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Emerging roles for HMGA2 in colorectal cancer

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ABSTRACT

HMGA2 (High Mobility Group AT-hook 2) has been reported to promote colorectal cancer (CRC) development by regulating the transcription of target genes. It participates in nearly all aspects of cellular processes, including cell transformation, proliferation, apoptosis, senescence, metastasis, epithelial-to-mesenchymal transition (EMT), DNA repair and stem cell self-renewal. In the past decades, a group of downstream targets and binding partners have been identified in a wide range of cancers. Our findings of HMGA2 as a key factor in the MDM2/p53, IL11/STAT3 and Wnt/β-catenin signaling pathways prompt us to summarize current advances in the functional and molecular basis of HMGA2 in CRC. In this review, we address the roles of HMGA2 in the oncogenic networks of CRC based on recent advances. We review its aberrant expression, explore underlying mechanisms, discuss its pro-tumorigenic effects, and highlight promising small-molecule inhibitors based on targeting HMGA2 here. However, the understanding of HMGA2 in CRC progression is still elusive, thus we also discuss the future perspectives in this review. Collectively, this review provides novel insights into the oncogenic properties of HMGA2, which has potential implications in the diagnosis and treatment of CRC.

Contents

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Introduction

High mobility group AT-hook 2 (HMGA2), is a member of the HMGA family that is distinguished by their rapid electrophoretic mobility in polyacrylamide gels. The HMGA family is composed of four members, HMGA1a, HMGA1b, HMGA1c and HMGA2. The human *HMGA2* gene is located at chromosome 12q13-15 and is encoded by 5 exons with an open reading frame of 330 bp [1,2]. The full-length human HMGA2 protein consists of 109 amino acid residues with an approximate molecular mass of 20 kDa. It is characterized by three highly conserved N-terminal motifs encoded by the first three exons, known as AT-hooks DNA-binding domains; also the linker encoded by the exon 4 and an acidic C-terminal tail encoded by the exon 5 [1,2]. Under normal physiologic conditions, HMGA2 content is low or absent in adult normal cells and tissues, whereas it expresses at high levels during embryogenesis. In disease states, such as cancer, HMGA2 expression has been found to be markedly induced. HMGA2 are characteristically present at high levels in a variety of human cancers, suggesting that HMGA2 is essential for tumorigenesis, including colorectal, ovarian, breast, lung, and pancreatic cancer [1,2]. Not surprisingly, therefore, ectopic expression of HMGA2 may lead to various diseases, including benign and malignant tumors [3,4]. Importantly, HMGA2 overexpression confers worse prognosis to patients of colorectal [5], gastric [6], ovarian [3], breast [7], oral cavity [8], pancreatic [9] and lung cancer [10].

Although HMGA2, as well as HMGA1, have no intrinsic transcriptional activity, they have been recognized as architectural transcription factors that induce “architectural” changes in the promoter regions of genes. Thus, a large number of target genes could be modulated by HMGA1 and HMGA2. HMGA1 and HMGA2 participate in the assembly of nuclear macromolecular complexes through protein-DNA and protein-protein interactions. They induce conformational changes by directly binding to AT-rich stretches of DNA, and thus negatively or positively regulate the transcriptional activity of target genes. In addition, they promote cooperative binding of additional transcription factors to their targeting regions, and then regulate gene expressions either in activation or in repression [1,2,11].

Growing evidences suggest that HMGA2 participates in numerous processes of cancer development and progression, such as proliferation, differentiation, transformation, apoptosis, epithelial-to-mesenchymal transition (EMT), metastasis, and angiogenesis. Most studies point to an oncogenic role for HMGA2. In cancer and embryonic stem cells, HMGA2 bound to and stabilized replication forks (RFs), thereby promoting cell proliferation [12]. Xie et al. illustrated that HMGA2 was of great importance to cadmium (Cd)-involved reactive oxygen species (ROS) production and proliferation in MRC-5 cells. Cd-induced overexpression of HMGA2 facilitated cell cycle progression mediated by upregulation of cyclin D1, cyclin B1, and cyclin E, ultimately stimulating cell growth [13].

HMGA2 is also a crucial regulator in stem cell maintenance and embryonic development. The study by Nishino and colleagues indicated that Hmga2 enhanced the self-renewal potential of neural stem cells by targeting $p16^{Ink4a}$ and $p19^{Arf}$ [14]. Li et al. demonstrated that HMGA2 was present at high-levels and interacted with nucleosomes in human embryonic stem cells [15]. In addition, proinflammatory macrophages (M1) were found to be crucial in formation and maintenance of cancer stem cells (CSCs), where HMGA2 could induce M1-mediated CSC phenotype in breast cancer [16]. Interestingly, as another HMGA family member, HMGA1 was reported to play essential roles in ISC (intestinal stem cell) maintenance and function. It induced self-renewal of ISCs and expansion of the ISC compartment via Wnt/β-catenin signaling in CRC [17,18]. In addition, they also found that HMGA1 facilitated the Paneth cell niche expansion by directly promoting the transcription of SOX9 in CRC [17,18]. In their study of the colorectal cancer stem cells (CSCs), Wei et al. also found that HMGA1 enhanced CSC self-renewal and expansion [19]. Given that ISCs and CSCs are critical for the maintenance of physiological homoeostasis and CRC development and progression, we speculated that HMGA2 might also be a key regulator in enhancing colorectal cancer cell stemness, thus contributing to colorectal carcinogenesis. HMGA1 and HMGA2 might serve as potential targets for treatment by suppressing chemoresistance and tumor recurrence in CRC.

Interestingly, Chaves-Pérez et al. found that URI (unconventional prefoldin RPB5 interactor) in slow-cycling label-retaining (LR) cells within the crypts promoted regeneration of the injured tissue after irradiation through modulating WNT/β-catenin signaling, thus protecting against gastrointestinal syndrome (GIS), whereas reducing URI expression increased sensitivity to radiation [20]. Several lines of evidence illustrated that HMGA2 regulated self-renewal in various tissues, and therefore could be important for intestinal regeneration and radiotherapy sensitization. We speculated that HMGA2 might promote intestinal regeneration and enhanced radiotherapy sensitivity via activating WNT/β-catenin signaling in CRC. Compared with monotherapy, knocking down HMGA2 expression in conjunction with ionizing radiation might help to overcome radioresistance and limit the side effects of radiotherapy on CRC patients.

Growing evidence showed that HMGA2, as a driver of inflammation, might be critical for the development of colitis-induced CRC. HMGA2 was determined as a driver of inflammation in acute liver injury by promoting the expression of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β [21]. Frankenberger et al. reported Raf kinase inhibitory protein (RKIP) reduced TAM recruitment by modulating the expression of HMGA2 in triple-negative breast cancer [22]. Of note, aspirin and sulindac sulfide were identified as HMGA2 inhibitors, and gene set enrichment analysis (GSEA) demonstrated a significant positive association between HMGA2 level and the gene expression signature of inflammation in CRC [23]. All above-mentioned studies suggested the involvement of HMGA2 in inflammation. Future studies will be necessary to elucidate the roles of HMGA2 in mediating colitis-induced tumorigenesis in CRC.

In their study of the influence of the gut microbiota on human gene expression by Richards and colleagues, many transcription factors that were active and responsive to microbiome exposure were identified by footprinting analysis, including HMGA2 motifs [24]. The interplay between commensal microbiota and host immune system is crucial for maintaining the gut homeostasis. Once it is disturbed, the dysregulated immune responses contribute to the initiation and progression of colorectal cancer [25]. As mentioned above, enrichment of accessible chromatin regions and the levels of transcription factor binding were changed after the microbiome treatments, resulting in alterations in HMGA2 motifs [24]. They offered evidences of potential mechanisms for overexpression of HMGA2 downstream targets in CRC. It suggested that the synergistic combination of HMGA2 inhibitors together with manipulating the microbiome would exhibit a promising antitumor effect for CRC treatment. Taken together, these findings underlined the potential importance of HMGA2 in the development and progression of inflammation-associated and microbiota-linked CRC.

Interestingly, in chromium VI (Cr (VI))-induced autophagy, HMGA2 was acted as a transcription factor to directly initiate transcription of the autophagy-associated protein Atg10, thereby promoting the Atg12-Atg5 conjugation [26]. Furthermore, HMGA2 is also involved in DNA repair in cancer cells. It participated in not only base excision repair (BER), but also nonhomologous end joining repair (NHEJ) [27,28]. Interestingly, HMGA2 was reported to extensively protect stalled replication forks against collapse leading to genotoxic double strand breaks (DSBs), thus implying that HMGA2 was required for the maintenance of genome stability in human cancer and stem cells [29].

HMGA2 and colorectal cancer

HMGA2 expression in colorectal cancer (CRC)

CRC is the most common gastrointestinal malignancy with a high incidence and mortality [30]. Based on its histological characteristics, over 90% of CRC are adenocarcinomas. Histologically, rare types include mucinous adenocarcinoma, medullary carcinoma, micropapillary adenocarcinoma, and signet ring cell carcinoma [31,32]. It is a heterogeneous

disease that is tightly related to loss-of-function of tumor suppressor genes and gain-of-function of oncogenes. Gene mutations in *p53*, *APC*, *PTEN*, *K-RAS*, *B-RAF*, *STAT3* and mismatch repair genes, and alterations of cell signaling pathways in Wnt/β-catenin, MAPK, PI3K, TGF-β and EGF networks, contribute to the development of CRC [32–34]. With the widespread adoption of the screening strategies, such as endoscopy, fecal occult blood tests, and radiology tests, CRC has been largely prevented [32,35]. In addition, evidence is mounting that the mortality of CRC has significantly declined due to the use of combined therapy, including surgery, chemotherapy, radiotherapy, molecular targeted therapy and other treatments [32,36–39]. As such, it is crucial to understand the underlying mechanisms that facilitate the development and progression of CRC. Here, we provide an overview of the current knowledge on the emerging roles of HMGA2 in CRC carcinogenesis.

Several studies supported that HMGA2 expressions significantly increased in CRC. Wang et al. observed high levels of HMGA2 in CRC tissues and HMGA2 overexpression was significantly related to distant metastasis of CRC patients. They also found that increased HMGA2 protein expression was associated with decreased survival of patients with CRC, implying that HMGA2 was responsible for poor prognosis. Furthermore, a subgroup analysis revealed that high HMGA2 level significantly correlated to worse patient prognosis in patients at stages III and IV [5]. In our study, CRC tissues with strong HMGA2 immunoreactivity were more common in patients with lymph node metastasis and advanced clinical stage. Overall survival was significantly improved in CRC patients with low HMGA2 expression in the subgroups of distal, low-grade and tumor size <5 cm [40]. Similarly, the study from Rizzi and colleagues supported that high HMGA2 expression in tumor cells and low HMGA2 in stromal fibroblasts were associated with poor outcome in CRC [41]. Similar findings were observed in TCGA database. *HMGA2* mRNA expression was substantially higher in CRC than in adjacent normal tissues from analysis of the TCGA dataset, suggesting an oncogenic role for HMGA2 in CRC [42]. Similarly, the expression of *HMGA2* by real-time PCR was statistically associated with advanced Dukes C and D stages [43].

Cell-free HMGA2 mRNA in CRC

It is well-known that cell-free nucleic acids (cfNAs) have emerged as potential screening tools for the early diagnosis of cancer [44]. We found that CRC patients showed higher levels of circulating cell-free *HMGA2* mRNA as compared to healthy controls. In addition, our results demonstrated that increased expressions of circulating *HMGA2* cfRNAs were observed more often in CRC patients with right-sided tumor location, positive vascular invasion, positive nerve infiltration, negative microsatellite instability (MSI) status and elevated serum CA199 levels. Considering the above-mentioned studies, the use of *HMGA2* cfRNAs in serum could be exploited for diagnosis and screening in CRC [45].

HMGA2 and signaling pathways in CRC

Studies have shown that HMGA2 has effects in cancer development via regulating various signaling pathways, such as MDM2/p53, IL11/STAT3, and Wnt/β-catenin pathways (Fig. 1) [40,46–49].

HMGA2 and MDM2/p53 pathway in CRC

p53, a widely known tumor suppressor, is the most frequently mutated gene in human tumors [50,51]. *p53* mutation occurs in approximately 50% of CRC. Under the physiological conditions, p53 is kept at a low level, being degraded through ubiquitin-mediated proteolysis by its negative regulator, the E3 ubiquitin ligase MDM2 [52–54]. However, it can be activated by a variety of stresses or cellular damages, including DNA damage, oncogenic activation and hypoxia [55]. As a key transcription factor, activated p53 protein directly regulates the transcriptions of target genes and then controls diverse cellular processes, such as cell cycle arrest, senescence, apoptosis, autophagy, metabolism and DNA repair [56–58]. Wei et al. indicated that HMGA2 complementary to p53 was a useful and promising marker for the early diagnosis of high-grade papillary serous carcinoma, probably hinting the interaction between HMGA2 and p53 [59]. In our study, to investigate Hmga2 in vivo, we generated intestinal epithelial cell-specific knock-in (KI) mice expressing Hmga2 ($Hmga2^{KI/KI}$:PVillin-Cre T). We

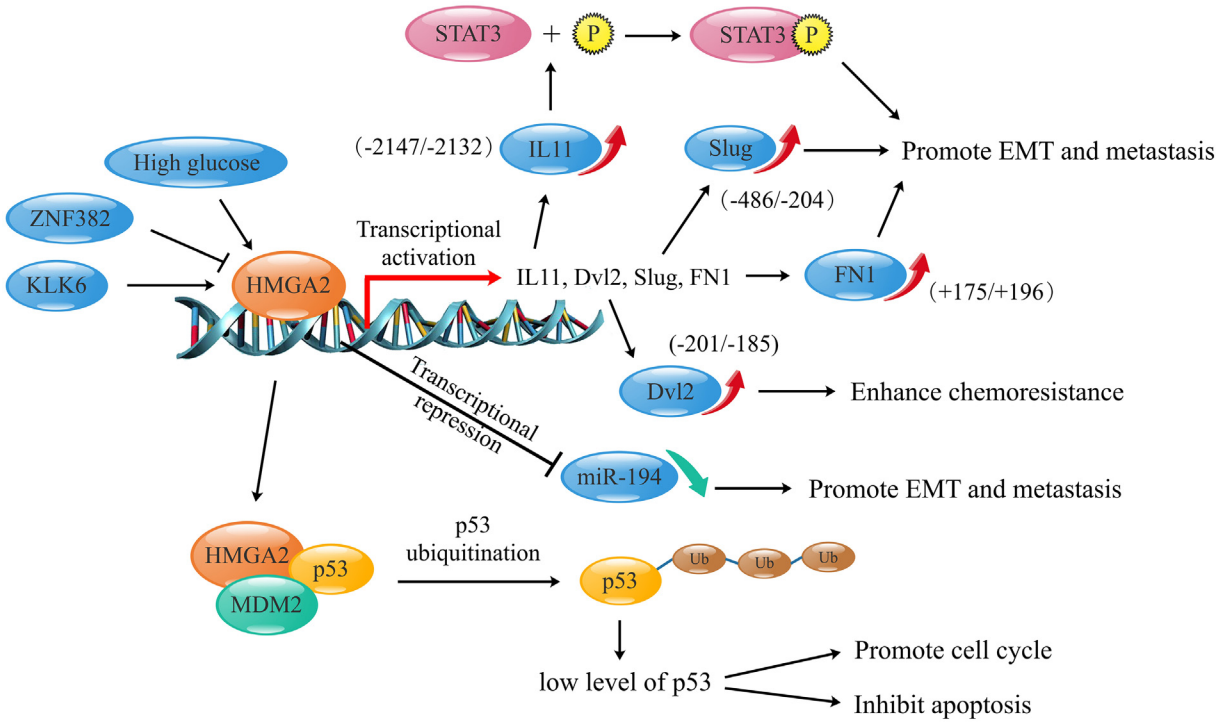

Fig. 1. Scheme of HMGA2-mediated signaling pathways and functions in CRC. HMGA2 directly activated the transcription of IL11, Slug, FN1 and Dvl2 in CRC. HMGA2 directly repressed the transcription of miR-194 in CRC. HMGA2 directly interacted with p53 and MDM2, thereby increasing MDM2-mediated p53 ubiquitination and subsequently decreasing its expression. Upstream factors accounted for dysregulation of HMGA2 in CRC, including KLK6, ZNF382 and high glucose.

found that Hmga2 KI promoted intestinal carcinogenesis in both the AOM-induced and AOM/DSS-induced mouse tumor models. Importantly, we found that HMGA2 had a strong binding to p53. A fragment containing the tetramerization domain of p53 protein (amino acids 294–393) could directly bind HMGA2, whereas the three AT-hook domains (amino acids 1–83) of HMGA2 mediated the interaction of HMGA2 and p53. In addition, we also found that HMGA2 physically interacted with MDM2. Deletion mapping studies demonstrated that the two (amino acids 1–73) or three AT-hook domains (amino acids 1–83) of HMGA2 and the central acidic and zinc finger domains of MDM2 (amino acids 111–360) were sufficient for their association. Our findings indicated that HMGA2 directly interacted with p53 and MDM2, thereby increasing MDM2-mediated p53 ubiquitination and subsequently decreasing p53 protein stability and expression [46].

HMGA2 and IL11/STAT3 pathway in CRC

The metastasis of cancer consists of sequential processes, including EMT [60–63]. EMT is a process in which epithelial cells lose their adherence junctions, lose epithelial morphology, and acquire mesenchymal features. It is an evolutionarily conserved program that is characterized by the downregulation of epithelial markers, including E-cadherin and ZO-1, and upregulation of mesenchymal markers, including N-cadherin, Vimentin, Fibronectin and MMPs. Several transcription factors (Snail, Slug, Twist, Zeb1 and Zeb2) and signaling pathways (TGF-β, Wnt/β-catenin and BMP) are implicated in EMT [60–65]. In our study, we found that HMGA2 promoted cell migration and invasion by directly activating the transcriptions of fibronectin1 (FN1) and interleukin (IL)-11 in CRC. As an extracellular matrix (ECM) protein, FN1 binds and interacts with cell surface integrins. It drives cell migration through PI3K/AKT, FAK, TGF-β and JNK signaling pathways [66–69]. IL11 belongs to the IL-6 family cytokines that share the common signaling receptor subunit, named as gp130. IL11 has multiple functions in the development and progression of cancer by activating JAK/STAT signaling pathway [70–73]. Our findings demonstrated that HMGA2 directly bound to the *FN1* promoter region of +175/+196 and *IL11* promoter region of −2147/−2132, and then transcriptionally induced their expressions, thus ultimately contributing to cancer metastasis in a pSTAT3-dependent pathway in CRC [40].

HMGA2 and other pathways in CRC

Of note, Tan et al. revealed that overexpression of HMGA2 triggered the proliferation of acute myeloid leukemia cells via activation of PI3K/AKT/mTOR signaling pathway [74]. In addition, HMGA2 was reported to be essential for the maintenance of stemness with co-activation of PI3K/AKT and RAS/MAPK pathway in prostate cancer [75]. Brandt et al. demonstrated that mTORC1 activation inhibited IBD-associated CRC, but promoted APC mutant-derived tumorigenesis in mouse models [76]. Faller et al. demonstrated the roles of mTORC1 in promoting Apc-driven tumorigenesis through increasing translational elongation rates following Wnt activation, thus rapamycin, the mTOR inhibitor, could be used as a target with potential therapeutic effects to block CRC [77]. In our study, we found that HMGA2 induced Wnt/β-catenin pathway by directly binding to the *Dvl2* promoter region of −201/−185 and promoted its expression at the transcriptional level in CRC [47]. Based on the above-mentioned findings, we speculated that HMGA2 might suppress growth of APC mutant-derived tumors, and combination of HMGA2 inhibitors with mTOR inhibitors (e.g., rapamycin) might show potential antitumor activity for patients with APC-deficient CRC.

The findings from Kao et al. indicated that Hsp90 directly interacted with HMGA2, and Hsp90 inhibitor downregulated HMGA2 expression by promoting its ubiquitination and indirectly suppressing ERK signaling pathway, suggesting that it could be used as a potential target for therapeutic intervention in CRC [48]. In addition, HMGA2 was also involved in ERK and TGF-β pathways. As mentioned above, EMT plays critical roles in embryonic development and carcinogenesis. ERK and TGF-β signaling induced HMGA2 expression. HMGA2 further directly bound to the *Slug* promoter region of −486/−204 and stimulated its transcription, ultimately promoting EMT and facilitating cancer progression in colon cancer [49].

In addition, different upstream factors accounted for dysregulation of HMGA2 in CRC. For instance, KLK6 enhanced cell invasion via promoting the expression of HMGA2 in CRC [78]. High glucose could facilitate EMT of CRC cells by increasing HMGA2 protein [79]. ZNF382 attenuated the expression of HMGA2 through heterochromatin silencing in CRC [80].

HMGA2 and non-coding RNAs in CRC

Non-coding RNAs (ncRNAs) that do not code for proteins play pivotal roles in regulating the expression of target genes at various levels under both physiological and pathological states. The ncRNAs are divided into different subgroups accordingly to their size and biologic function, including short interfering RNAs (siRNAs), microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) [81–84]. Several ncRNAs are involved in regulating HMGA2 in CRC (Fig. 2).

MiRNAs are a class of small non-coding RNAs (18–25 nucleotides in length) that mainly influence gene expression at the post-transcriptional level via base pairing to the 3′-untranslated region (3′-UTR) of the target mRNAs, thus degrading mRNA or repressing translation [85,86]. By acting as tumor suppressors or oncogenes (onco-miRs), depending on the target mRNAs they act on, the aberrant expression of miRNAs may contribute to the progression of cancers [87–89]. Moreover, numerous miRNAs are reported to be involved in HMGA2-mediated cancer development.

Several independent studies had identified HMGA2 as a downstream target of the let-7 miRNA family, which were widely known as tumor suppressor miRNAs [90–92]. Liu et al. indicated that the levels of let-7a-5p in serum and tumor tissue could be used as biomarkers for lymph node metastasis and clinical outcome in CRC [93]. In addition, miR-4500 and miR-204 were reported to target HMGA2 by binding to its 3'-UTR, then negatively regulating HMGA2 expression in CRC [94,95]. Chen et al. indicated that p53 transcriptionally increased the expression of miR-1249, which then post-transcriptionally repressed VEGFA and HMGA2 to suppress CRC migration and invasion [96]. Fan et al. showed that miR-543 targeted KRAS, MTA1 and HMGA2, and then attenuated pro-oncogenic signaling pathways, finally inhibiting CRC progression [97]. MiR-330 mediated antitumor effects by attenuating HMGA2 expression; these findings provided a

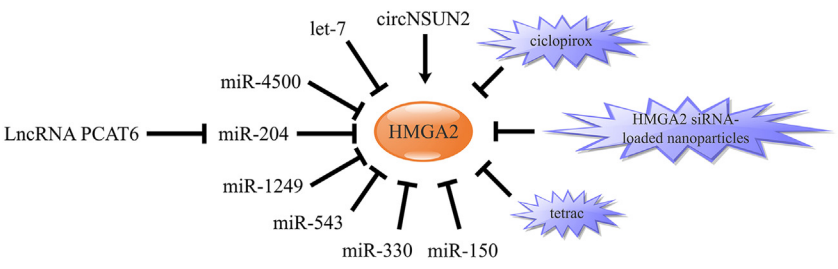

Fig. 2. Scheme of ncRNAs and inhibitors that regulate HMGA2 in CRC.

new insight for understanding the role of HMGA2 in CRC [42]. MicroRNA-204-3p and miR-150 were identified as upstream regulators of HMGA2, which might explain their roles of tumor suppression in colon cancer [98,99].

On the other hand, as an architectural factor, HMGA2 could directly bind to the upstream promoters of miRNAs to influence their expressions. The study by Chang and colleagues demonstrated that HMGA2 decreased miR-194 expression by directly binding to its promoter in CRC [100].

In addition, lncRNAs and circRNAs are also involved in HMGA2-mediated pathways in CRC. Acting as miRNAs "sponges", lncRNAs compete with mRNAs for miRNA binding, thus regulating the expression of mRNAs [101]. Compared with miRNAs, the regulatory mechanism of lncRNA is rather complex. It influences gene expression at multiple levels [101,102]. LncRNA PCAT6 reduced the sensitivity of CRC cells to 5-fluorouracil-based chemotherapy by hindering miR-204 and inducing HMGA2 expression [103].

CircRNAs are a group of endogenous non-coding RNAs, which have a covalently closed loop structure without 5′ or 3′ terminals generated by a back-splicing process. They reported to be associated with various processes, including cancer pathogenesis [104,105]. CircNSUN2 interacted with IGF2BP2 and *HMGA2* mRNA to form circNSUN2/IGF2BP2/*HMGA2* RNA-protein complex, which consequently increased the stability of *HMGA2* mRNA and promoted liver metastasis in CRC [105].

HMGA2 in radiotherapy and chemoresistance of CRC

There have been extraordinary progresses for the treatment of CRC in the past decades. Application of multiple approaches, such as surgery, chemotherapy, radiotherapy, neoadjuvant therapy, targeted therapy and immunotherapy, lead to the improvement of the therapeutic efficacy and patient survival [36–39].

It had been shown that overexpression of HMGA2 prolonged the clearance of γ-irradiation-induced γ-H2AX and increased radiotherapy efficacy in CRC, suggesting that HMGA2 could be used as a potential indicator for predicting radiotherapy response in CRC patients [5]. Consistently, HMGA2 induced genomic instability by impairing NHEJ and promoted the accumulation of γ-H2AX, indicating that HMGA2 sensitized cancer cells to radiotherapy. Both suggested the probable mechanism for the HMGA2-augmented sensitivity to radiotherapy in cancer patients [28].

Until recently, 5-Fluorouracil (5-FU) still serves as the first-line chemotherapeutic agent in CRC management. It is a pyrimidine analogue by inhibiting thymidylate synthase [106,107]. Emerging evidences implicated the roles of HMGA2 in chemoresistance. HMGA2 promoted the chemoresistance of CRC cells to 5-FU. In addition, we also found that HMGA2 overexpression increased the 5-FU chemoresistance via modulation of Wnt/β-catenin pathway in CRC [47]. It was reported that high miR-204 expression induced cell sensitivity to 5-FU-based treatment through negatively regulating HMGA2 in CRC [95]. Together, these data indicated crucial roles of HMGA2 in regulating CRC chemoresistance.

HMGA2 inhibitors in CRC

Considering the vital roles of HMGA2 in carcinogenesis, silencing of HMGA2 expression can be used as potential intervention independently or in combination with other therapeutic approaches in CRC. Discovering biomolecules that inhibit HMGA2 expression has given us a new perspective on CRC management. Several inhibitors are reported to participate in silencing HMGA2 in CRC (Fig. 2). In their study of the pharmacologic inhibition of HMGA2 in CRC, Huang et al. found that the antifungal drug ciclopirox (CPX) directly interacted with HMGA2 and attenuated its expression, which subsequently promoted cell cycle arrest and apoptosis, ultimately suppressing CRC growth using in vitro cell models and in vivo xenograft mice models. This study provided extremely strong evidence to suggest that CPX could serve as a potential therapeutic candidate by directly targeting HMGA2 in CRC [108]. The study by Leung and colleagues identified S100A4 as a potential target for CRC with HMGA2 overexpression by the Connectivity Map (CMap) analysis. They also reported that the antihelminthic agent niclosamide could be used as a potential therapeutic drug by targeting S100A4 in HMGA2-overexpressing CRC cells in vitro and in xenograft mice in vivo [109]. Nana et al. found that tetrac inhibited β-catenin and HMGA2, and then induced resveratrol-mediated anti-proliferation in CRC cell lines, primary colon cancer cells and in xenograft mice model [110]. Intriguingly, HMGA2 was also involved in the process of oxidative stress responses in colon cancer. Chen et al. stated that HMGA2 facilitated antioxidant response activation. And dicoumarol suppressed migration in HMGA2-overexpressing colon cancer cells in vitro [111].

Importantly, RNA interference (RNAi) has become as a powerful tool to silence gene expression. Moreover, because of the advantages of siRNA therapy, such as high specificity, low cytotoxicity, and high efficacy, it opens a potential perspective for the development of novel therapeutic strategy by inhibiting specific oncogenes in CRC treatment [112–114]. HMGA2 siRNA-loaded nanoliposomes were developed to target HMGA2, which was shown to exhibit anti-tumorous activities significantly by in vitro cell models [115]. Furthermore, the co-delivery system of encapsulated HMGA2 siRNA and doxorubicin (DOX) in nanoparticles significantly enhanced anti-cancer effects of DOX even at low concentrations, and sensitized CRC cells to DOX in HT-29 cell lines in vitro. It served as a potential therapeutic approach in CRC management [91].

Conclusion

As described above, numerous studies have defined HMGA2 as an oncoprotein in CRC. HMGA2 is not only aberrantly overexpressed, but also correlates with metastasis and poor prognosis in CRC. Circulating cell-free *HMGA2* mRNA has been identified as a potential screening marker in discriminating between CRC patients and healthy controls. HMGA2 appears to be a key factor in the complex networks of MDM2/p53, IL11/STAT3 and Wnt/β-catenin signaling pathways in CRC (Fig. 1). It participates in various biological processes, such as cell proliferation, apoptosis, DNA repair and EMT, through its ability to regulate the transcription of target genes. In particular, it is well recognized that a variety of ncRNAs (miRNAs, lncRNAs and circRNAs) are involved in the modulation of HMGA2 in CRC (Fig. 2). Intriguingly, there is also evidence suggesting that HMGA2 overexpression sensitizes cells to radiotherapy and increases the chemoresistance to 5-FU in CRC. Interestingly, many agents and siRNAs serve as potential therapeutic approaches by targeting HMGA2 for the treatment of CRC (Fig. 2). In aggregate, an in-depth understanding of the intrinsic HMGA2-mediated machinery at the crossroads of the oncogenic network will help to control chemoresistance, conceive more effective therapy strategies, and develop novel small-molecule inhibitors of HMGA2 in CRC. Although there is emerging knowledge about HMGA2, detailed investigations into its mechanistic function are only beginning to emerge. Several questions remain to be elucidated: is there any interplay between HMGA2 and mutant p53 protein; how CRC cells adopt immunotolerant phenotype to escape surveillance, and whether HMGA2 exerts a role in this network; if so, how HMGA2 shapes and establishes immunosuppressive tumor environment in CRC; is there any relationship between HMGA2 expression and the efficacy and responsiveness of immune checkpoint blockade immunotherapy (e.g., PD-1/PD-L1 and CTLA-4); how to develop potential therapeutic targets (e.g., HMGA2 inhibitors) in personalized medicine for CRC patients and improve their benefit from treatment. In conclusion, these findings help to invent worthy diagnostic tools and develop innovative therapeutics for targeting HMGA2 in CRC.

CRediT authorship contribution statement

Xin Wang: Conceptualization, Writing-Original Draft, Writing-Review & Editing. Jian Wang: Conceptualization, Writing-Review & Editing, Supervision, Funding acquisition. Jingjing Wu: Conceptualization, Writing-Original Draft, Writing-Review & Editing, Supervision, Funding acquisition. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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