of tumors.[48] While genetic evidence indicates that autophagy functions as a tumor suppressor mechanism, it is also apparent that autophagy can promote the survival of established tumors under stress conditions and in response to chemotherapy[49-51] (Figs 3 and 4). Recent findings show that modulation of autophagy affects the immune response and the biology of cancer in general.[52-56] Genetic alterations in autophagy may predispose individuals to autoimmune, autoinflammatory, or infectious diseases. For instance, *ATG5* mutations are associated with systemic lupus erythematosus and Crohn disease.[57,58] Furthermore, stimulation or suppression of genes important for autophagy can regulate immune responses via antigen donor cells, antigen presenting cells, or downstream

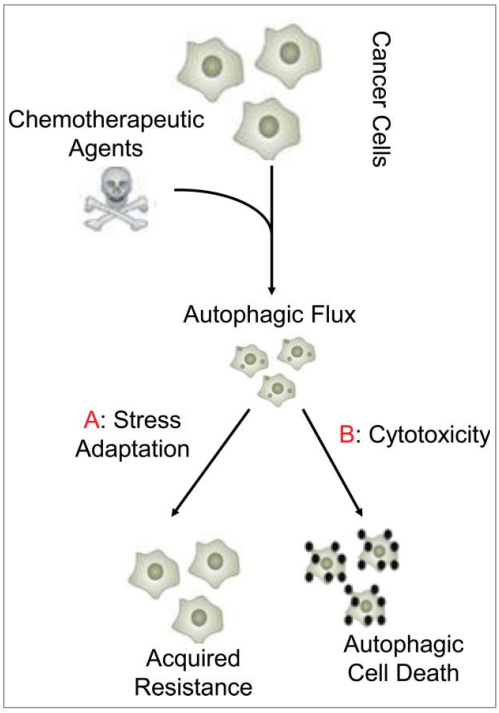

Figure 3. Dual role of autophagy in cancer chemotherapy. Autophagy may induce stress adaptation (A) in cancer cells allowing them to obtain a resistance phenotype against cancer chemotherapy agents, or it may induce cytotoxicity (B) resulting in autophagic cell death of cancer cells (adapted from ref. 49).

effectors of the immune system.[59] From an immunological point of view, cancer can progress when malignant cells escape the control of the immune system by altering their antigenic properties or by reducing or suppressing antitumor immune responses.[59] They accumulate genetic and epigenetic alterations, including, among others, loss of heterozygosity of *BECN1*, constitutive signaling via MTOR, activating phosphoinisotide 3-kinase (PI3K) mutations, loss of *PTEN*, accumulation of mutant *TP53*, or the overexpression of anti-apoptotic BCL2-family proteins. Such changes facilitate (directly or indirectly) genomic instability in cancerous cells, leading to malignant cells escaping immunosurveillance.[59]

Manipulation of key elements of the autophagy pathway can be exploited as a novel therapeutic approach for CRC.[60] In eukaryotic cells, autophagy is an important protein degradation system and mainly responsible for the degradation of long-lived proteins and damaged organelles.[61] Autophagy refers to a collection of tightly regulated catabolic processes, all of which deliver cytoplasmic components to the lysosome for degradation. These are broadly classified into 3 types: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA).[62] Macroautophagy involves the formation of phagophores that engulf cytoplasmic proteins and organelles, maturing into double-membrane-bound vesicles called autophagosomes. These autophagosomes are trafficked to lysosomes and the sequestered cargo is degraded.[62] Microautophagy refers to the invagination of the lysosomal or endosomal membrane, resulting in the direct engulfment of substrates that are subsequently degraded by lysosomal proteases.[62-64] CMA is distinct from macroautophagy and microautophagy because the cargo is not sequestered within a membrane vesicle. Instead, proteins targeted by CMA contain a KFERQ-like pentapetide motif that is recognized by HSPA8/HSC70 (heat shock protein family A [Hsp70] member 8). HSPA8 promotes the translocation of these targets across lysosomal membranes into the lysosomal lumen via LAMP2A (lysosomal-associated membrane protein 2A).[65]

Usually the term “autophagy” refers to “macroautophagy” in the literature.[65] Autophagy dysregulation leads to various human diseases, including neurodegenerative disorders and cancer.[63,66] In both normal and malignant cells, autophagy may be induced in response to cellular stress,[62] including nutrient deprivation, hypoxia, and toxin accumulation.[62] The outcome of autophagy induction however, affects the cell in various ways, being protective, and promoting survival, or causing growth arrest and triggering programmed cell death.[67] The molecular components of this pathway were first discovered in yeasts and include more than 40 autophagy-related (ATG) proteins. Most

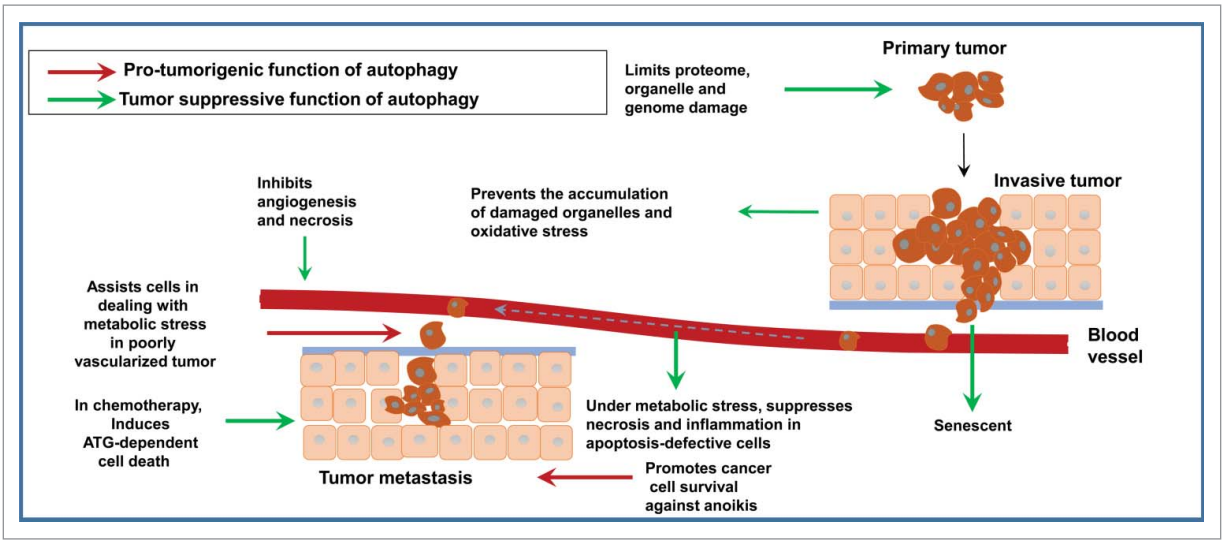

Figure 4. Dual role of autophagy during tumorigenesis: Autophagy may suppress tumorigenesis by eliminating damaged organelles in transformed cells and protect them against oxidative stress, resulting in subsequent genome stabilization and prevention of malignant transformation. Autophagy may also initiate an oncogene-induced senescence, thus preventing malignant transformation. It may prevent necrosis in apoptosis-deficient cells in tumors in response to metabolic stress. This reduces pro-tumorigenic inflammation and release of tumorigenic compounds from necrotic tumor cells. Tumor-supportive functions of autophagy are fulfilled mainly by stimulating tumor cell survival and protection against detachment-induced apoptosis (anoikis), which can facilitate chemoresistance and EMT induced-metastasis (adapted from. refs. 50,51).

autophagy stimuli converge at MTOR (mechanistic target of rapamycin) and the class III phosphatidylinositol 3-kinase (PtdIns3K) complex, which serve as autophagy-related key regulators. Several core autophagy machineries are required for autophagosome formation.[62,65] The core machinery of the initiation stage during induction of autophagy is the ULK (unc51-like autophagy activating kinase) complex consisting of ULK1, ATG13, ATG101 and RB1CC1/FIP200. Upon initiation of autophagy, a complex nucleation arises when the PtdIns3K complex binds to its core units, such as BECN1/Beclin-1 (the human ortholog of yeast Vps30/Atg6) and PIK3R4/p150.[65,68] This complex resides on the phagophore membrane and facilitates recruitment of other ATGs to the unit (Fig 5A).[62,69] During phagophore elongation and maturation, the Atg8/LC3 protein, a ubiquitin-like protein, is conjugated to the membrane lipid phosphatidylethanolamine (PE) or possibly to phosphatidylserine.[70] In yeast, and several other organisms, the conjugated form is referred to as Atg8–PE. The mammalian homologs of Atg8 constitute a family of proteins subdivided into 2 major subfamilies: MAP1LC3/LC3 and GABARAP. The former consists of LC3A, B, B2 and C, whereas the latter family includes GABARAP, GABARAPL1 and GABARAPL2/GATE-16.[71] After cleavage of the precursor protein, mostly by the cysteine protease ATG4B,[72] the nonlipidated and lipidated forms are usually referred to as LC3-I and LC3-II, and GABARAP-I and GABARAP-II (Fig 5A), respectively. The increased level of LC3-II in the presence of lysosomal proteases inhibitors (bafilomycin A_1 or chloroquine) typically serve as an analytical marker of autophagic flux because it confirms the autophagy flow from autophagosome formation to recycling in lysosomes (reviewed in refs. 65,69). In the final stage, cargo is degraded by lysosomal hydrolases in the autolysosomes (Fig 5A) and the resulting products are transported back to the cytosol by lysosomal permeases.

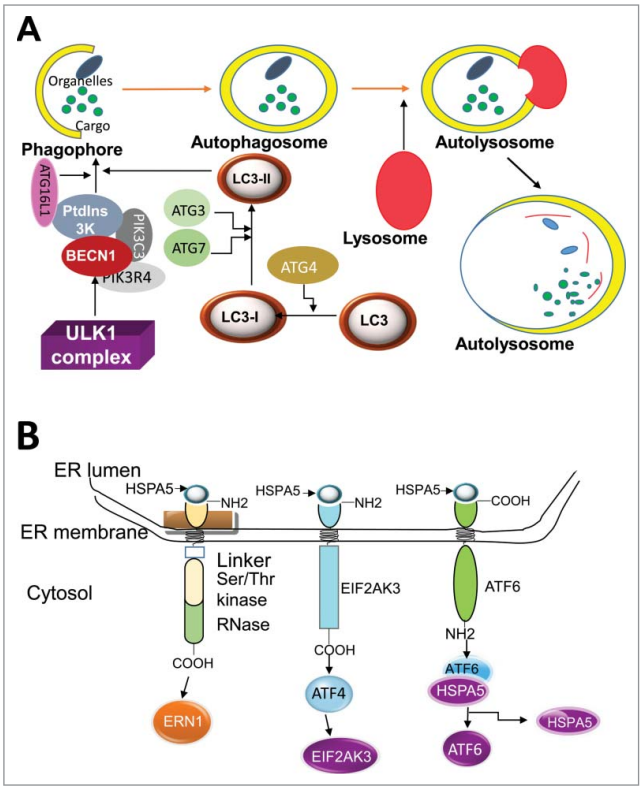

Figure 5. Autophagy and the UPR signaling pathways. (A) Depiction of autophagy pathways. Autophagy is a catabolic process that sequesters specific intracellular cargo by engulfing them within a cytosolic double-membraned vesicle, called an autophagosome. Extracellular stimuli or recognition of a cargo material induces the formation of the phagophore. ULK1 is an important upstream initiator that induces activation of nucleation complex, including PtdIns3K and BECN1, to engage phagophores for autophagy. LC3 is conjugated to the phagophores and controls their maturation and elongation. Upon vesicle completion, the autophagosome fuses with a lysosome, releasing its contents to be degraded by hydrolases. (B) Initiation of the UPR: The domain structures of ERN1, EIF2AK3, and ATF6 and their associations with HSPA5 are illustrated. ERN1, EIF2AK3, and ATF6 are docked and inactive in non-ER stress condition by binding to HSPA5. Upon ER stress, HSPA5 is released from the lumenal domain of ERN1, EIF2AK3 and ATF6 and this initiates the UPR.[64,416]

General aspects of the unfolded protein response

The endoplasmic reticulum serves as a subcellular compartment involved in maturation and folding of proteins, and plays important roles in maintaining normal cellular functions.[73,74] An imbalance between cellular demand for ER function and ER capacity can lead to ER stress.[75] To cope with ER stress, mammalian cells are able to activate the unfolded protein response (UPR) which aims to maintain the homeostasis of proteins within the ER.[76] The UPR is initially associated with a stress-inducible chaperone, a glucose-regulated protein, which mainly resides in the ER and is encoded by the *HSPA5/GRP78/BIP* (heat shock protein family A [Hsp70] member 5) gene (Fig 5B).[77] The ER contains 3 transmembrane receptors (Fig 5B) including EIF2AK3/PERK (eukaryotic translation initiation factor 2 α kinase 3), ATF6 (activating transcription factor 6) and ERN1/IRE1α (endoplasmic reticulum to nucleus signaling 1).[77] These 3 arms of the UPR sense the protein-folding status in the ER and transmit the information to the cytosol to regulate UPR-related gene expression.[78]

Activation of ERN1 starts from the dissociation from HSPA5 and results in the splicing of XBP1 to form its active form (XBP1s). This modulates prosurvival signals by regulating genes involved in protein folding, maturation and ER-associated degradation.[79] Activation of ERN1 also targets MAP3K5/ASK1 and MAPK/JNK proteins, followed by triggering of TRAF2, which subsequently can promote apoptosis.[80] ERN1 is much more activated at the beginning of stress and its activity fades over time.[79]

ATF6 is a basic leucine zipper (bZIP)-containing transcription factor in the ER which include ATF6/ATF6α, ATF6B/ATF6β, CREB3L1/OASIS, CREB3/LUMAN, CREB3L2/BBF2H7, CREB3L3/CREBH and CREB3L4.[81] ER stress causes dissociation of HSPA5 from ATF6 (Fig 5B) and the translocation of ATF6 from the ER to the Golgi apparatus where it is processed by serine protease MBTPS1/S1P and the metalloprotease MBTPS2/S2P to produce an active cytosolic fragment.[82] This active product translocates to the nucleus and activates the expression of several genes that are involved in protein folding, including the ER chaperone proteins DDIT3/CHOP/GADD153, PDIA4/ERp72, PDI, EDEM1 and XBP1.[83]

The third transducer of the UPR is EIF2AK3, which is the most immediate sensor to respond to ER stress.[84] Under ER stress condition, EIF2AK3 is released from HSPA5 (Fig 5). Upon activation, EIF2AK3 phosphorylates EIF2A (eukaryotic translation initiation factor 2A) and subsequently inhibits protein synthesis by reducing activity of the EIF2A complex.[85] Despite global inhibition of protein synthesis, ATF4 is translationally upregulated by EIF2AK3 to increase the expression of stress-related genes and downstream ER chaperones.[86] Moreover, EIF2AK3 triggers antioxidant activity via phosphorylation of NFE2L2/NRF2 (nuclear factor, erythroid 2 like 2).[87] NFE2L2 is a pro-survival factor and cells without NFE2L2 display increased cell death during ER stress.[87]

CMA and its relevance to CRC

Chaperone-mediated autophagy (CMA) is a selective mechanism for the degradation of proteins through a lysosomal-dependent machinery.[88] Basal CMA activity is evident in most cells but is highly stimulated in response to cellular stress.[88,89] CMA contributes to the degradation of proteins that are no longer needed under stress conditions, leading to recycling and promoting of cell survival.[90,91] The cellular pathways and physiological importance of CMA in cancer still needs to be delineated.[91] It has been reported that high basal CMA activity is a common feature among different types of human tumors.[92] In contrast to normal cells, this upregulation of CMA occurs independent of the macroautophagy status of cancerous cells. For example, inhibition of CMA reduces cell proliferation and induces cell death in human lung cancer cell lines. In contrast to nontumor cells, cancer cells with blocked CMA upregulate their ubiquitin-proteasome system to ensure protein quality control. Blockade of CMA delays tumor growth and induces regression of already formed human lung cancer xenografts in mice. The fact that similar manipulations of CMA reduce tumor growth of other human cancer cell lines, such as melanoma, highlights that targeting this autophagic pathway may have broad antitumor activity.[93]

Recently, an increased level of CMA activity was detected by immunostaining for LAMP2A in primary tumors of different human tissues (e.g., liver, lung, skin, stomach, colon, uterus, ovary). Although the intensity of LAMP2A staining varied depending on the type of tumor, the overall LAMP2A signal was significantly higher in all tumor samples when compared with respective normal tissues. In some cases, a gradual increase in LAMP2A staining was observed in parallel with the transition from a normal region to peri-neoplastic and neoplastic regions and with the stage of malignancy. The observed increase in LAMP2A reflects an expansion of the lysosomal compartment in tumor cells because control and tumor samples revealed no difference in staining for LAMP2B, a lysosomal protein splice variant of the same *LAMP2* gene[94] with 95% sequence homology to LAMP2A. Importantly, LAMP2B is not involved in CMA.[93] In another study on HCT116 human colorectal cancer cells, inhibition of autophagy by the compound spautin-1 or genetic knockdown of autophagy-related genes promotes degradation of accumulated missense mutant TP53 proteins through the CMA pathway. These findings suggest that degradation of mutant TP53 is specifically mediated by the CMA-lysosomal pathway during stress conditions and reveals involvement of CMA in a unique pathway that regulates mutant TP53 expression-dependent cell death.[91]

Organellophagy and its importance in CRC

Macroautophagy can also selectively eliminate organelles, a process termed organellophagy.[95] Organellophagy is common for organelles such as mitochondrion (mitophagy), ER (reticulophagy/ER-phagy), peroxisomes (pexophagy), lysosomes (lysophagy), nucleus (nucleophagy), and even ribosomes (ribophagy).[95] Mitophagy is a specific form of macroautophagy by which damaged mitochondria are selectively degraded.[96,97] Previous investigations demonstrated that mitophagy prevents the accumulation of damaged organelles that are sources of ROS.[98] To maintain proliferative capacity and constantly generate progeny, cancer cells must continuously supply sufficient energy and building blocks such as amino acids, lipids and

sugars.[99] Many solid tumors depend on activated glycolysis to cope with the energy requirement for faster proliferation (the Warburg effect). This process requires efficient glucose uptake even in a stressful environment, such as hypoxia frequently experienced by tumor cells.[100] If glycolysis can meet the cellular energy requirement for cancer cells, then the maintenance of a high level of mitochondrial mass is not essential for ATP production. Therefore, autophagy-dependent degradation of unnecessary mitochondria may serve as a useful mechanism to resupply nutrients and expedite glycolysis. This hypothesis is well supported by recent reports that autophagy facilitates glycolysis;[101] hence, transformed cells maintain small numbers of mitochondria during periods of rapid proliferation.[102] Further support in favor of this hypothesis comes from electron microscopy images which show a decreased number of intracellular organelles within the cytosol of proliferating cancer cells. This could mean that cancer cells may activate autophagy-mediated organelle degradation to maintain cellular ATP levels and resupply nutrients when glucose levels are insufficient.[102] Selective autophagy is also a backup mechanism for the failed proteasomal degradation of ubiquitinated aggregation-prone and misfolded proteins. Because ubiquitination has also been implicated in mitophagy,[103] modulation of the expression levels of the ubiquitin-binding autophagic receptors SQSTM1/p62 and NBR1 (cargo receptors for selective autophagy) by selective autophagy might also play a role in mitophagy. Thus, failures in selective autophagy may cause accumulation of protein aggregates and damaged organelles that mediate neoplastic transformation. In contrast, established tumors depend on autophagy to fuel their increased metabolic demands. Selective autophagy may ensure tumor survival via degradation of misfolded proteins and damaged organelles that accumulate in genetically unstable tumor cells.[104]

Defective autophagy is linked to colonic tumor formation through a mechanism involving the aberrant activation of WNT-signaling from impaired degradation of DVL (disheveled segment polarity protein) by autophagy.[105] Therefore, pharmacological activators of autophagy may be of potential benefit for cancer chemoprevention.[106,107] However, there is only indirect evidence for a role of organellophagy in CRC. In a recent report, TP53 inactivation in HCT116 colon cancer cells induced both reticulophagy and mitophagy.[108] When TP53 was inhibited in an acute fashion by addition of pifithrin-α,[107] reticulophagy was induced more rapidly than mitophagy, suggesting an intimate relationship between TP53 inhibition and ER stress-induced reticulophagy.[108] Interestingly, new findings show that some tumor suppressor proteins play a role in organellophagy, especially mitophagy, in various types of cancers, including CRC.[109]

Autophagy and the microbiome in CRC

A growing body of evidence suggests that alterations in the population of gut microorganisms, the microbiome, contribute to the development of CRC.[110,111] CRC patients show a distinct microbial signature in their gut which may predispose them to a tumor-promoting inflammation.[112,113] Analysis of next-generation sequencing data[112,114] indicate that the colonic mucosa is initially colonized by pathogenic bacteria driving CRC via inducing persistent inflammation. This fuels increased cell proliferation and/or production of genotoxic substances involved in development of premalignant lesions and the accumulation of gene mutations such as in *TP53*.[115] As a consequence of alterations in colonic barrier permeability and cellular metabolism, pathogenic "driver" bacteria are replaced by "passenger" bacteria such as tumor-feeding opportunistic and commensal bacteria. Collectively, a "driver-passenger model" has been proposed to explain the role of the gut microbiome in CRC. The intestinal bacteria are more likely to play a "driver" role in the course of tumorigenesis rather than being passive "passengers."[116]

Basic studies in a mouse model of CRC have revealed that perturbations to the gut microbiota can lead to colon tumorigenesis in which transfer of the tumor-associated microbiome to the germ-free mice exacerbates tumor formation compared with the control germ-free mice that received microbiota from healthy mice.[117] Modulation of the gut microbiome has been proposed as a therapeutic or preventative approach for CRC. However, several mechanistic issues need to be precisely addressed before translational modification of the gut microbiome in CRC.

From an immunological point of view, IL23A produced by tumor-associated myeloid cells is a master initiator of the inflammatory response to tumor-infiltrating microbes and this induces expression of IL17 as a pro-tumorigenic mediator. Interestingly, prolonged administration of antibiotics suppresses tumor growth induced by IL23A.[118] Furthermore, colonic innate lymphoid cells (ILCs) play a pivotal role in microbiome-influenced CRC via regulation of IL23A-dependent on IL22 secretion, which is mediated by inducing phosphorylation of STAT3 in a mouse model.[119]

Autophagy is activated in the intestinal epithelium of CRC patients and a mouse model of CRC.[120] Specific genetic ablation of *Atg7* in murine intestinal epithelial cells leads to a significant suppression of pre-cancerous lesion development. The role of ATG7 in CRC is mediated by intestinal dysbiosis in which the gut microbiome is an essential component for an effective antitumor immune response. Inhibition of autophagy by epithelial deletion of *Atg7* leads to bacterial invasion of the crypts which dramatically changes microbiome composition in the gut. This effect is mediated by controlling a stress response associated with activation of AMP-activated protein kinase (AMPK) signaling and TP53-mediated cell-cycle arrest specifically in tumor cells.[120] The lack of a protective response against colonic tumor upon antibiotic treatment further confirms the crucial role of the gut microbiome in ATG7-deficient mice.[120] Decreased levels of antimicrobial defenses mediated by Paneth cells (secretory cells of the intestinal crypts) and goblet cells may explain how the inhibition of autophagy in intestinal epithelial cells can downregulate host immunity.[121]

The role of the microbiome in energy homeostasis is significantly more pronounced in colon than other tissues, which is mainly because of consuming bacterial butyrate as the primary energy source in colon cells. Interestingly, enhanced levels of autophagy are observed in colon cells of mice lacking a microbiome and this increase is rescued upon addition of butyrate to germ-free colon cells.[122] It has been suggested that butyrate, as a short chain fatty acid, has a protective role in colon

tumorigenesis via induction of apoptosis and inhibition of proliferation and regulation of cell differentiation.[123]

While investigating the mechanisms underlying the regulation of the gut microbiome by VDR (vitamin D [1,25 dihydroxyvitamin D3] receptor), Jin et al. demonstrated that VDR status influences the intestinal bacteria at both the taxonomic and functional level, and correlates with the VDR-associated bacterial changes in clinical diseases. Since VDR is a nuclear receptor that regulates the expression of antimicrobial peptides and the autophagy regulator ATG16L1, future studies need to address a crucial unknown link between the gut microbiome and autophagy mediated by VDR in the context of CRC.[124] Understanding the precise impact of the microbiome on autophagy in CRC will open new avenues, leading to the development of novel therapeutic strategies for CRC.

Mutations in autophagy-related genes in CRC

UVRAG

Recently, the role of *UVRAG* (UV radiation resistance associated) as a tumor suppressor gene has been described and the first reports of cancer-specific mutations in *UVRAG* have been published.[125] A 10-polyadenine repeat in exon 8 in MSI colorectal tumors was identified with mono-allelic frame-shift mutations. *UVRAG* positively regulates *BECN1*, suggesting that the interaction with *BECN1* is necessary for the tumor suppressor function of *UVRAG*. In a colon cancer cell line carrying a deletion in *UVRAG* (c.709delA), a reduction in endogenous *UVRAG* levels and impaired autophagy induction were observed.[50,125]

ATG16L1

ATG16L1 is an autophagy gene that also controls host immune responses against bacteria and viruses. The nonsynonymous SNP in *ATG16L1* (Thr300Ala) is associated with improved OS in human CRC and increased basal production of type I IFN, providing a mechanism to influence clinical outcome.[126] SNP may also explain why some patients have a higher risk of CRC or are prone to more mucosal inflammation than others. Autophagy gene polymorphisms correlate with the development of human CRC. The *ATG16L1* (+898A>G [Thr300Ala] SNP) GG genotype is found at higher frequencies in moderately and poorly differentiated CRC cases. Whereas the AA genotype is correlated with a lower risk for CRC, the SNP switch to the GG genotype is correlated with a higher risk for CRC.[127]

Autophagy and the UPR pathways provide a link between inflammation and cancer in CRC

Malignancies are the second most common cause of death after cardiovascular disease in both genders in patients with IBD.[128] IBD has etiological links to CRC at multiple levels and autophagy plays a crucial protective role.[129] The intestinal tract is the interface between the organism and its outer environment and a potential site of infection/inflammation and cancer formation. Clearance of invading microbes and intracellular waste components seems to be a protective function of autophagy in inflammatory disease.[130]

Entero-pathogenic *Escherichia coli* (EPEC) are equipped with a well-developed infectious machinery by which they evade the host defenses and deplete host DNA mismatch repair (MMR) proteins in colonic cell lines. Alterations in the MutS or MutL complexes of mammalian cells may be associated with EPEC pathogenesis and the development of CRC. The MMR proteins of *E. coli* have been considered as potential therapeutic targets and early detection biomarkers for CRC.[131] The role of gut microbiota in the development of human CRC is influenced by diet and inflammation.[132] Importantly, autophagy deregulation in IBD and CRC development is associated with alterations in immune responses, defects in bacterial clearance, and malfunction of goblet and Paneth cells.[60]

There is tight crosstalk between inflammation and the ER stress pathway, which can influence the pathology and progression of several diseases. ER stress-induced inflammation may aid the progression of type 2 diabetes, obesity, and cause IBD progression in Crohn disease and ulcerative colitis.[133] In addition, pro-inflammatory diets (i.e., high carbohydrates along with low antioxidants) are associated with increased risk of CRC.[134]

Chronic inflammation in IBD can lead to prostaglandin release, production of ROS, and secretion of tumor-promoting cytokines. These cytokines promote the survival, growth, and metastasis of tumor cells through NFKB/NFκB (nuclear factor kappa B; mediators downstream of the UPR), STAT3 (signal transducer and activator of transcription 3) and AP-1 (AP-1 transcription factor) signaling pathways as well as cytokines such as IL1B/IL1β, IL6, IL11, and IL23A.[131] Prostaglandin E2 (PGE2) induces cancer stem cell (CSC) expansion by activating NFKB via E-type PTGER4/EP4-PtdIns3K and PTGER4-MAPK (mitogen activated protein kinase) signaling and promotes the formation of CRC liver metastases in mice. The PGE2 signaling pathway may serve as a therapeutic target to counteract CRC metastasis.[135] Dysregulation of PTGS/COX (prostaglandin-endoperoxide synthase) pathway may lead to the accumulation of pro-inflammatory mediators such as PGE2. In particular, PTGS, PTGER3 (prostaglandin E receptor 3), PTGFR (prostaglandin F receptor), and AKR1B1 (aldo-keto reductase family 1 member B) were found hyper-methylated in more than 40% of colorectal tumors.[136] A recent study on 618 participants diagnosed with CRC showed that CRC-specific mortality was higher in patients with PTGS2-positive tumors, when GDF15/MIC1 (growth differentiation factor 15) plasma levels were high preceding diagnosis.[137] When visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) compartments were analyzed for metabolic and transcriptomic differences to elucidate a link between obesity and colorectal carcinogenesis, results showed that VAT compartments displayed elevated markers of inflammatory lipid metabolism, prostaglandin synthesis-related enzymes (PTGDS/PGS2S), PLA2G10 (phospholipase A2 group X), and free arachidonic acid. The presence of these inflammation markers in VAT supports a role of visceral adiposity in promoting cancer.[138,139]

CRC incidence is higher in wild type than in *ppp1r15a/gadd34* (protein phosphatase 1, regulatory [inhibitor] subunit 15A) knockout mice.[140] PPP1R15A/GADD34 is part of a family of DNA damage-inducible proteins and it is a target of ATF4 during ER stress that regulates inflammation and host

defense systems. For example, dextran sodium sulfate-induced inflammatory responses are curbed as a result of PPP1R15A deficiency. In addition, both expression of pro-inflammatory mediators and epithelial cell proliferation are lower in *ppp1r15a* KO mice.[140]

Various ER-stress-associated proteins, such as HSPA5, ATF6, HSP90B1/GRP94, and XBP1s, are upregulated in cancer.[141] Therefore, a model of association between ER stress-induced tumor and pro-inflammatory gene pathways has been proposed.[133] In this model, ER stress induces NFKB and AP-1 activation in tumor cells followed by cytokine secretion in cancer cells.[142,143] Continuous infiltration of immune cells into the tumor microenvironment,[142,144] and induction of ER stress in tumor cells can affect both immune cells and cancer cells by triggering cytokine secretion from tumor cells.[145,146] Finally, ER stress is also induced in tumor-infiltrating immune cells because of their high cytokine production in the tumor microenvironment.[147] Hence, it has been shown that inflammation can induce the UPR via pathways that are activated by ER stress. All 3 sensors of the UPR, EIF2AK3, ERN1, and also ATF6, are involved in activation of inflammatory processes. ER stress-induced inflammation contributes in the pathogenesis and progression of several diseases, including obesity, type 2 diabetes, and cancer. However, based on the type of stress, the UPR arms might either promote or prevent cancer progression, depending on activated inflammatory pathways, cell type and stage of disease.[133]

Neutrophils have critical roles in tumorigenesis through their production of cytokines and chemokines, which influence inflammatory cell recruitment and regulate tumor cell proliferation, angiogenesis, and metastasis. Thus, neutrophils have been recognized as new targets for cancer therapy.[148] Infiltration of natural killer cells and $CD8^+$ T lymphocytes into the CRC micro-environment is a good prognostic sign in CRC patients and suggests potential antitumor effects of natural killer cells and $CD8^+$ T cells.[149] In addition to elevated levels of cytokines, chemokines, and ROS production, inflammasomes are strongly linked to increased rates of epithelial proliferation and angiogenesis, and play critical roles in colitis-associated CRC progression.[150] Furthermore, the role of proteases and their receptors on intestinal inflammation and cancer provide a rationale to explore the potential role of protease-activated receptor-induced PTGS2/COX2 in colitis-associated cancer.[151] American ginseng may have potential value in CRC chemoprevention via reduction of gene expression of inflammatory cytokines, including IL1A/IL1α (interleukin 1 α), IL1B, IL6, TNF, CSF3/G-CSF, and CSF2/GM-CSF in both the small intestine and the colon.[152]

Changes in molecular mediators of the UPR in CRC

Alteration of ER stress-associated molecules has been extensively studies by various genetic and pharmacological approaches (both inhibitors and inducers) in different cells.[153] In the context of CRC, Lu et al., showed that dihydroartemisinin can trigger ER stress in human colorectal carcinoma HCT116 cells through inducing the expression of HSPA5 and DDIT3 at both mRNA and protein levels.[153] Paclitaxel induces all 3 arms of the endoplasmic reticulum stress response in CRC cells by upregulating HSPA5 and phosphorylation of EIF2A.[154] Other studies revealed that HSPA5 expression is elevated in CRC.[155,156] Knocking down EIF2AK3, ERN1, or ATF6 in CRC HCT116 cells shows that EIF2AK3 has an important role in hypoxia-dependent induction of MAP1LC3B and ATG5.[157] SELENOS (selenoprotein S), which is involved in the metabolism of unfolded or misfolded proteins, is also associated with increased CRC risk.[158] In addition, high expression levels of XBP1 have been detected in CRC cells, emphasizing that upregulation of the corresponding gene may be one of key players in colon carcinogenesis.[159] Moreover, STC2 (stanniocalcin 2), as a main survival component of the UPR, is overexpressed in CRC to provide tolerance to ER stress.[160]

Upon treatment of HCT116 cells with celecoxib, ER chaperones and particularly HSPA5 are upregulated, followed by an increased level of VEGF production, and finally, apoptosis.[161] Similarly, dihydroartemisinin chemotherapy induces mitochondria-dependent apoptosis via ER stress pathways in CRC HCT116 cells.[162] The ERN1-XBP1 pathway is also important for promotion and progression of CRC.[163] Recent report shows a pivotal role of XBP1 in CRC invasion.[164] Inhibiting ATF4 sensitizes CRC cells to chemotherapy and counteracts drug-induced apoptosis, showing that the HSPA5-EIF2AK3-ATF4 pathway is active in CRC.[165] The above-mentioned ER stress-associated molecules seem to have therapeutic potential in CRC and more research is required to elucidate their importance.

Inhibitors and activators of autophagy and the UPR in CRC

Autophagy modulators

HMGB1 (high mobility group box 1) may have different functions including proliferation, invasion, and metastasis by ligating its multi-ligand AGER/RAGE (advanced glycosylation end product specific receptor) in different cancer models.[166,167] Necrotic cells release HMGB1 and are involved in inflammation induction.[168,169] HMGB1 plays a fundamental role in the carcinogenesis and progression of CRC.[170,171] HMGB1 colonic mucosa concentration is continuously increased in a rat azoxymethane model of CRC.[171] Several reports have shown that HMGB1 activates autophagy.[172,173] HMGB1 can also bind to TLR4 (toll like receptor 4), which subsequently activates innate immunity and immunological autophagy by triggering the dissociation of BECN1 from BCL2.[174,175] Cytosolic HMGB1 can directly bind to BECN1 to assist in the dissociation from BCL2 and consequently initiate an autophagic response.[176]

Luo et al. reported that proteolysis associated with autophagy is induced in the presence of HMGB1.[177] Autophagy selectively degrades cellular components, including aged proteins, protein debris, and damaged organelles, which contributes to energy production, and to supply amino acids.[178,179] HMGB1 is involved in the dephosphorylation of MTOR, which subsequently induces the proteins involved in autophagy, including BECN1 and LC3-II via AGER-mediated MAPK p38 phosphorylation.[177] An autophagy-induced glutamine supply might be important for maintaining mitochondrial energy production in muscles.[180] In contrast, cancer cells use glucose and

glutamine as a source of energy for the lactate fermentation pathway.[181] Cancer cells use plasma glutamine released from the muscle, and HMGB1 treatment increases lactate fermentation in colorectal cancer cells in culture conditions.[177,182] This underlines a cancer-host interaction in energy acquisition for cancer progression.

Initiation of the autophagy pathway involves BECN1, and the interaction with several cofactors, including AMBRA1, SH3GLB1/BIF (SH3 domain containing GRB2 like endophilin B1), and UVRAG, to activate the lipid kinase PIK3C3/VPS34.[62,68] Immortalized kidney and mammary epithelial cells that harbor a mono-allelic deletion of *BECN1* show increased growth rates when compared with their wild-type counterparts. Conversely, the tumor-suppressing property of BECN1 is associated with interactions of BECN1 and autophagy-related proteins downstream of BECN1, such as UVRAG and ATG4.[183] UVRAG overexpression suppresses the tumorigenicity of human colon cancer cells and, not surprisingly, one copy of the *UVRAG* gene is often deleted in human CRC. Furthermore, bi-allelic deletion of *Atg4* in mice favors the development of chemically induced fibrosarcomas as a result of tissue-specific defects in the autophagy pathway.[183] BECN1 expression is low in human breast tumors, glioblastoma multiforme and other high-grade brain tumors.[184] In contrast, high expression of BECN1 is observed in the majority of colorectal (95%) and gastric (83%) carcinomas when compared with normal stomach and colon mucosa.[185] In another study, 363 colorectal tissues from CRC patients were evaluated by tissue microarray and immunohistochemistry to investigate the expression and prognostic role of BECN1 in CRC. The findings link high expression of BECN1 with better OS and disease-free survival, suggesting that BECN1 may serve as an independent prognostic marker in CRC.[184]

Ectopic expression of the essential autophagy protein BECN1 reduces proliferation of cancer cells, suggesting its tumor suppressor properties. Indeed, BECN1 has been identified as a tumor suppressor complex. BECN1 serves as a scaffold for the formation of autophagosomes. MicroRNA (miRNA)-dependent decrease of BECN1 expression is an indication of poor prognosis and presumably promotes anti-apoptotic pathways.[184] Conversely, overexpression of BECN1 is associated with tumor hypoxia and these subgroups of tumors exhibit aggressive clinical behavior. In CRC tissues, BECN1 can be either up- or downregulated.[184] The activation of autophagy by overexpressing BECN1 may be an effective treatment of CRC with defects in BECN1.[186] In one study, the expression and significance of 3 autophagy-related proteins, namely BECN1, LC3, and MTOR, were investigated in the tumorigenesis and development of CRC. Immuno-histochemical studies revealed that the expression of these 3 proteins was significantly higher in CRC than in adjacent normal tissues.[186] In CRC tissues, the expression of LC3 was positively correlated with BECN1 and cell differentiation, but negatively correlated with MTOR, whereas the expression of MTOR was positively associated with cell differentiation and lymph node metastasis.[187] BECN1 and LC3 can predict the efficacy of cetuximab therapy, as low levels of autophagy are associated with a high antitumor efficacy of cetuximab.[188]

Besides *BECN1*, alterations in other autophagy genes, such as deletion of the *ATG5* gene or mutations in the key autophagic tumor suppressor *UVRAG* gene have been detected in colon cancer. We conclude that different components of the autophagic pathway mutually contribute to the regulation of cancer cell fate. The cancer-associated frame-shift mutation of *UVRAG* leads to the expression of its truncated form in CRC with MSI, and promotes tumorigenesis. The expression of truncated UVRAG can cause CRC metastatic spread through activation of the mall GTPase RAC1 and the epithelial-to-mesenchymal transition (EMT).[189]

Increased expression of ATG10 in CRC is associated with lympho-vascular invasion and lymph node metastasis. *ATG10* may serve as a potential prognostic maker in CRC.[190] ATG5 expression is lost in 23% of CRC patients and plays important roles in intestinal tumor growth. Heterozygous deletion of *Atg5* in Apc^{Min} mice increased the number and size of adenomas when compared with Apc^{Min} $Atg5^{+/+}$ mice.[189] Early treatment of Apc^{Min} $Atg5^{+/-}$ mice with IFNG lowered the tumor incidence to 16.7% and reduced the number of adenomas by 95.5%.[189] IFNG treatment also led to tumor regression.[189] Heterozygous deletion of *Atg5* activates EGFR-MAPK1/ERK2-MAPK3/ERK1 and WNT-CTNNB1/β-catenin pathways in adenomas of Apc^{Min} mice and enhances the effects of IFNG-dependent inhibition of tumor growth. A combination of IFNG and ATG5 deficiency or ATG5-targeted inhibition may offer promising strategies for the prevention and treatment of CRC.[189] Besides the paradoxical role of autophagy in tumorigenesis and cancer progression, the lack of expression of 3 autophagy-related proteins (ATG5, BECN1, and MAP1LC3B/LC3B [microtubule associated protein 1 light chain 3 β) is associated with poor prognosis in CRC, suggesting that these proteins have a potential to serve as new prognostic markers in CRC.[191]

Identified as a key autophagy-related protein and prosurvival factor in CRC cell lines, VMP1 (vacuole membrane protein 1) promotes autophagy via binding to BECN1 and triggering the BECN1-autophagy pathway. Upon specific VMP1 knockdown, CRC cells become more susceptible to apoptosis suggesting that VMP1 is an important negative regulator of the apoptotic pathways.[192]

Ectopic expression of *MIR140–5p* in colorectal CSC inhibits CSC growth and sphere formation in vitro by disrupting autophagy. There is progressive loss of *MIR140–5p* expression from normal colorectal mucosa to CRC tissues and a further reduction in liver metastatic tissues. The functional and clinical significance of *MIR140–5p* suggests that it is an important regulator of CRC progression and metastatic potential, and may serve as a lead for the development of novel therapeutic molecules to treat CRC.[193]

UPR modulators

Elevated HSPA5, a marker of the UPR, correlates with higher pathological grade, tumor recurrence, and poor survival in patients with breast, gastric, liver, colon, and prostate cancer.[194] The activation of several members of the UPR pathway, including HSPA5, has been reported in colon cancer.[195] In a cancer

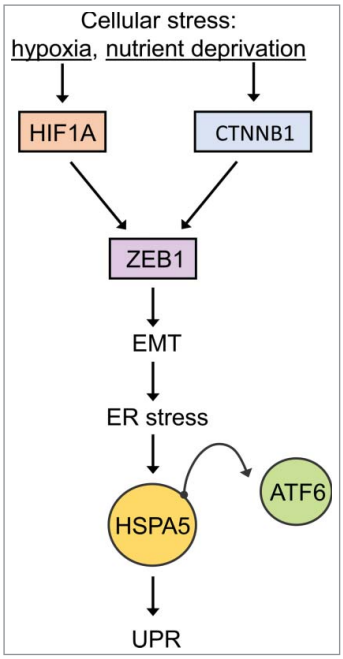

Figure 6. Hypoxia- and nutrient deprivation-induced stress cause EMT-mediated UPR. The relationship between EMT and ER stress. At the invasive front of CRCs, cellular stress conditions (hypoxia or changes in the microenvironment) induce EMT via activation of HIF1A or CTNNB1/β-catenin, which consequently leads to ZEB1 activation and EMT induction. EMT activates the UPR which induces the activation of UPR-related transcription factors (ATF6) (adapted from ref. 199).

xenograft animal model, reduction of HSPA5 inhibited tumor formation and growth. In early tumor stages, increased expression of HSPA5 may be responsible for controlling local tumor growth, whereas in advanced stages high expression of HSPA5 and HSP90B1 is dependent on other cellular stress reactions such as glucose deprivation and hypoxia.[194]

SEL1L is a member of the ER-associated protein degradation (ERAD) and UPR pathways. When associated with the E3-ligase SYVN1/HRD1, SEL1L assists in clearing unfolded proteins in the ER.[196] SEL1L expression is low in the normal gut mucosa but significantly correlates with the progression from adenoma to carcinoma, suggesting that it may become a potential target for CRC therapy.[196]

Hypoxia-like conditions (oxygen deprivation and nutrient stress) lead to EMT and ER stress in CRC cells and alter the localization of CTNNB1/β-catenin and CDH1/E-cadherin in SW480 and HCT116 colon cancer cells. Nuclear CTNNB1/β-catenin is an inducer of EMT and serves as an indicator for CRC stem cells (CSC), which promote tumor progression and a chemoresistance phenotype.[197] When cultured under hypoxia conditions, CRC upregulate the mesenchymal marker VIM (vimentin) as well as HSPA5, HIF1A/HIF1α, ZEB1, and the 50-k_D ATF6 fragment. It can be inferred that cellular stress activates HIF1A and/or CTNNB1/β-catenin signaling pathways, resulting in the induction of the EMT and ER stress. Several methods based on differential live staining of cells are being developed that should allow for the identification of CSC.[198] Figure 6 depicts an interconnected network of cellular stress-EMT-ER stress.[199]

Oncoproteins and tumor suppressor proteins involved in the UPR and autophagy in CRC

MYB/cMyb

The expression of ER-located HSPA5 is mandatory for protein folding in most cells.[200] MYB is a conserved transcription factor involved in normal colon development and hematopoiesis.[201] Overexpression of MYB induces *HSPA5* gene expression. The promoters of human and murine *HSPA5* and *HSP90B1* contain functional *MYB* binding sites as demonstrated by chromatin immunoprecipitation assays using recombinant MYB and nuclear extracts of colon cell lines. Amplification of *MYB* in tumor cells may lead to *HSPA5* gene induction, and in turn, this promotes cell survival during oxygen deprivation and nutrient stress conditions.[202] This reinforces the view that UPR modulation may be a new attractive therapeutic target for the eradication of glucose-deprived solid tumors. Table 4 shows a list of oncogenes and tumor suppressors involved in CRC.

TAGLN/SM22

TAGLN (transgelin) is considered a tumor suppressor and its expression changes under many pathological conditions, including CRC.[203] TAGLN binds to the actin protein network

Table 4. Oncogenes and tumor suppressors and their link to autophagy and tumorigenesis.

Name	Link(s) to tumorigenesis	Link(s) to autophagy
	Oncogenes[183]	
BCL2, BCL2L1	Overexpressed in a relevant proportion of human cancers, and notably in hematological malignancies	Negative regulator of autophagy by sequestering BECN1
	Tumorsuppressor genes	
ATG4C	Implicated in the development of chemically-induced fibrosarcomas	Operating a proper autophagy response under ER stress conditions
BECN1 (*VPS30/ATG6*)	Deleted in a relevant fraction of human breast, ovarian and prostate tumors. Brain tumors are characterized by reduced expression of BECN1	Essential modulator of autophagy
Encoding BH3-only proteins	Loss of expression due to inactivating mutations in multiple human tumors (e.g., melanoma, renal cell carcinoma)	Promoting autophagy by liberating BECN1 from inhibitory interactions with anti-apoptotic members of the BCL2 protein family
DAPK1	Frequently silenced in human tumors by epigenetic mechanisms	Induces autophagy by interaction with the microtubule-associated factor MAP1B. Also promotes autophagy via activation of TP53
TP53	Mutated in >50% of all human tumors	Nuclear TP53 trans-activates autophagy-promoting factors (e.g., DAPK1, DRAM). Cytoplasmic TP53 exerts a tonic inhibition on autophagy
UVRAG	Mono-allelic deletion at high frequency in human colon cancers	Defective in autophagy pathways

and is also considered a marker for smooth muscle differentiation.[204] The expression of the tumor suppressor TAGLN is significantly decreased in CRC tissues and a link exists between low TAGLN expression and inhibition of autophagy in human CRC tissues and CRC cell lines.[203]

SQSTM1/p62 (sequestosome 1) is a multifunctional receptor protein implicated in the delivery of cargo to phagophores.[63] SQSTM1 is a ubiquitin-binding scaffold protein that colocalizes with and guides ubiquitinated proteins to the autophagic machinery via binding to LC3.[205] SQSTM1 is a marker of autophagy flux and its upregulation could be interpreted as inhibition of lysosomal digestion of autophagosomes.[206] SQSTM1 is also involved in autophagy-related cell signaling pathways and tumorigenesis. SQSTM1 and LC3 are upregulated in a subset of CRC.[207] The increase in SQSTM1 is thought to be a crucial contributing factor in CRC tumorigenesis. Knockdown of *Sqstm1* expression significantly inhibits autophagy activation and tumor growth, both in vitro and in xenograft tumor models.[207] SQSTM1 and autophagy have been suggested as therapeutic targets for the treatment of CRC.[207]

SH3GLB1/BIF1 is a tumor suppressor gene of the endophilin protein family. SH3GLB1 colocalizes with ATG5 and LC3, which suggests its involvement in early autophagosome formation. Loss of SH3GLB1 reduces PIK3CVPS34 kinase activity and suppresses autophagy induction in response to nutrient starvation.[50] SH3GLB1 regulates autophagy by forming a multiprotein complex with the PtdIns3K and BECN1 through UVRAG.[208] The transition from normal epithelium to CRC coincides with a downregulation of SH3GLB1.[209] Furthermore, SH3GLB1 interacts with BAX to regulate apoptosis. Loss of SH3GLB1 suppresses apoptotic cell death by inhibiting BAX-BAK1 conformational change and caspase activation, hence promoting tumorigenesis.[209-211]

PCDH17

PCDH17 (protocadherin 17) exerts its tumor-suppressing activity through apoptosis and autophagy induction. PCDH17 is frequently silenced by promoter methylation in most gastric and colorectal tumor cell lines, as well as in 95% of primary CRC tumors. *PCDH17* deletion was detected in only 18% of gastric and 12% of CRC tissues, suggesting that both epigenetic and genetic inactivation of *PCDH17* are involved in gastric and colorectal tumorigenesis. *PCDH17* methylation status has been suggested as an epigenetic biomarker for these tumors.[212] In gastric and CRC patients, high PCDH17 expression was significantly correlated with low tumor stage and lower frequency of lymph node metastasis, indicating a promising role for PCDH17 as a prognostic marker.[212] Restoring PCDH17 expression promotes apoptosis and blocks tumor cell growth both in vitro and in vivo.[212] Furthermore, PCDH17 induces autophagy through the upregulation of autophagic proteins (such as ATG5, ATG12 and LC3B-II) and formation of autophagic vacuoles.

PARK2/parkin

Frequent loss of heterozygosity and deletions in the *PARK2* gene are found in several cancers. Consistent with PARK2s property as a tumor suppressor, several studies showed that ectopic expression of PARK2 reduces cell growth and increases apoptosis in hepatocellular and lung cancer. In a colon cancer model, alternatively spliced variants of PARK2 failed to degrade CCNE (cyclin E). This finding suggests that loss of CCNE regulation by PARK2 contributes to colon cancer. Tumor cells often suppress their mitochondria in response to hypoxia and ER stress to reduce oxidative stress, a process that also utilizes autophagy. PARK2's role in mitophagy might also in part account for its tumor suppressor functions. PARK2 induces autophagy via BNIP3L/NIX, which causes mitochondrial depolarization and MTOR inhibition. PARK2 ubiquitinates effector proteins and can select mitochondria for autophagy. The HSP90/HSP70-based chaperone machinery plays a key role in the degradation of aberrant proteins via the ubiquitin-proteasome pathway.[213] The ability of PARK2 to ubiquitinate HSP70 proteins suggests that PARK2 may play a role in the degradation of substrates normally stabilized by HSP90 and important for tumor cell survival and proliferation.[214]

Class I PI3K

Class I PI3Ks phosphorylate PtdIns4P and PtdIns(4,5)P_2. The deregulation of class I PI3Ks has been described in the course of tumorigenesis and resistance to therapy in cancer. Class I PI3K activation and its products PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 inhibit autophagy in HT-29 cells.[142,185] The activation of MTOR and the resulting inhibition of autophagy in response to cellular stress can occur through the activation of the class I PI3K and its downstream effector AKT/PKB. The inhibition of AKT potently induces autophagy through inactivation of MTORC1. Likewise, overexpression of PTEN, a dual lipid/protein phosphatase, tumor suppressor, and negative regulator of the PI3K-AKT pathway, induces autophagy.[50] The PI3K-AKT pathway is a potent activator of cell proliferation and cell survival, and it is regulated at multiple levels.[215] A dominant

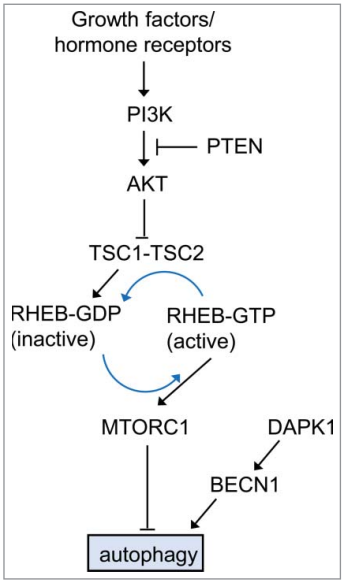

Figure 7. The role of MTOR in cancer-associated signaling pathways that regulate autophagy in mammalian cells. The best known regulator of autophagy is MTOR (mechanistic target of rapamycin), a serine/threonine kinase conserved throughout eukaryotes. The activity of MTORC1 is inversely correlated with autophagy induction. The μTORC1 inhibitor rapamycin potently induces autophagy, even in the presence of abundant nutrients (adapted from ref. 50). The PI3K-AKT regulates autophagy. This regulation is mediated via the small RHO-GTPase RHEB.

negative AKT mutant enhances autophagy whereas expression of active AKT decreases autophagy. Figure 7 depicts the role of MTOR in cancer and its association with autophagy.

Class III PtdIns3K

In contrast to class I PI3Ks, class III PtdIns3Ks are autophagy stimulators. Inhibition of class III PtdIns3K (by e.g. 3-methyladenine; 3-MA) decreases the rate of autophagy, whereas the class III PtdIns3K adaptor (PIK3R4/p150) overexpression or the addition of PtdIns3P induces autophagy.[185,216] BECN1 plays an integral role in the class III PtdIns3K pathway.[185] Knockdown of BECN1 inhibits autophagy and promotes cell death through nutrient starvation. BECN1 and PTEN are important for autophagy induction and are therefore considered potential targets in the treatment of cancer.[185] Justicidin A (JA), a novel and pure arylnaphthalide lignan isolated from *Justicia procumbens*, induces class III PtdIns3K-dependent autophagy in a colorectal cancer cell line (HT29). This enhances JA-mediated apoptotic activity and antitumor effects in these cells.[217]

HPGD/15-PGDH

Recently, HPGD (hydroxyprostaglandin dehydrogenase 15-[NAD]), a key enzyme in PGE2 degradation, has been indicated as a tumor suppressor in several cancers, including colon cancer.[218] Glucose deprivation in colon tumors elevates PTGS2/COX2 expression and simultaneously reduces the expression of HPGD.[218] Depriving colon tumor cells of glucose, results in upregulation of PGE2 with both an increase in PTGS2 expression and a decrease in HPGD expression, which is mediated via enhanced PI3K-AKT signaling. Glucose deprivation leads to activation of the UPR, which, through increased levels of DDIT3, can lead to the suppression of the key tumor suppressor gene HPGD. This inverse regulation between DDIT3 and HPGD suggests that tumor cells could manage to survive in the presence of therapeutic agents that activate the UPR. In this way, regulation of PTGS2 and HPGD might be critical via effective PGE2 target-based chemotherapy approaches to suppress tumor development. Figure 8 shows how glucose deprivation increases PGE2 expression during tumorigenesis.[218]

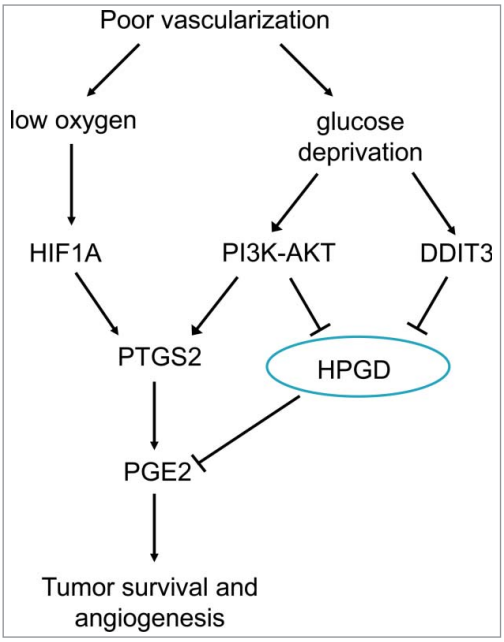

Figure 8. Regulation of tumor survival and angiogenesis via glucose and oxygen supply. Glucose deprivation increases PGE2 by upregulating PTGS2 and downregulating HPGD expression via PI3K-AKT and DDIT3-dependent mechanisms. Hypoxia increases PGE2 levels by upregulating PTGS2 expression via HIF1A). Elevated PGE2 increases survival of colon cancer cells exposed to both glucose deprivation and hypoxic conditions (adapted from ref. 218).

Association between obesity and CRC through autophagy and the UPR

Obesity is a significant risk factor for various types of cancers.[138,219] Diets high in fat and genetic predisposition to obesity in Apc1638N mice, a mouse model for familial adenomatous polyposis, differentially alter the composition of microorganisms and metabolites in the intestine. A reduction in *P. distasonis* and adenosine is anti-inflammatory in the colon and could promote tumorigenesis.[220] A study has been recently conducted on 451 Hispanic participants, of whom 218 had CRC, 77 had colorectal adenomas, and 156 were colonoscopy-negative controls. The study found an increased risk of adenoma, especially in proximal locations, among Hispanic women with type 2 diabetes providing a rationale for increased screening in this population.[221]

The MTOR pathway integrates signals from growth factors, nutrients, mutagens, and hormones, to induce cell proliferation and resistance to apoptosis, and autophagy.[222] Glucose deprivation is a form of nutritional stress in tumor cells. ADIPOQ (adiponectin, C1Q and collagen domain containing) negatively influences cancer progression during glucose deprivation.[130] Under normal conditions, ADIPOQ inhibits IGF1 (insulin like growth factor 1) signaling in tumor cells and activates both PRKAA/AMPKα and PPARA/PPARα (peroxisome proliferator activated receptor α) to inhibit the PI3K-AKT-MTOR pathway and enhance autophagy.[130] Hence, ADIPOQ provides an important molecular link between cancer and obesity. Epidemiological and clinical data show a relationship between obesity-related inflammation via pro-inflammatory cytokines, such as TNF secreted by macrophages. Low level of LEP (leptin) and ADIPOQ are additional factors that play an important role in physiological responses to inflammation and can promote the development of CRC in obese individuals. The role of LEP and ADIPOQ in carcinogenesis is attributed to several signaling pathways, including the activation of JAK-STAT, MAPK, PI3K, MTOR, and AMPK, and downregulation of PTGS2,[223] and upregulation of CDH13/T-cadherin (cadherin 13), a unique member of the cadherin superfamily lacking the transmembrane and cytoplasmic domains that anchors to the cell membrane of HCT116 cells.[224]

Hypoglycemic agents and autophagy and the UPR in CRC

Metformin, an oral hypoglycemic agent, has recently being receiving increased attention due to its antitumorigenic effects in breast and colon malignancies that have an association with obesity and hyper-insulinemia. Chemotherapy with metformin is associated with decreased incidence of colon and pancreatic

cancer but does not affect the outcomes in breast or prostate cancer. A randomized pilot study involving nondiabetic patients showed that low-dose metformin (250 mg/d) given for 1 mo suppresses the formation of aberrant crypt foci (ACF), an early indicator of colon cancer.[225]

Mechanisms of action of metformin include activation of the STK11/LKB1 (serine/threonine kinase 11)-AMPK pathway, induction of cell cycle arrest and/or apoptosis, inhibition of protein synthesis, reduction in circulating insulin, inhibition of the UPR, activation of the immune system, and eradication of cancer stem cells. Using a tumor xenograft model, Buzzai et al. showed that metformin was able to selectively inhibit cell growth and induce autophagy in TP53-deficient colon cancer cells. In glucose-starved cultures of human colon, fibrosarcoma, renal, and stomach cancer, gene expression profiling techniques revealed that metformin was able to inhibit UPR activators and lead to cell death.[225]

Aspirin, in combination with metformin, enhances AMPK activation and this leads to MTOR suppression and autophagy induction, which could contribute to the tumor supressor role of AMPK in the development of CRC. The PI3K-MTOR signaling pathway controls cell survival and regulates cell metabolism, and deregulated PI3K-MTOR signaling is associated with CRC development. Pharmacological AMPK activators, such as 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR) and metformin, inhibit growth and delay tumor initiation.[226] These findings suggest a possible mechanism by which metformin and aspirin may inhibit cancer growth through MTOR signaling/autophagy and the UPR.

The UPR and autophagy pathways as potential treatment strategies for IBD and CRC

Autophagic adaptive responses in CRC can increase the sensitivity against autophagy inhibition and improve the efficacy of chemotherapy. Autophagosomes are actively produced in CRC cells under conditions of nutrient starvation. Autolysosome inhibitors suppress autophagosome formation and enhance apoptosis under amino acid- and glucose-deprived conditions.[227] We will also discuss the critical role of combinatorial therapies with particular attention to genetic and molecular markers associated with the autophagy and UPR pathways.

Therapeutic targeting of the autophagy pathway

Silibinin, a flavonolignan isolated from the milk thistle plant (*Silybum marianum*), inhibits autophagy and enhances apoptotic pathways in the SW480 and SW620 CRC cell lines.[228] Also, curcumin and a curcumin analog G0-Y030 inhibit tumor sphere formation in $ALDHA^{+}$ $CD133^{+}$ colon CSCs.[229] Multiple signaling pathways are inhibited by curcumin in epithelial cancers and this contributes to apoptotic cell death. Besides apoptosis, curcumin induces autophagy in cancer cells.[229] Chemoprotective properties of plant-derived phytochemicals (e.g., curcumin) may be induced through several effects, including cell restorative processes, stimulation of antimetastatic and antiangiogenic responses and/or increased antioxidant and anti-inflammatory activity.[230,231] In the future, it may be possible to avoid toxic effects of radio/chemotherapy by using combinatorial strategies with nontoxic agents such as curcumin, which can target CSC.[232] The oncogenic microRNA *MIR22* is thought to be a switch between apoptosis and autophagy. *MIR22* also inhibits autophagy and promotes apoptosis both in vitro and in vivo and increases CRC cell sensitivity to 5-FU treatment.[149] The oncogenic *MIR22* may be considered a predictor of 5-FU sensitivity and a target for CRC therapy.[149]

Mammalian MAPK14/p38α activity is required for CRC cell growth in vitro and in mouse models of human colon cancer. Inhibition of MAPK14 in CRC cells reduces tumor growth and induces autophagic cell death. Combination therapy using inhibitors of MAPK14 (SB202190) and MAP2K1/MEK1 (PD98059) significantly reduces cell survival and induces apoptosis through TNFSF10/TRAIL signaling in both HT-29 and HCT-116 cells. Several MAPK14 and MAP2K1 inhibitors are in phase II clinical trials for the treatment of inflammation and cancer.[233,234] Also, MAPK14 is required to sustain the expression of HIF1A target genes. Inhibition of MAPK14 causes a rapid drop in ATP levels in CRC cells. The AMPK-FOXO3 (forkhead box O3) axis is a metabolic switch that senses variations in the AMP:ATP ratio. Manipulation of this pathway in combination with drugs targeting the 'Warburg effect' and/or autophagy may be an effective strategy for selective targeting of cancer cells.[235-237] In addition, AMPK is a major regulator of energy metabolism with key roles in the inhibition of biosynthetic pathways and enhancement of ATP-generating pathways. Compound C, a small molecule inhibitor of AMPK, causes an increase in the sub-G_1 cell population (apoptotic cells), in HCT116 and KM12C cells. Compound C also triggers acidic vesicular formation, conversion of LC3-I to autophagosome-associated LC3-II, and finally autophagic cell death in DLD1 and SW480 cells.[238]

Ectopic expression of *MIR124–2HG*, a modulator of energy metabolism and tumor suppressor, enhances oxidative stress. The *MIR124–2HG*-PTBP1/PTB1-PKLR/PKM1-PKM/PKM2 axis induces apoptosis and autophagy in colon cancer cells.[239] MAPKs are activated by 5-FU. SB203580 compound-mediated inhibition, or the shRNA-specific knockdown of MAPK p38, are associated with resistance to 5-FU-induced apoptosis in HCT116 cells.[240] This resistance is correlated with an autophagic response mediated by a decrease in TP53-induced apoptosis but does not affect TP53-dependent autophagy. The critical role of the MAPK p38 signaling pathway in modulating the rates of autophagy and apoptosis in response to 5-FU has been outlined in Figure 9.[240] We have summarized agents targeting autophagy pathways in vivo and in vitro in CRC in Figure 10.

Autophagy and Immunotherapy in CRC

Immunotherapy has emerged as a powerful weapon to combat different types of cancer, as it targets tumor-specific antigens.[241] In the context of CRC, considering drawbacks of current treatment options such as chemo- and radiotherapy, development of novel alternative specific strategies with more efficacies and less side effects is an unmet clinical need. In general, immunotherapeutic approaches to treat CRC include peptide vaccines, dendritic cell (DC)-based vaccines, whole tumor cell vaccines, viral vector-based vaccines,[242] adoptive cell transfer therapy,

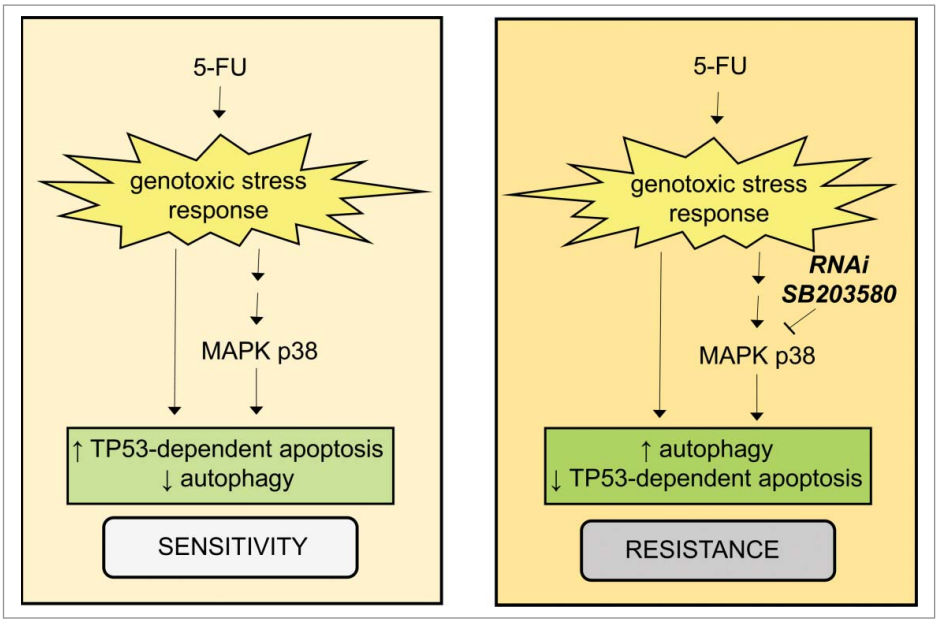

Figure 9. The role for the MAPK p38 signaling pathway in cellular response to 5-FU. There is a critical role for the MAPK p38-signaling pathway in the cellular response to 5-FU by controlling the balance between apoptosis and autophagy (adapted from ref. 240). This pathway is tightly controlled by the TP53-mediated regulation of autophagy.

antibody-based cancer therapy,[243] cytokine therapy,[241] checkpoint inhibitors, and combined therapy.[241,244]

CRC peptide vaccines are well-characterized epitopes able to elicit a specific immune response against colorectal tumor-associated antigens (TAAs). For example, CRC cells often express CEACAM5/CEA (carcinoembryonic antigen related cell adhesion molecule 5),[245] EGFR (epidermal growth factor receptor),[246] TP53,[247] or KRAS,[248] which are potential targets for CRC immunotherapy. DCs can provide necessary signals to induce an efficient antitumor immune response.[249] Therefore, several DC-based immunotherapeutic approaches have been developed by using TAA-pulsed DCs. These approaches include the known TAAs,[250] tumor cell lysates,[251] apoptotic tumor cells,[252] and tumor RNA.[253]

Adoptive cell transfer therapy is a passive immunotherapy in which specific effector cells, e.g. cytotoxic T lymphocytes, are directly infused within the CRC patient. Autologous T cells are removed from CRC patients, activated, expanded to large numbers in vitro and transferred back into the patients.[254,255] Immune checkpoint blockade by targeting the inhibitory immune receptors CTLA4 (cytotoxic T-lymphocyte associated protein 4), PDCD1/PD1 (programmed cell death 1), and CD274/PDL1 is a novel immunotherapeutic approach to treat CRC patients.[256,257] A combined approach by using both chemo/radiotherapy and immunotherapy seems to be more effective for CRC.[258] For instance, it has been shown that chemotherapy increases the antitumor effects of cancer immunotherapy by depleting regulatory T cells (T_{reg}).[259,260]

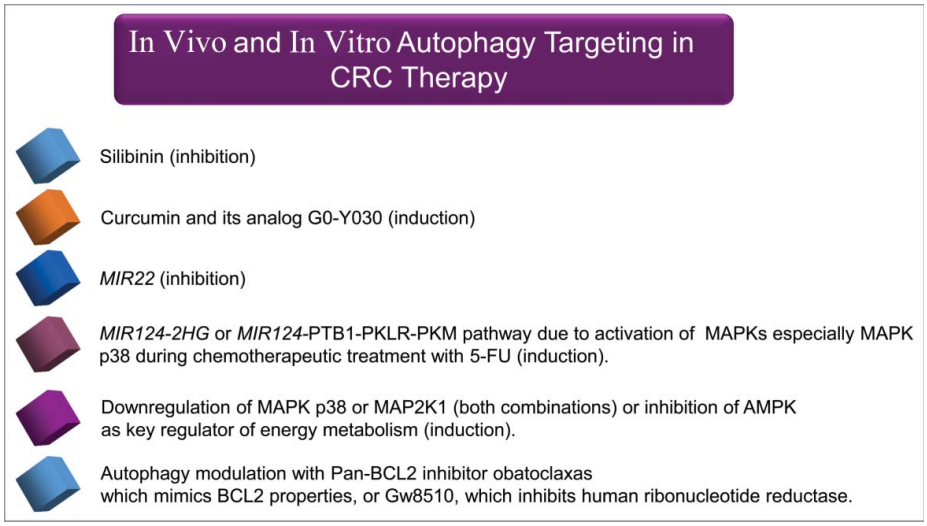

Figure 10. Autophagy targeting strategies in in vitro and in vivo models of CRC. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Therapeutic targeting of the autophagy pathway*."

Several lines of evidence suggest that autophagy is involved in development and progression of CRC and it could be considered as a potential target for treatment of CRC.[261] However, there are several issues, which remain to be addressed. It is not clear whether targeting autophagy machinery in CRC patients or experimental models will affect the antitumor immune response. Furthermore, current CRC immunotherapeutic modalities might function at least in part through modulation of autophagy. In addition to its direct antitumorigenic roles, autophagy can inhibit CRC by attenuating the inflammatory response in the tumor microenvironment. Autophagy could increase the processing and presentation of TAAs that result in antitumor immunity. Tumor cells have the ability to escape immunosurveillance by tuning down autophagy, though some chemotherapies have been revealed to exert immunogenic antitumor properties via inducing autophagic cell death.[262]

It has been demonstrated that the cell wall of *Mycobacterium bovis*, and *Bacillus Calmette-Guerin* (BCG) induces a radiosensitizing effect on colorectal cell lines via induction of autophagic cell death through TLR2 and TLR4 signaling. In vivo evidence further supports the idea that BCG-mediated radiosensitization is an autophagy-dependent phenomenon. These data suggest that the BCG cell wall in combination with ionizing radiation provides a promising strategy for enhancing radiation therapy in CRC through the induction of autophagy.[263]

Wei et al. have recently reported that autophagy is active in T_{reg} cells, and involved in their lineage stability and survival fitness. Genetic abrogation of autophagy in these cells has led to loss of T_{reg} cells, greater tumor resistance and development of inflammatory disorders in a mouse model of colon cancer.[264] Specific deletion of the *Atg7* gene in T_{reg} cells has been associated with increased apoptosis and downregulation of transcription factor FOXP3. Loss of autophagy leads to upregulation of metabolic mediators such as MTORC1 and MYC as the mechanism underlying the defective T_{reg} phenotype in this CRC model.[264] These findings indicate that targeting autophagy in T_{reg} cells along with tumor cells could heighten the efficacy of treatment in CRC.

Considering the inhibitory effect of chloroquine as an autophagy inhibitor on colon cancer cell growth,[265] and also development of systemic autophagic syndrome upon recombinant IL2 immunotherapy, Liang et al. demonstrated that co-administration of chloroquine increases IL2 immunotherapeutic efficacy and also limits toxicity in an advanced murine metastatic liver tumor model. This beneficial dose-dependent combinatorial therapy is associated with increased long-term survival, vascular leakage and enhanced immune cell proliferation and infiltration.[266] From a mechanistic point of view, IL2 treatment alone induces autophagy and overexpression of HMGB1, IFNG, IL6, and IL18 within the liver and translocation of HMGB1 from the nucleus to the cytosol in hepatocytes, which is significantly inhibited upon addition of chloroquine.[266] Furthermore, the chloroquine effect could be directly mediated on tumor cells by several mechanisms such as increased autophagic vacuoles and LC3-II levels, cell death, CASP3/caspase-3 cleavage and CYCS (cytochrome c, somatic) release from mitochondria as well as decreased oxidative phosphorylation and ATP production.[266]

Collectively, in combination with chemotherapeutics and immune checkpoint inhibitors, autophagy regulators might strengthen the efficacy of CRC immunotherapy in a more targeted manner. One has to keep in mind that the interaction between cell proliferation and immunity is a complex one.[267] Future investigations aiming to understand the effect of these combinatorial approaches on antitumor immunity could address several unknown issues regarding this complex problem.

Therapeutic targeting of ER stress and the UPR

Falcarindiol (FAD) is a natural polyacetylene in carrots that induces intracellular buildup of ubiquitinated proteins in cancer cells, including CRC. This leads to the accumulation of unfolded/misfolded proteins in the ER and causes an increase in ER stress-induced cell death via FAD.[268] Treatments leading to increased ER stress enhance FAD-induced cell death.[269]

Cancer cells, in poorly vascularized solid tumors, are frequently exposed to nutrient starvation, which activates the UPR pathway. In a glucose-deprived environment, anticancer agents, such as arctigenin (ARC-G), which targets the UPR, could preferentially cause tumor cell death.[34] Another target for cancer therapy is *HSPA5* because it is considered a main target of UPR signaling for survival and often upregulated in most cancers. Verrucosidin can disrupt HSPA5 expression during glucose deprivation in HT-29 human colon cancer cells.[270] In addition to being an inhibitor of HSPA5 expression, versipelostatin, blocks the UPR and induces cytotoxicity in glucose-deprived colon tumor cells both in vitro and in vivo.[269] This cytotoxic effect of versipelostatin is mediated through suppression of HSP90B1 expression and the UPR transcriptional activators XBP1 and ATF4.[271,272]

Brefeldin A (BFA), an inhibitor of protein transfer from the ER to the Golgi, leads to an accumulation of proteins in the ER and this results in the activation of apoptotic UPR signals. BFA triggers apoptosis in HT-29 cells.[195] These results suggest 2 approaches to target the UPR: (*i*) designing inhibitors of the UPR pathway to block the adaptive response needed for survival of tumor cells, and (*ii*) using inducers of the UPR to overload stress and induce UPR-mediated cell death pathways in cancerous cells.[195] Targeting autophagy leads to increased cell death in HCT116 colon cancer cells.[273] Table 5 lists the drugs targeting ER stress and autophagy for anticancer therapy. High doses of selenium induce ER stress and cause subsequent EIF2AK3-dependent ElF2 phosphorylation and apoptotic cell death. Selenium can also contribute to an increase in ER stress upon irradiation and may promote radio-sensitization.[273]

The expression of FASN (fatty acid synthase) and the autophagy marker SQSTM1 is increased specifically in

Table 5. Drugs that target ER stress and autophagy for anticancer therapy.

Treatment	Category	Cancer type
Bortezomtib	Proteasome inhibitor	Prostate and multiple myeloma
17-AAG, IPI-504	HSP inhibitor	Many solid tumors
Tubacin	HDAC inhibitor	Breast
Selenium	Trace element	Colorectal and prostate
Cerulenin or C75	FASN inhibitor	Breast and prostate
Reference:[273]		

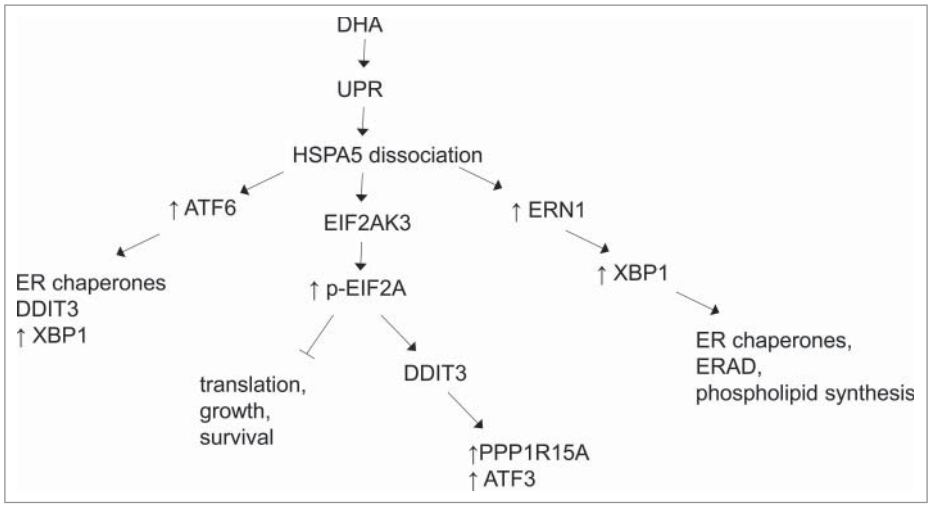

Figure 11. Endoplasmic reticulum (ER) stress induction by docosahexaenoic acid (DHA). DHA induces ER stress in colorectal cells. Diagram showing transcripts affected by DHA treatment in SW620 colon cancer cells by gene expression analysis in the main pathways of ER stress signaling. Three transmembrane proteins mediate the unfolded protein response (UPR) across the ER membrane after dissociation from HSPA5-ATF6, EIF2AK3 and ERN1 (adapted from ref. 278).

primary CRCs and liver metastases of CRC.[274] The activation of fatty acid oxidation and the downregulation of stress-response signaling pathways may be key adaptation mechanisms to facilitate the effects of FASN on cancer cell survival and metastasis. This provides a strong rationale for targeting this pathway in advanced CRC.[274] Importantly, ER stress can be induced in tumor cells by FASN inhibitors, such as cerulenin or C75, but not in normal cells. FASN inhibitors exhibit selective apoptosis-inducing cytotoxicity particularly in therapy-resistant, TP53-deficient cells. The selective activation of the FASN pathway could be responsible directly for CRC destruction by apoptosis and/or target them for immunological attack. FASN inhibitors were toxic to HT-29 cells expressing a dominant negative EIF2AK3. This was also observed in cells expressing normal levels of EIF2AK3 and is mediated by FASN inhibitor-induced persistent phosphorylation of EIF2A by EIF2AK3.[275] In this context, FASN causes inhibition of protein synthesis and the activation of ERN1 to increase the expression of the ER stress regulated genes *ATF4, DDIT3*, and *HSPA5*. This suggests that an approach combining irradiation-induced ER stress with FASN inhibitors could potentially improve the outcome of cancer treatment.[275]

To prevent protein misfolding and degradation, cells upregulate protein chaperone members of the heat shock protein (HSP) family. HSPs form interactions with key proteins in the UPR pathway. HSP90 inhibitors, such as 17-allylamino-17-demethoxygeldanamycin (17AAG), act as UPR activators and can activate all 3 major UPR arms (Fig 5B). All HSP90 inhibitors tested repress cell proliferation and increase the expression of the chaperones HSP90B1 and HSPA5. In 17AAG-treated myeloma cells, exposure to HSP90 inhibitors changed the LC3 expression levels consistent with autophagosome formation. HSP90 inhibitors may be interesting targets for the treatment of myeloma, breast cancer, and CSC.[194] Analogous to the ER responses initiated by defective protein folding, a mitochondrial UPR may play a role in HSP90- and proteasome inhibitor-mediated apoptotic pathways. Application of HSP inhibitors blocks chaperone function and increases mitochondrial protein expression. This is associated with increased cytochrome oxidase activity, leading to mitochondrial dysfunction.

ER stress inducers, such as thapsigargin or bortezomib, exhibit significantly higher cytotoxicity along with enhanced UPR activation when used under hypoxic conditions. Despite being generally more resistant to genotoxic agents, these drugs may induce hypersensitivity to proteasome inhibitors via increased UPR signals in hypoxic tumor cells.[276]

N-3 poly-unsaturated fatty acids, such as docosahexaenoic acid (DHA), induce apoptosis by altering the expression and localization of HSPA5 in colon cancer cell lines (i.e., HT-29, HCT116 and SW480). Transfection of SW480 cells with HSPA5-GFP induced increased cell growth and inhibited the DHA induced apoptosis.[277] As shown in Figure 11, DHA induces key mediators of ER stress and the UPR and it may also coordinate many downstream pathways, including the regulators of cholesterol metabolism, calcium homeostasis, ubiquitination, and proteasomal degradation. DHA may cause cholesterol depletion in the ER due to reduced *de novo* cholesterol synthesis and inhibition of cholesterol transport to the ER through redistribution of cholesterol from the ER to DHA-cholesteryl ester-enriched lipid droplets.[278] Accompanied by increased cholesterol esterification, this is an important factor for the initiation of calcium mobilization. Subsequent ER stress may lead to growth inhibition and cell death. Therefore, compounds that decrease cellular cholesterol stores activate a network of stress responses leading to cell death.[278]

Synthetic 3-thia fatty acid, tetradecylthioacetic acid, can inhibit proliferation in SW620 cells. Like DHA, tetradecylthioacetic acid induces growth inhibition, which is mediated via ER stress and the UPR and involves EIF2A phosphorylation and downstream regulation of ATF4.[279] Riproximin (RPX) is a component of a plant extract and cytotoxic to breast and colorectal cancer cells by targeting type II ribosome inactivating proteins with high selectivity in certain tumor cell lines. This increases the expression of the UPR genes *ATF6* and *ERN1*. A higher concentration of RPX induces the UPR pathway via the EIF2AK3 branch, which results in numerous complex effects,

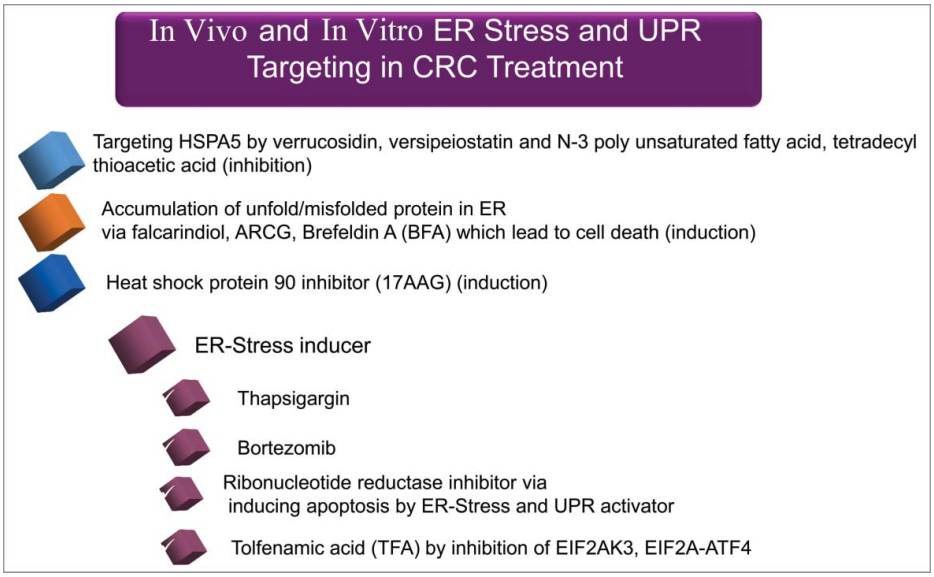

Figure 12. ER stress and UPR targeting strategies in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Therapeutic targeting of ER stress and the UPR.*"

such as translational arrest, growth inhibition, and apoptosis by enhanced EIF2A phosphorylation that includes elevated expression of transcription factors such as ATF3 and DDIT3.[280] The antioxidant 2-(3, 4-dihydroxyphenyl) ethanol (DPE) derived from olive oil induces growth arrest and apoptosis in HT-29 cells. Like DHA, DPE acts via ER stress induction and leads to the activation of 2 routes of the UPR, the ERN1-XBP1-HSPA5 and EIF2AK3-EIF2A pathway, resulting in enhanced expression of the pro-apoptotic factor DDIT3.[281]

Treatment of colon cancer cells with the RRM (ribonucleotide reductase) inhibitor Triapine (3-AP; 3-aminopyridine-2-carboxaldehyde thiosemicarbazone) activated all 3 ER stress pathways (EIF2AK3, ERN1, ATF6). In particular, 3-AP-Me led to 16-fold upregulation of an mRNA variant of *XBP1*. 3-AP and 3-AP-Me activated the cellular stress kinases, MAPK/JNK and MAPK p38 with subsequent UPR activation and apoptosis. These data suggest that 3-AP and 3-AP-Me could induce apoptosis via ER stress in colon cancer cells.[282]

The nonsteroid anti-inflammatory drug tolfenamic acid (TFA) suppresses cancer cell growth and tumorigenesis in various cancer models. TFA markedly reduced the number of polyps and tumor load in an experimental rodent model of CRC. TFA promotes ER stress and UPR activation, which leads to CCND1 (cyclin D1) translation inhibition. The EIF2AK3-EIF2A-ATF4 autophagy branch plays a role in TFA-induced apoptosis in CRC cells since the silencing of ATF4 attenuated TFA-induced apoptosis. This implicates ER stress being involved in TFA-induced inhibition of CRC cell growth in mice.[283]

The EIF2AK3-EIF2A-ATF4 pathway is critical for the adaptation to hypoxic stress in tumor cells. HT29 cells expressing dominant negative EIF2AK3 are more sensitive to hypoxic conditions and die by apoptosis. Autophagy acts in a prosurvival manner by removing aggregated proteins accumulating in the cytosol, thereby preventing manifestation of the UPR. The accumulation of polyglutamine proteins causes the activation of autophagy by a EIF2AK3-EIF2A-ATF4 mediated upregulation of ATG12 after ER stress. Although this may qualify the EIF2AK3 pathway as a bona fide target to impede the survival of tumor cells under hypoxia, EIF2AK3 targeting does not always produce desirable effects. For example, activation of EIF2AK3 and EIF2A signaling in highly malignant squamous THEP3 or SW620 CRC cells induces both survival and suppression of tumor growth both in vitro and in vivo. Moreover, despite its prosurvival properties, EIF2AK3 may also suppress advanced tumor growth. This dual function of EIF2AK3 should be considered when developing EIF2AK3-targeted anticancer strategies, as EIF2AK3 inhibition might stimulate the proliferation of quiescent state tumor cells.[142] We have summarized agents targeting ER stress and the UPR pathway in vivo and in vitro in CRC in Figure 12.

Cancer therapy using lysosomal targeting

There is profound interest in using demethylating agents, such as 5-aza-dC or 5-azacytidine, in the treatment of several tumors, including CRC and other malignancies harboring *KRAS* mutations. 5-aza-dC also serves as a chemosensitizer via interconnection between BNIP3 protein and hypoxia. BNIP3 expression is initially silenced via methylation but becomes activated in a KRAS-dependent manner in colon cancer cells. Reactivated BNIP3 contributes to 5-FU resistance.[284] Furthermore, mutants of KRAS act via an inflammatory pathway, involving the kinase IKK, which activates NFKB. In contrast to mutant *KRAS*, the *BRAF* (*V600E*) mutant triggered the phosphorylation of a proteolytic fragment of CHUK/IKKα (CHUK p45) in CRC cells, which is necessary for transformation of NIH-3T3 cells and BRAF-dependent transcription. CHUK p45 is further phosphorylated by MAP3K7/TAK1, which is associated with the endosomal compartment. Bafilomycin A_1 or chloroquine-induced inhibition of the endosomal vacuolar-type H^+-translocating ATPase (V-ATPase), blocked CHUK p45 phosphorylation and induced apoptosis in *BRAF*-mutant

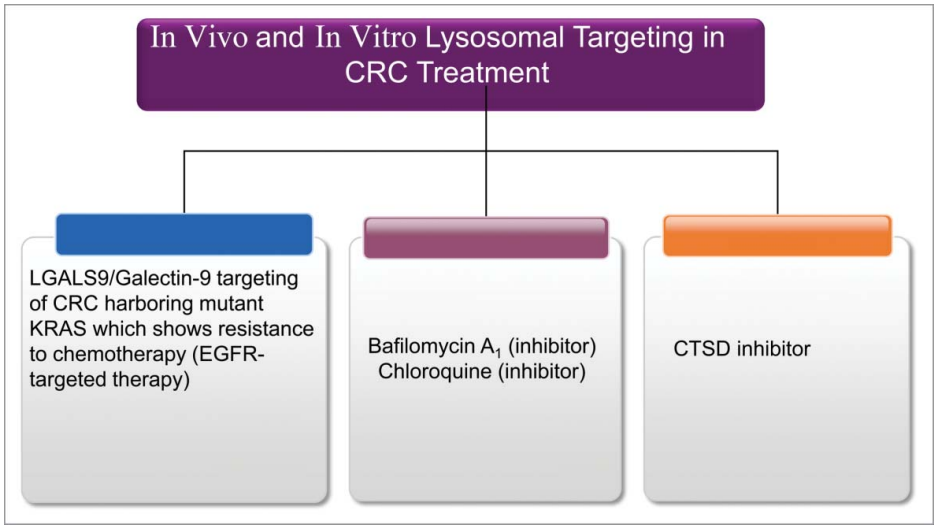

Figure 13. Lysosomal targeting strategies in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Cancer therapy using lysosomal targeting.*"

CRC cells independent of autophagy.[16] CRC cells harboring mutant *KRAS*, but not mutant *BRAF*, show resistance to chemotherapy and EGFR-targeted therapy. However, these CRC cells are sensitive to the treatment with recombinant LGALS9/Galectin-9 (rLGALS9), a lysosomal inhibitor. Treatment with rLGALS9 leads to elevated autophagic flux, excessive lysosomal swelling and death in *KRAS* mutant CRC cells.[285]

In addition to lysosomal membrane permeabilization, acetate, a short-chain fatty acid secreted by *Propionibacteria* in the human intestine, induces mitochondrial apoptotic death in CRC cells. Lysosomal membrane permeabilization results in the release of the anti-apoptotic protease CTSD (cathepsin D). Moreover, pepstatin A (CTSD inhibitor) can increase acetate-induced apoptosis. Hence, CTSD inhibitors could serve as novel strategy for the prevention and/or treatment of CRC by enhancing acetate-mediated cancer cell death.[286] We have summarized agents targeting the lysosomal pathway in vivo and in vitro in CRC in Figure 13.

Anticancer potential of MTOR inhibitors

Inhibitors of TORC1 (rapamycin and rapalogs) have been effective in IBD and in many CRC models. Second generation MTOR inhibitors are more effective, particularly when combined with proteasome inhibitors or histone deacetylase inhibitors (HDACi).[287] Studies also showed an inverse association between TYMP (thymidine phosphorylase), deoxyribose, and rapamycin. TYMP has an important role in the MTOR-RPS6KB/p70S6K pathway and activation of RPS6KB and subsequent inhibition of autophagy was observed in the human Colo320 cells and transfected variant Colo320 TYMP1/TP1$^{+/-}$ cells when treated with deoxyribose and rapamycin. Thus, deoxyribose protects from rapamycin-induced cytotoxicity in CRC cells.[130] Conversely, the MTOR inhibitor Torin-1 negatively affected the growth, motility, invasion, and survival of CSCs in vitro, and suppressed tumor growth in vivo. Thus, Torin-1 may serve as a potential lead compound for the treatment of metastatic CRC therapy.[288]

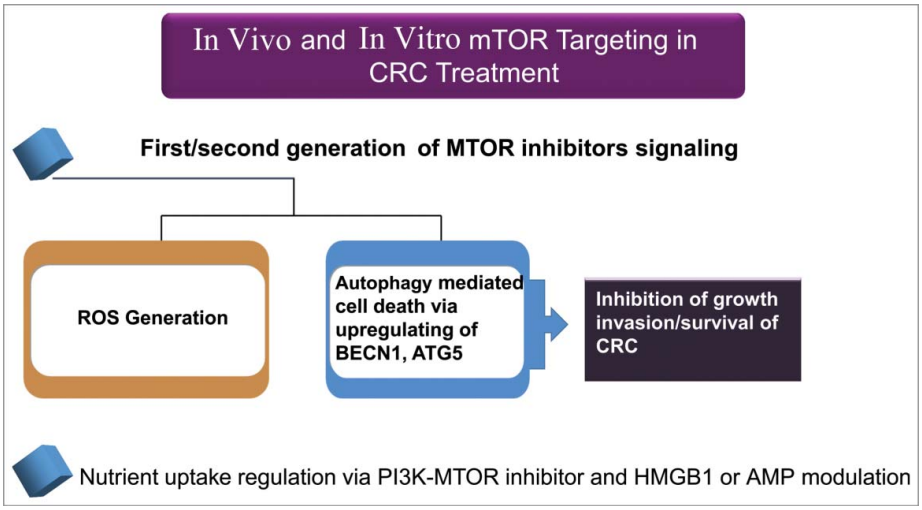

Figure 14. MTOR targeting strategies in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Anticancer potential of MTOR inhibitors.*"

The second-generation MTOR inhibitor AZD-2014 blocks MTORC1 and MTORC2 and induces autophagic death in CRC cells.[289] AZD-2014 can inhibit the growth of tumors in SCID mice bearing HT-29 xenografts.[289] Oral AZD-2014 administration inhibits MTORC1/2 activation and HT-29 cell growth, while inducing autophagy in vivo by upregulation of LC3B-II and BECN1.[289] In apoptosis-resistant CRC cells, autophagic cell death is known as a major contributor of growth inhibition.[289] Aspirin also induces autophagic cell death in CRC cells through inhibition of MTOR signaling.[226,289] Similar to AZD-2014 and aspirin, bufalin induced autophagic cell death in HT-29 and Caco-2 colon cells and this involves both ROS and the MAPK/JNK pathway. MAPK/JNK activation is required for the upregulation of ATG5 and BECN1, subsequent ROS generation, and autophagy-mediated cell death.[203] We have summarized agents targeting the MTOR pathway in CRC in vivo and in vitro in Figure 14.

Therapeutic targeting of epigenetic regulators

Recent findings show that the anticancer effects of HDACi compound LBH589 are augmented by the activity of the tumor suppressor DAPK (death associated protein kinase). In autophagy-deficient cells, DAPK is necessary for HDACi-induced apoptosis. In in vitro and in vivo CRC studies, LBH589 upregulated and activated DAPK, inhibited cell proliferation, and reduced cell survival.[290] LBH589 induced an accumulation of LC3-II, promoted acidic vesicular organelle formation, and enhanced the degradation of SQSTM1, thus, causing DAPK-dependent autophagy. Conversely, autophagy inhibition sensitized tumor cells to LBH589-induced apoptosis, which involves DAPK. Hence, upon autophagy inhibition, DAPK acts as a switch between autophagy and apoptosis.[290] We have summarized agents targeting the epigenetic pathway in CRC in vivo and in vitro in Figure 15.

Other pharmacological autophagy inducers

Other drugs contributing to autophagy induction include the chimeric anti-EGFR antibody, cetuximab, which exerts its anticancer effect, at least in part, via autophagy-induced cell death. The rapamycin derivative everolimus that has recently been proposed for the treatment of neuroendocrine and colorectal tumors may function as autophagy inducer. Blockade of VEGF can inhibit vascularization of tumor cells and subsequent tumor growth. Co-administration of anti-angiogenic therapy (i.e., bevazucimab or avastin) with irinotecan may produce a favorable treatment response and prolong the progression-free survival.[291] A combination of the VEGFR tyrosine kinase inhibitor tivozanib and everolimus resulted in stabilization of the disease in 50% of all patients with metastatic colon cancer.[292]

Due to a broad overlap of apoptosis and autophagy signaling networks, BH3-mimetics induce both apoptosis and autophagy. For instance, in CRC cells, ABT-737 along with the PTGS2 inhibitor celecoxib synergistically induce cell death by modulating autophagy and apoptosis.[292] Cellular senescence acts as a physiological barrier to tumor development and many studies have proposed its exploitation as a potential therapeutic strategy in cancer. In HCT116 cells, addition of melatonin might inhibit overgrowth through regulation of cell death and senescence in a time-dependent manner. Within 18 h of melatonin treatment, HCT116 cells upregulate both pro-apoptotic BAX and anti-apoptotic BCL2L1/BCL⁻XL, thus, activating both the autophagic and apoptotic machinery.[293] Pathways affecting cell death in senescent cells include: (*i*) methylation of HIST2H2/histone H2 lysine9 by the enzyme SUV39H1, (*ii*) telomerase-based therapies involve the use of gene promoters of the various telomerases for gene-therapy "suicide" strategies, and telomerase-derived peptides, proteins, or RNA as vaccines for immunotherapy, (*iii*) telomerase inhibitor, GRN163L, a lipidated 13-mer oligonucleotide complementary to the RNA template region of human telomerase RNA.[294] We have summarized this section in Figure 16.

TP53 status-dependent therapeutic strategies

Zebularine (ZEB), a cytidine deaminase inhibitor, inhibits CRC tumorigenesis via TP53-dependent ER stress. ZEB is very stable and preferentially targets cancer cells in human and mouse models. Microarray analysis revealed that ZEB causes the upregulation of ER stress-related genes as well as UPR genes and stabilizes TP53 through RPS7 (ribosomal protein S7-MDM2. ZEB also causes DNA damage and induces TP53-dependent apoptosis and autophagy. Colonospheres enriched in cancer stem cells derived from HCT116 'side populations' expressed higher levels of HSPA5 and SQSTM1. Treatment with ZEB induced TP53 stabilization, EIF2A phosphorylation, and blocked SQSTM1 expression. Hence, ZEB downregulates pro-survival markers of ER stress and the UPR and these result in autophagy induction in tumor tissues of CRC patients, mice with azoxymethane- or dextran sodium sulfate-induced CRC, and HCT116-derived colonospheres.[284,295] ZEB-mediated modulation of epigenetic signals converts ER stress-mediated prosurvival into a pro-apoptotic response.

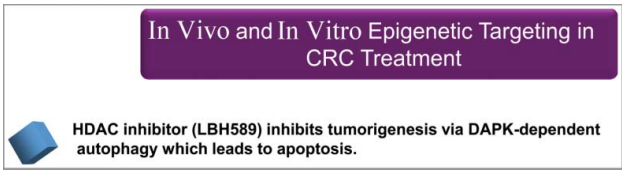

Figure 15. Therapeutic targeting of epigenetic regulators in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Therapeutic targeting of epigenetic regulators.*"

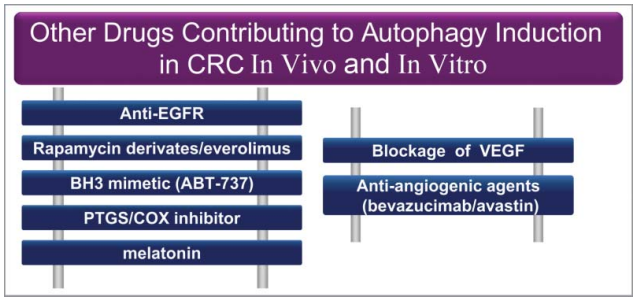

Figure 16. Miscellaneous drugs targeting autophagy in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Other pharmacological autophagy inducers.*"

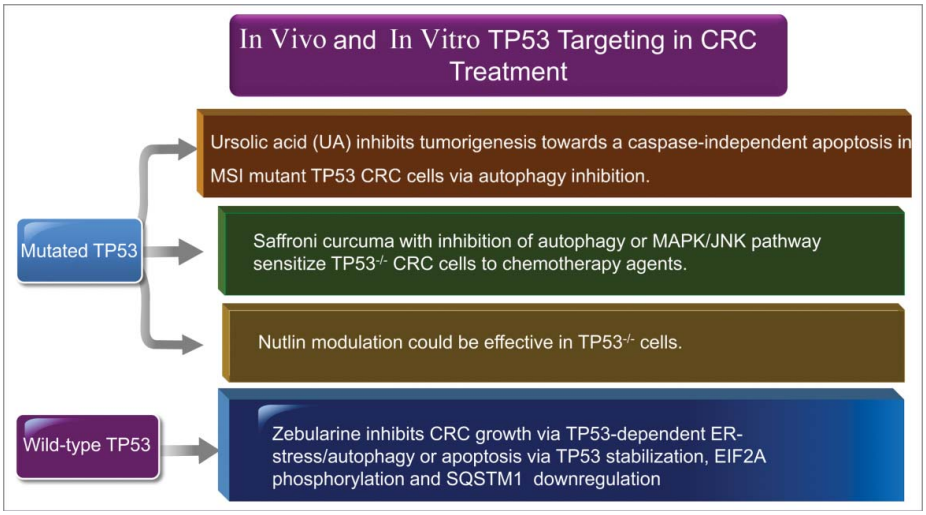

Figure 17. TP53 status of CRC and the respective targeting strategies in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*TP53 status-dependent therapeutic strategies.*"

TP53 has been linked to regulation of autophagy by affecting nutrient availability. The loss of TP53 drives LC3 overproduction and forces cells to maintain high autophagy rates. A study involving HCT116 cells showed that TP53 promotes selective downregulation of *LC3* mRNA and protein under conditions of prolonged nutrient deprivation. Initially, autophagy occurs to protect the cells. However, after complete nutrient depletion, this process becomes stalled, causing the accumulation of aberrant metabolic intermediates which eventually leads to apoptotic cell death.[296] TP53 dysfunction commonly occurs in human cancers and contributes to disease progression and chemotherapy resistance. Using HCT116 ($TP53^{-/-}$) and HT-29 ($TP53^{WT}$) colon cancer cells, it was shown that 5-FU treatment causes aberrant autophagosome accumulation and augmented autophagy in HCT116 cells. This counteracted 5-FU toxicity but 5-FU resistance can be overcome by specific inhibition of autophagy by 3-MA, chloroquine, or siRNA-targeted knockdown of ATG5 and BECN1. MAPK/JNK activation and BCL2 phosphorylation are key events in 5-FU-induced autophagy. MAPK/JNK inhibition by siRNA or SP600125 suppressed autophagy by blocking the phosphorylation of JUN; it also blocked phosphorylation of BCL2, leading to increased 5-FU-induced apoptosis. Thus, targeting key proteins within the autophagy pathway in CRC patients harboring TP53-mutation may be a promising strategy to improve 5-FU efficacy.[232]

Recent studies have demonstrated that a combination of nutlin (an MMD2 antagonist and inducer of E2F1 transcription) with conventional antitumor agents or irradiation may afford therapeutic benefit in cancers harboring mutant TP53. A large proportion of human cancers have defective or hyperubiquitinated TP53 and are partially resistant to nutlin due to MDM2 overexpression. However, even in cancer cells overexpressing MDM2, nutlin and CDK inhibitors (roscovitine and 5,6-dichloro-1-ribofuranosylbenzimidazole) still exert anti-proliferative activity by inhibition of TP53-MDM2 interaction.[297] This has been observed in a variety of cancers, including melanoma, colon carcinoma, breast adenocarcinoma, and hepatocellular-carcinoma.[297] Another approach will be the delivery of adenoviral vectors containing wild-type TP53 directly to tumors.[294]

CRC with mutated TP53 is resistant to 5-FU. Ursolic acid (UA), a triterpenoid in fruits and herbs, has anticarcinogenic potential through inhibitory effects on the PI3K pathway in HCT15, an MSI mutant TP53 CRC cell line. UA also induces caspase-independent apoptosis in HCT15 cells, enhances 5-FU toxicity related to MAPK/JNK activation, promotes the induction of BECN1 expression, and enhances TP53 phosphorylation. UA induces autophagy in a MAPK/JNK-dependent manner. Experiments in xenografted nude mice showed that UA simultaneously decreased tumor growth while increasing expression of autophagy markers SQSTM1 and MAPK/JNK.[298] Saffron is a natural compound and toxic toward a TP53-non-mutated CRC. In $TP53^{-/-}$ tumors, saffron induces a prosurvival autophagic response.[127] Interestingly, curcumin (diferuloylmethane), the yellow pigment in Indian saffron, can sensitize tumors to different chemotherapeutic agents including doxorubicin, 5-FU, paclitaxel, vincristine, melphalan, butyrate, cisplatin, celecoxib, vinorelbine, gemcitabine, oxaliplatin, etoposide, sulfinosine, thalidomide, and bortezomib.[299] Overall, 5-FU may induce prosurvival autophagy that partly reverses its apoptosis-inducing effect. This may explain why the inhibition of autophagy by 3-MA or *ATG7* siRNA significantly augments the induction of apoptosis by 5-FU.[300] We have summarized agents targeting TP53 in CRC in vivo and in vitro in Figure 17.

Proteasome inhibitor-based antitumor strategies

Epoxomicin, one of the earliest documented proteasome inhibitors, also activates the transcription of both BBC3/PUMA (a TP53 upregulated modulator of apoptosis) and BCL2L11/BIM in human colon cancer cells. Upregulation of BBC3 and BCL2L11 are typical features of ER stress-induced apoptosis. The combination of bortezomib and the death receptor ligand TNFS10, provoked a synergistic apoptotic response in prostate and colon cancer cell lines. In tumor-bearing mice, the mechanistic synergism between bortezomib and TNF involves CASP3 and CASP12 proteolytic activation, TP53 accumulation,

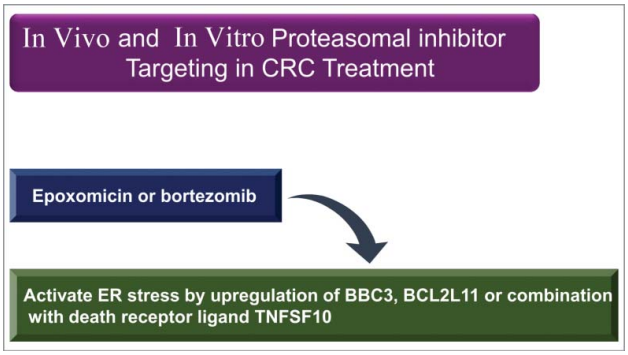

Figure 18. Proteasome activity modulators in in vitro and in vivo models for CRC therapy. All chemical compounds, drugs, and inhibitors have been introduced in the section "*Proteasome inhibitor-based antitumor strategies.*"

increased MAPK9/SAPK-MAPK/JNK phosphorylation, and upregulation of HSPA5, and PDI. These events collectively contribute to the suppression of tumor growth.[301] We have schematically depicted proteasome inhibitors affecting CRC in vivo and in vitro in Figure 18.

Targeting CRC via combinatorial therapy strategies focusing on autophagy and the UPR/ER stress pathway

The inhibition of autophagy is an attractive new therapeutic target in colon cancer. Targeting autophagy leads to increased cell death in HCT116 cancer cells.[227,273] Inhibition of autophagy in combination with modern anticancer therapies are being tested in colon cancer.[50] A list of autophagy inhibitors in combination with chemotherapeutic agents for the treatment of CRC is shown in Table 6. Autophagy inhibition is an effective way to promote the anticancer activity of agents such as sulforaphane (SUL) and fluorouracil (5-FU).[300,302] Trifluorothymidine (TFT) is a more potent inducer of cell death than 5-FU because it induces higher levels of cell death without autophagic survival responses in colon cancer. Thus, TFT is an attractive candidate for new treatment strategy in CRC.[303] Many studies support the combinatorial use of chloroquine as a novel therapeutic agent to improve the efficacy of 5-FU to inhibit autophagy-dependent resistance to chemotherapy. HT-29 cells activate autophagy as a defense mechanism against 5-FU. Hence, chloroquine-induced inhibition of autophagy may potentiate the anticancer effect of 5-FU.[300,304]

Autophagy inhibition by chloroquine, which prevents the fusion of autophagosomes and lysosomes sensitizes HT-29 CRC cells to chemotherapy and irradiation. Presurgical treatment with hydroxychloroquine improves the treatment response to 5-FU and irradiation in patients with advanced CRC.[305] Resistance to oxaliplatin has been shown in Caco-2 cells. Agents such as 3-MA, bafilomycin A_1, or RNAi knockdown of essential autophagy genes, such as *ATG5* or *BECN1*, enhanced cell death and ROS production in Caco-2 treated with oxaliplatin. Hence, increasing ROS production via inhibiting autophagy may be a therapeutic strategy for the sensitization of cells to oxaliplatin in the management of CRC.[300,306] Furthermore, bufalin enhances colon cancer sensitivity through ROS-mediated autophagy.[307] Common therapeutic agents may promote autophagy in cancer cells, while disruption of autophagy alone does not necessarily enhance cell death. Blocking ROS production by scavengers such as NAC or Tiron decreased autophagy in tumor cells. However, blocking ER stress by RNAi targeting *NUPR1/COM1/p8* (nuclear protein 1, transcriptional regulator) and DDIT3 decreased autophagy and ROS production. Hence, ER stress is upstream of autophagy and ROS generation. A combination therapy that causes a subsequent increase in ROS production is more efficient.[304]

Other treatments exploit the antineoplastic activation of apoptosis and autophagy using iron core-gold shell nanoparticles,[308] and anti-VEGF therapy.[291,309,310] When used in combination with drugs like cisplatin, doxorubicin, docetaxel, or 5-FU, *Solanum nigrum* leaves, a common component in traditional Chinese medicine for the treatment of cancer; treatment efficacy in colorectal DLD-1 and HT-29 cells improves by inducing autophagy and enhancing cytotoxicity. Since DLD-1 and HT-29 cell lines have TP53 mutations and are resistant to the TP53-mediated apoptosis, cell death might be induced in a CASP3-independent manner with the activation of autophagy. The inclusion of *Solanum nigrum* leaves in chemotherapeutic therapies has been suggested to improve the efficacy of CRC treatment.[311] Hence, rather than autophagy inhibition, activation of the autophagy pathway that leads to cell death is able to improve CRC treatment. In HCT116 colon cells, combined use of oxaliplatin and bortezomib resulted in increased caspase activation and subsequent induction of apoptosis. This treatment modulated the synergistic effect through the mitochondria-dependent apoptotic pathway by promoting the MAPK/JNK-BCL2L1-BAX pathway. BCL2L1 affects autophagy through alteration of its interaction with BECN1. BECN1 dissociates from BCL2L1 and initiates autophagy during combined oxaliplatin- bortezomib treatment, which was shown to significantly inhibit tumor growth in CRC xenografts.[312] A better understanding of the crosstalk between apoptosis and autophagy may lead to new and improved treatment options for CRC.[312] Furthermore, tumor recurrence was significantly

Table 6. Autophagy inhibition during cancer chemotherapy.

Cancer type	Primary treatment	Target	Method(s) of autophagy inhibition
Colon	Vorinostat	Histone deacetylases	Chloroquine, *RNAi (ATG7)*
	Radiation	DNA damage	*RNAi (ATG3, ATG4B, ATG5)*
Breast	Trastuzumab	ERBB2/HER2/NEU-antigen	3-MA, Baf*, RNAi (LC3)
	Camptothecin	TOP1	3-MA, Baf, *RNAi (BECN1, ATG7)*
Multiple myeloma	8-Aminoadenosine	DNA synthesis	Chloroquine
Prostate	ADI-PEG20	Arginine in blood	Chloroquine, 3-MA, *RNAi (BECN1)*

Abbreviations: Baf, bafilomycin A1; 3-MA, 3-methyladenine; LC3, microtubule associated protein 1 light chain 3; RNAi, RNA interference (*ATG* target is in parentheses).
Adapted from Chen & Debnath, FEBS Lett, 2010.50

delayed with chloroquine cotreatment, and chloroquine enhanced TP53-mediated apoptosis via inhibition of autophagy. Chloroquine and its derivatives have been used in clinical trials to evaluate its use as a sensitizing agent for tumor, which would otherwise be unresponsive to standard chemotherapy.[50]

The MTOR inhibitor temsirolimus and chloroquine, with an autophagy-inhibitor function, exhibit a potent cooperative antitumor effect against CRC cells. Temsirolimus was effective in inhibiting tumor growth in CaR-1 and HT-29 cells, possibly through the induction of G_1 cell cycle arrest and a reduction in HIF1A and VEGF levels. Chloroquine significantly potentiated this antitumor activity. The combined therapy with temsirolimus and chloroquine enhanced the level of apoptosis and increased the BAX:BCL2 ratio.[313] Temsirolimus and chloroquine are already in clinical use as anticancer and antimalarial drugs, respectively, and represent a new option in the treatment of CRC.

Photodynamic therapy (PDT) combined with bortezomib could be a potential therapeutic strategy in CRC. Bortezomib and other proteasome inhibitors effectively sensitize cells to other therapeutics and enhance their cytotoxicity. PDT can lead to the accumulation of carbonylated proteins, normally degraded by proteasomes in the ER. This leads to ER stress due to oxidative damage of cellular macromolecules, resulting in cytotoxicity toward tumor cells.[314] It has been recently reported that Protoporphyrin IX-mediated PDT induced autophagy in colorectal CSC. The inhibition of PDT-induced autophagy by genetic and pharmacological means induced apoptosis in colorectal CSC, decreased their clonogenic potential and tumorigenicity in vitro and in vivo, respectively.[315] These findings suggest that targeting autophagy increases the PDT sensitivity of CSC, and thus can aid in designing new therapeutic approaches for targeting this population of cancerous cells that show high resistance to current therapies.

UPR induction can cause tumor cell sensitization to cisplatin-induced death. The mechanism of action of cisplatin is thought to involve DNA binding and interference with DNA-repair processes. In addition, a correlation between the UPR and sensitization to other DNA-crosslinking agents, such as carboplatin, melphalan, and BCNU, has been observed.[269] It seems that manipulation of other signaling pathways rather than autophagy such as MTOR or using proteasome inhibitors, can increase cytotoxicity in tumor cells through inducing apoptosis or ER stress.

Conclusions and future direction

When searching for new CRC therapeutic strategies aimed at manipulating autophagy, particular attention should be paid to the specific type, stage, and metabolic characteristics of CRC. During the course of CRC, autophagy could either promote tumor survival or cause cancer cell death, depending on the tumor type, CRC stage and the metabolic context. In human CRC cells, autophagy is activated in response to high-energy demands in the initial stage of cell transformation or as an adaptive tumor cell response at later stages. Combinatorial therapeutic approaches have great potential in the treatment of colorectal tumors. Hence a better understanding of the molecular mechanisms of crosstalk between apoptosis and autophagy will be the key in identifying novel applications of combinatorial treatment to CRC. Beside important diet modifications, chemopreventive measures, such as, for example, administration of low-dose aspirin, especially in combination with metformin, and/or intake of curcumin and statins lowers cancer incidence.[230,316] It is unlikely that any type of cancer, including CRC could easily be defeated by applying a singular approach, therefore combined effort, using the plethora of available interventions, is the most likely path to successful CRC-prevention and treatment. Novel experimental therapies that utilize natural and modified biologics inspired by derivates from the animal kingdom, and from plants and viruses, are a rich source of potential anticancer therapeutics.[317-319]

Abbreviations

3-AP-Me	N^4,N^4-dimethyl-triapine
5-Aza-Cd	5-aza-2′-deoxycytidine
3-MA	3-methyladenine
5-FU	5-fluorouracil
6TG	6-thioguanine
AGER/RAGE	advanced glycosylation end product specific receptor
AICAR	5-aminoimidazole-4-carboxyamide ribonucleoside
AKR1B1	aldo-keto reductase family 1 member B1
AMBRA1	autophagy and Beclin 1 regulator 1
AMPK	5′-adenosine monophosphate-activated protein kinase
AP-1	AP-1 transcription factor
AKR	aldo-keto reductase
ATF6	activating transcription factor 6
BBC3/PUMA	BCL2 binding component 3
BCL2, BCL2	apoptosis regulator
BCL2L1	BCL2 like 1
BECN1	Beclin 1
BFA	brefeldin A
BNIP3	BCL2 interacting protein 3
CQ	chloroquine
CRC	colorectal cancer
CSC	cancer stem cell
DC	dendritic cell
DDIT3/ CHOP	DNA damage inducible transcript 3
DHA	docosahexaenoic acid
DPE	2–3,4-dihydroxyphenylethanol
EIF2AK3/PERK	eukaryotic translation initiation factor 2 α kinase 3
EMT	epithelial-to-mesenchymal transition
ERAD	ER-associated degradation
ERN1/IRE1a	endoplasmic reticulum to nucleus signaling 1
FASN	fatty acid synthase
GDF15/MIC1	growth/differentiation factor 15
HDACi	histone deacetylase inhibitor

HMGB1	high mobility group box 1
HPGD/15PGDH	hydroxyprostaglandin dehydrogenase 15-(NAD)
MLH1	mutL homolog 1
HPD	high-protein diet
HSP	heat shock protein
HSPA5	heat shock protein family A (Hsp70) member 5
IBD	inflammatory bowel disease
IDO1	indoleamine 2,3-dioxygenase 1
MAP1LC3/LC3	microtubule-associated protein 1 light chain 3
MetS	metabolic syndrome
MMR	mismatch repair protein
MSI	microsatellite instability
MTOR	mechanistic target of rapamycin
NFKB/NF□B	nuclear factor kappa B
NOS2/iNOS	nitric oxide synthase 2
OS	overall survival
OR	odds ratios
PCD	programmed cell death
PCDH17	protocadherin 17
PDI	protein disulfide isomerase
PDT	photodynamic therapy
PE	*phosphatidylethanolamine*
PG	prostaglandin
PGE2	prostaglandin E2
PLA2G10	phospholipase A2 group X
PLAUR/uPAR	plasminogen activator, urokinase receptor
PPP1R15A/GADD34	protein phosphatase 1 regulatory subunit 15A
PTGER3	prostaglandin E receptor 3
PTGER4/EP4	prostaglandin E receptor 4
PTGFR	prostaglandin F receptor
PTGS2/COX2	prostaglandin-endoperoxide synthase 2
RIP	ribosome-inactivating protein
ROS	reactive oxygen species
SAT	subcutaneous adipose tissue
SEL1L	SEL1L ERAD E3 ligase adaptor subunit
SH3GLB1/BIF-1	SH3 domain containing GRB2 like, endophilin B1
SIRT1	sirtuin 1
SNP	single nucleotide polymorphism
STAT3	signal transducer and activator of transcription 3
STK11/LKB1	serine/threonine kinase 11
SUL	sulforaphane
TAA	tumor-associated antigen
TFA	tolfenamic acid
TNF/TNFα	tumor necrosis factor
TNFSF10/TRAIL	tumor necrosis factor superfamily member 10
TP53	tumor protein p53
T_{reg}	regulatory T cells
UPR	unfolded protein response
UVRAG	UV radiation resistance associated
VAT	visceral adipose tissue
VEGF	vascular endothelial growth factor
VMP1	vacuole membrane protein 1
XBP1	X-box binding protein 1.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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