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Tumor Protein p63/microRNA Network in Epithelial Cancer Cells

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Abstract: Non-coding microRNAs are involved in multiple regulatory mechanisms underlying response of cancer cells to stress leading to apoptosis, cell cycle arrest and autophagy. Many molecular layers are implicated in such cellular response including epigenetic regulation of transcription, RNA processing, metabolism, signaling. The molecular interrelationship between tumor protein (TP)-p53 family members and specific microRNAs is a key functional network supporting tumor cell response to chemotherapy and potentially playing a decisive role in chemoresistance of human epithelial cancers. TP63 was shown to modulate the expression of numerous microRNAs involved in regulation of epithelial cell proliferation, differentiation, senescence, "stemness" and skin maintenance, epithelial/ mesenchymal transition, and tumorigenesis in several types of epithelial cancers (e.g. squamous cell carcinoma, ovarian carcinoma, prostate carcinoma, gastric cancer, bladder cancer, and breast tumors), as well as in chemoresistance of cancer cells. TP63/microRNA network was shown to be involved in cell cycle arrest, apoptosis, autophagy, metabolism and epigenetic transcriptional regulation, thereby providing the groundwork for novel chemotherapeutic venues.

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1. INTRODUCTION

Multiple molecular mechanisms are implicated in regulation of gene expression in human cells in various physiologic and pathophysiologic conditions [1]. They include but not limited to epigenetic alterations of DNA methylation, histone methylation or demethylation, histone acetylation or deacetylation, formation of multiple complexes between distinct chromatin components and transcription factors, RNA processing and RNA translation, post-translational modifications of nascent proteins [1, 2]. Finally, a modulation of gene expression by non-coding small interfering microRNAs is also implicated in epigenetic control of gene expression [2-5].

MicroRNAs (miRs) are small 18-24-nucleotide non-coding RNAs, which act through the RNA interference pathway; repress target gene expression largely by modulating translation and mRNA stability [6]. MicroRNAs are sequentially processed from longer precursor molecules that are encoded by the microRNA genes [6]. Primary microRNA transcript (pri-miRNA) is processed in the nucleus by the RNA-induced silencing complex (RISC) to generate mature microRNA [6]. The pri-miRNAs contain one or more ~ 7 base pair stem-loop structures. The ribonuclease DROSHA excises the stem-loop structure to form the precursor microRNA (or pre-miRNA) [7]. After export into the cytoplasm, the pre-miRNA is cleaved by the ribonuclease DICER to generate a short RNA duplex [6-8]. Mature microRNAs bind to RISC and to target mRNAs by base pairing [usually within the 3′ -untranslated region (UTR)] subsequently causing an inhibition of protein translation and/or degradation of the mRNA [9, 10]. Levels of the target proteins are consequently reduced, whereas mRNA levels may or may not be decreased [10]. One microRNA could potentially modulate several mRNAs and a few microRNAs might regulate the expression of the same mRNA target [9-11].

MicroRNA expression is deregulated in a wide range of human diseases including cancer [12-14]. Altered expression of microRNA genes has been found in a variety of tumor types and specific microRNAs have shown the oncogenic, tumor-suppressive or apoptotic properties [15, 16]. Certain microRNAs were shown to mediate epigenetic regulation of gene transcription and metabolism, the induction of cell death, cell cycle arrest, autophagy and senescence and contribute to epithelial stem cell maturation [16-19]. On one hand, microRNAs were recently shown to directly bind to gene promoter and gene terminus sequences, thereby modulating specific gene expression at the transcription level [20-23]. On the other hand, transcriptional networks that are often deregulated in cancer cells may lead to altered transcription of specific microRNA genes [24-26]. For example, miR-34 was shown to be regulated by the tumor protein (TP)-p53 transcription factor, "the guardian of the genome", which regulates the cellular response to stress and cancer-initiating events such as DNA damage [24, 26].

Non-coding regulatory microRNAs may also have therapeutic applications by which cancer-causing microRNAs could be modulated to restore the normal cellular function (27, 28). The modified cholesterol-conjugated antisense RNAs designated "antagomirs" were shown to effectively inhibit microRNA function *in vivo* in the adult mouse [29]. The competitive microRNA inhibitors ("microRNA

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sponges") were reported to de-repress microRNA targets as strongly as chemically modified antisense oligonucleotides [30].

Accumulating evidence supports that microRNAs, whose transcription regulated by TP53 family factors (TP53, TP63, and TP73), could contribute in multiple signaling pathways involved in cell cycle arrest, apoptosis, autophagy, metabolism and epigenetic transcriptional regulation, thereby potentially underlying the mechanisms leading to epithelial cell maintenance, and tumor development and chemoresistance [4, 19, 24, 26, 31-46]. As a member of the TP53 family, TP63 transcription factor is likely to play its decisive role in transcriptional and post-transcriptional regulation of microRNAs in epithelial cancers, epithelial differentiation and epithelial/mesenchymal transition (EMT) [31-38, 41, 42, 45, 46]. Complex gene expression machinery complicates to fully recognize the role for *TP63* in modulation of microRNA expression [47]. Due to distinct promoters and multiple splicing events, *TP63* encodes six protein isoforms; three of them contain the long transactivation (TA-) domain (TAp63 isoforms α, β and γ), whereas other three are lacking this TA domain (ΔNp63 isoforms α, β and γ), as reviewed in [47]. Emerging data strongly suggests that TAp63 isoforms function in similar manner as TP53 or TP73 by inducing cell death and tumor suppression, while ΔNp63 isoforms are frequently acting in an opposite manner by promoting the oncogenic function and modulating the cell death contributing to tumor cell chemoresistance [47].

Number of reports showed that upon ATM-dependent phosphorylation of ΔNp63α, this transcription factor is able to regulate expression of downstream gene targets implicated in control of cell death (e.g. cell cycle arrest, apoptosis, and autophagy). Moreover, the phosphorylated (p)-ΔNp63α was shown to induced or reduce the transcription and processing of microRNAs, which subsequently contributed to modulation of targets involved in cell death and survival [48-53]. This review is designed to give a first glimpse on potential roles of TP63-regulated microRNAs in a few key cellular processes that contribute to tumor cell proliferation, cell death, cell metabolism and epigenetic regulation of gene expression.

2. TP63 TRANSCRIPTIONALLY REGULATE VARIOUS microRNAs THAT MODULATE NUMEROUS TARGETS IN EPITHELIAL CANCER CELLS

TP53 family members were shown acting as candidate drivers of microRNA overexpression [43]. Expression of both TP73 and TP63 is significantly correlated with expression of microRNAs whose promoters contain TP53 family binding sites in head/neck and ovarian carcinomas [33, 43]. Validated data showed that TP53 family binding sites modulate promoter activity of the miR-200 family and miR-429, which are known regulators of cancer stem cells and epithelial/mesenchymal transitions, as well as promoters for miR-181a-5p, miR-374a-5p, miR-519a-3p miR-630 and miR-885-3p, which were reported to play a regulatory role in cell cycle arrest, apoptosis, and autophagy [32, 33, 36, 38, 41, 45, 46, 52]. Moreover, miR-200 family, miR-1246 and miR-155 were shown to be direct targets for TP53 and TP63, respectively, while miR-193a-5p is regulated negatively by TP63 and positively by TP73 at the transcriptional level [31, 33, 36, 39, 40]. ΔNp63α was shown to inhibit miR-138, -181a, -181b, and -130b expression by binding directly to TP63-responsive elements located in close proximity to the genomic loci of these microRNAs in primary keratinocytes [41]. TP63 was shown to maintain cell cycle progression by directly repressing miR-34a and miR-34c in primary keratinocytes and in embryonic skin [46]. TP63 directly binds to TP53-consensus sites in both miR-34a and miR-34c regulatory regions resulting in reduction of their transcription, which leads to a restored cell cycle progression and expression of cyclin D1 (CCND1) and cyclin-dependent kinase (CDK)-4 [46]. ΔNp63α was found to promote miR-205 transcription and to subsequently control EMT via modulation of ZEB1/2 levels in human bladder cancer cells [45]. Multiple TP63-regulated microRNAs (miR-17, miR-20b, miR-30a, miR-106a, miR-143 and miR-455-3p) were involved in epidermal differentiation [44].

Using the microRNA expression chip arrays, subsequently validated by quantitative PCR expression analysis several reports showed altered expression of miR-485-5p, miR-297, miR-185-5p miR-194-5p, miR-574a-3p, miR-720, miR-98-5p, miR-29c-3p, miR-101-3p, miR-22-3p, miR-34c-3p, miR-206, miR-429, miR-339-3p, miR-203a, miR-25-3p, miR-155-5p, miR-148a-3p, miR-125b, miR-181a-5p, miR-374a-5p, miR-519a-3p, miR-630, miR-885-3p and miR-1246 in human epithelial cancers including squamous cell carcinoma, ovarian carcinoma, prostate carcinoma, gastric cancer, bladder cancer, and breast tumors [31-46, 49-54]. Accumulating evidence shows that a number of above-listed microRNAs were found to modulate the expression of critical proteins involved in tumor cell response to DNA damage, tumorigenesis, tumor cell death, and tumor metastasis, such as EGFR, SIRT1, ZNF652, CARM1, TP63, SKP2, STMN1, MSI2, ROCK1, NOTCH1, ZEB1/2, BMI, CCND1, CDK4, ULK1, ATG2, ATG4, ATG5, ATG7, ATG9, ATG10, ATG12, ATG16, BECN1, RAB5A, and MAPK8/9 [31-46, 49-54].

Using the luciferase activity assays mediated by the target mRNA 3'-untranslated regions (UTR), we and others further found that several direct targets of tested microRNAs, including ataxia telangiectasia mutated kinase (ATM), autophagy-related 5 and 10 (ATG5 and ATG10), caspase/apoptosis-related cysteine peptidases 2 and 3 (CASP2 and 3); cyclin-dependent kinase 1 and 2 (CDK1 and 2); cyclin-dependent kinase inhibitor 1C and 2B (CDKN1C and 2B), and nuclear factor Y beta (NFYB), as reviewed in [51, 53, and Table].

The selected microRNA mimics inhibited the luciferase activity fused to the specific mRNA 3'-UTR by ~32-56% compared to scrambled microRNA, while their protein targets were found downregulated subsequently affecting the tumor cell response to chemotherapeutic platinum agents [49-53]. In order to classify the effect of TP63/microRNA circuitry, we divided the microRNA-regulated products on the following categories: epigenetic regulation of transcription, cell metabolism, autophagy, cell cycle arrest and apoptosis.

3. TP63-DEPENDENT microRNAs AND EPIGENETIC REGULATION OF TRANSCRIPTION

While the binding of transcription factors and other chromatin accessory components to the corresponding promoter element is essential for transcriptional function, the final outcome (activation or repression) is very likely to be determined by numerous chromatin accessory/remodeling proteins [1, 3, 55-58]. Transcriptional activating mechanisms include: demethylation of promoter DNA sequences, acetylation or demethylation of histones altering histone interactions with other chromatin proteins and nucleosome properties subsequently affecting the chromatin remodeling. However, the transcription repression mechanisms include: methylation of promoter DNA sequences and methylation or deacetylation of histone molecules forming nucleosome structures around promoter sequences [55-61].

Previous studies shed a light on the role for TP63 (e.g. ΔNp63α) in many of these epigenetic regulatory layers. Recent reports showed that ΔNp63α represses anti-proliferative genes via accumulation of acetylated H2A.Z, while physical association of HDAC1 and HDAC2 with TP63 mediates transcriptional repression of BCL2 and PUMA and tumor maintenance in squamous cell carcinoma [62, 63]. Moreover, the ATM-dependent p-ΔNp63α is capable to regulate a plethora of various microRNAs that showed a potential to affect the expression levels of many components of epigenetic regulatory machinery (Table, Part **A**).

Using a set of bioinformatics tools, p-ΔNp63α- dependent microRNAs were predicted to modulate the protein targets (Table, part **A**) involved in DNA methylation (DNMT1, DNMT3A, DNMT3B, MBD1 and MECP2), histone acetylation (KAT2B, KAT3B and KAT6B), histone deacetylation (HDAC4, HDAC9, SIRT1, SIRT3 and SIRT5), histone demethylation (KDM2A, KDM3A and KDM4C), polycomb repressive complex (EZH2, SIN3A), transcription factors (ATF3, ATF5, ATF6, E2F1, E2F3, SREBF2, SP1, SP3, NFYA, NFYB and TP53), co-activators (CITED2 and CRTC2), co-repressors (BHLHE41 and ZBTB2) and RNA splicing (SRSF2), as reviewed in [52]. Intriguingly, many protein targets listed above are likely to be affected by several microRNAs, while certain microRNAs could potentially modulate several targets (Table, Category **A**). Since expression of specific microRNAs is upregulated or downregulated through the cisplatin-/p-ΔNp63α- dependent mechanism, the final outcome on specific epigenetic regulators is not easy to predict. For example, specific microRNAs (miR-185-5p or miR-297) that are upregulated in cisplatin-treated squamous cell carcinoma cells (SCC-11) appeared to decrease the protein levels for DNMT1 or DNMT3A, while downregulated microRNAs (148a-3p and 101-3p) could potentially lead to increase of these proteins [53, Ratovitski, in preparation]. Similarly, miR-92-3p could decrease the HDAC9, while miR-25-3p and 27a-3p would increase this protein level in SCC-11 cells exposed to cisplatin treatment [53, Ratovitski, in preparation].

The repression of gene transcription could occur directly by hypermethylation of CpG dinucleotides within the promoter DNA regions by DNA methyltransferases (DNMT1, 3A and 3B), or indirectly through interaction with methyl-CpG-binding proteins (e.g. MBD1 or MECP2) leading ultimately to inability of transcription factors to bind their recognition sites [1, 2, 64]. DNMT1 preserves the methylation DNA patterns throughout each cell division, while DNMT3A and 3B transfer a methyl group to unmethylated DNA sequences [64]. There are other enzymes involved in adding or removing methyl or acetyl groups to histones: histone methyltransferases (EZH1 and 2), histone demethylases (KDM1-KDM8), histone acetyltransferases (KAT2A-KAT8), and histone deacetylases (HDAC1-9, SIN3 complex), as reviewed in [65-67].

Although methylation of the promoter DNA leads to transcriptional repression, the methylated histones can either activate or repress gene transcription [65-67]. For example, the trimethylation of H3 lysine 4 or H3 lysine 36 leads to gene activation, whereas the trimethylation of H3 lysine 27, or di- and tri-methylation of H3 lysine 9, or trimethylation of H4 lysine 20 would lead to gene repression [65-67]. Similarly, histone demethylases would affect the gene transcription in an opposite fashion [65-67]. On the other hand, histone acetylation catalyzed by histone acetyltransferases is linked to transcriptional activation, while deacetylation of histones by HDACs is often leading to a transcriptional repression [62]. An increased DNA methylation can silence tumor suppressor and pro-apoptotic genes, whereas the demethylation of DNA can induce the oncogenic and anti-apoptotic genes, thereby such epigenetic mechanisms, which control transcription of genes involved in cell differentiation, proliferation, survival and apoptosis are often deregulated in cancer cells leading to malignant phenotypes [1, 2, 65-67].

Finally, the intricate network of epigenetic regulation of gene expression has been further enriched by the non-coding microRNAs, whose ability to modulate the level of target proteins via binding to their respective mRNA 3'-UTR sequences was complemented by the direct effect of microRNAs on the epigenetic machinery [20-23, 68-71].

The expression of microRNA, which is altered in almost all human cancers, is affected by the same epigenetic mechanisms as mRNA transcription [66]. The ability of microRNAs to regulate the components of the epigenetic machinery, targeting molecules involved in the DNA methylation, histone acetylation, and modulation of transcription factors is also started to emerge creating a controlled feedback mechanism [2, 4, 72-74]. For example, the introduction of miR-148a and miR-34b/c in cancer cells inhibited their motility, reduced tumor growth, and impaired metastasis formation in tumorgraft models, and led to a down-regulation of the microRNA oncogenic targets, such as c-MYB, c-MYC, E2F3, CDK6, HDAC, and TGIF2 [72-74]. miR-29 family was reported to directly target DNMT3A, -3B, and indirectly DNMT1 through regulation of the transactivator Sp1 [74, 75]. miR-148a was shown to directly target DNMT3B by binding a recognition site located in the coding region [76, 77]. miR-140, miR-148a, miR-152 and miR-301 were shown to modulate DNMT1, while miR-101a-3p was found to regulate the expression of EZH2, catalytic subunit of the polycomb repressive complex 2, which mediates epigenetic gene silencing by trimethylating histone H3 lysine 27, and miR-449a was found to modulate HDAC1 inducing cell cycle arrest, apoptosis and a senescent phenotype in many cancer cells [82]. Taken together, these data strongly

support the notion that alterations of microRNA landscape in cancers cells are very likely to affect the epigenetic regulation of genes involved in cell death and survival, and thereby could be useful biomarkers and targets for the future development of anti-cancer biotherapies.

4. TP63-DEPENDENT microRNAs AND CELL METABOLISM

Under many environmental stresses that induce DNA damage, including chemotherapy, tumor cells respond by changing their metabolism, which allows sustaining tumor growth under the fluctuations in energy availability. Mounting evidence shows the interplay between microRNAs and oncogenes/tumor suppressors, via key metabolic enzyme effecters, which could facilitate the Warburg Effect (anaerobic production of energy) in cancer cells [83-85]. Changing levels of glucose modulate miR-451 expression, thereby affecting cell proliferation but enhancing migration and survival [86]. miR-451 was shown to repress CAB39, the binding partner of LKB1 leading to a subsequent regulation of the LKB1/AMPK pathway [86]. miR-33a/b plays a crucial role in controlling cholesterol and lipid metabolism by targeting phosphoenol-pyruvate carboxykinase (PCK1), glucose-6-phosphatase (G6PC), carnitine palmitoyltransferase 1A (CPT1A), and AMP-activated protein kinase (AMPK α 1) via the sterol-regulatory element-binding transcription factors (SREBF) [87]. Additionally, miR-103 and miR-107 were reported to regulate insulin and glucose homeostasis through a modulation of pantothenate kinase, while miR-34a affects hepatic lipid homeostasis [88].

TP53 transcription factor that controls cell cycle arrest, cell death, autophagy, and glucose metabolism was shown to trigger a metabolic switch to the Warburg effect found in the most cancer cells [89]. Recent studies show that TP53-inducible miR-34a modulates the expression of glucose metabolic enzymes (e.g. (hexokinase 1 and 2, glucose-6-phosphate isomerase, and pyruvate dehydrogenase kinase 1), as well as a nucleotide biosynthesis by repression of inosine 5'-monophosphate dehydrogenase, a rate-limiting enzyme for de novo purine biosynthesis, needed for a sustained tumor cell proliferation [90, 91]. Moreover, phosphatidylinositol 3-kinase that regulates the levels of phosphorylated phosphatidylinositol at the plasma membrane, and plays a key role in cancer cell metabolism is targeted by miR-123a, miR-136, miR-320, miR-422, and miR-506 [92]. Additionally, miR-152, miR-148a, miR-148b, miR-299-5p, miR-19a/b, miR-122a, miR-421, and miR-494 regulate the citrate synthase gene, which encodes a major enzyme in tricarboxylic acid (Krebs) cycle [85, 92]. miR-101a-3p was found to play a critical role in the regulation of cyclooxygenase-2 (COX-2) expression gastric cancer specimens and cell lines leading to a decreased cell proliferation and increased apoptosis *in vitro* and *in vivo* [93]. miR-185-5p and miR-342 were shown to inhibit SREBF-1 and 2 expression and downregulate their targets, fatty acid synthase 1 and 3-hydroxy-3-methylglutaryl CoA reductase in prostate cancer, as well as inhibited tumorigenicity, cell growth, migration and invasion in prostate cancer cell culture and xenograft models [94].

The cisplatin-/p-ΔNp63α- dependent microRNAs could potentially affect the critical metabolic pathways through a modulation of specific protein levels (e.g. ATOX1, ATP7A, ATP7B, ETNK, H6PD, CPS1, CPS2/CAD, FADS1, AKT1 and AKT2), as shown in Table (Category **B**). Future studies are underway to provide a proof of concept for this notion. Previous reports showed that TP63-dependent microRNAs (e.g. miR-885-3p) modulated the 3'-UTR activity driven by AKT1 [50], while p-ΔNp63α was found to transcriptionally regulate many metabolic enzymes by interacting with SREBF1 [95]. Interestingly, CPS1 expression is likely to be increased in SCC-11 cells upon cisplatin exposure since four microRNAs (miR-29c-3p, miR-203a, miR-18a-5p and miR-146b-3p) are downregulated under these experimental conditions [53]. Interestingly that a few proteins involved in intracellular copper binding, transport and regulation (ATOX1, ATP7A and ATP7B) are also shown to bind cisplatin, thereby are likely to play a role in platinum chemoresistance [96]. p-ΔNp63α-dependent microRNAs are likely to modulate the metabolic enzymes implicated in carbohydrate (H6PD), lipid (ETNK, FADS1), amino acid (CPS1) and pyrimidine (CPS2/CAD) metabolism (Table). Finally, miR-101a by modulating the activation of serine/threonine kinases, AKT1 and AKT2, was shown to suppress apoptosis by phosphorylation of components of the apoptotic machinery [97, 98] subsequently linking the tumor cell metabolism to the apoptotic response or lack thereof. These data support further studies, which are needed to establish a mechanistic link between TP63-dependent regulation of metabolic enzymes through transcription and microRNA modulation. Overall this microRNA network could potentially contribute to dramatic alterations of metabolism and biosynthesis of many metabolic compounds leading to energy imbalance and deregulated tumor cell proliferation, as reviewed in [95].

5. TP63-DEPENDENT microRNAs AND CELL CYCLE ARREST AND APOPTOSIS

As well known, cell cycle regulation occurs through modulation of activity of CDK by cyclins (positive regulation) leading to cell proliferation and CDK inhibitors (negative regulation) inducing a temporary cell cycle arrest in G1 phase, or a permanent cell cycle arrest, if induced by damaged DNA, often resulting in a cell death [99, 100]. MiR-449a, -b, and -c are potent inducers of cell death, cell cycle arrest, and/or cell differentiation, as well as miR-34 regulated by TP53, while also induced by the cell cycle regulatory transcription factor E2F1 [71]. These microRNAs were shown to downregulate histone acetyltransferases and activate TP53, while modulating CDK and their association partners provide an asymmetric feedback loop to balance E2F and p53 activities [101, 102]. A few reports showed that CDK inhibitors could also be targets for a microRNA regulation (e.g. miR-22, miR-296, miR-423 and miR-519a-3p for CDKN1A; miR-221 and miR-222 for CDKN1A, CDKN1B and CDKN1C), as shown elsewhere [101, 102]. The cell cycle-regulating microRNAs are incorporated into a large regulatory network to control the self-renewal of stem cells by inducing or inhibiting differentiation and function of cell cycle-regulating microRNAs in cancer [103].

Alternatively to cell cycle arrest, the caspase-dependent and -independent pathways could also lead to the cell death through apoptosis when cells face irreversible stress [104-106]. Members of the BCL2 family play crucial roles in

regulating intrinsic apoptotic pathway, while in the extrinsic apoptotic pathway CASP8 and CASP10 are activated upon stimuli [105, 106]. Both apoptotic pathways converge on the level of CASP3 activation, which in turn cleaves various intracellular substrates and cause the specific morphological changes [104-106]. During the caspase-dependent apoptosis, the caspase cascade pathways are being initiated, which include initiator caspases (e.g., CASP2, CASP8, CASP9, and CASP10), and effector (executioner) caspases (e.g., CASP3, CASP6, CASP7). The latter are being activated by the former and subsequently cleave other protein substrates within the cell, to trigger the apoptotic process [106].

MicroRNAs were shown to modulate the function of various pro- and anti- apoptotic proteins under cisplatin pressure [107, 108]. For example, miR-885-3p (or miR-708), Let7a-1 (or miR-24), and miR-155-5p were shown to decrease CASP3, XIAP, and APAF1 levels, respectively [50, 109-112]. Multiple microRNAs designated as 'apoptomirs' (e.g. miR-15a, miR-16, miR-125b, miR-153, miR-519a-3p, miR-205, miR-210, miR-214, miR-429, miR-503, miR-26a, miR-29b, miR-193a-3p and miR-133a) were reported to reduce the expression of BCL2 family members through their respective 3-'UTR region binding sites in various cancer cells [113-122]. Intriguingly, downregulation of PDGFR-α/β by siRNA or miR-34a/c strongly augmented the response to TNF-related apoptosis inducing ligand (TRAIL) while reducing migratory and invasive capacity of non-small cell lung carcinomas [123]. The TRAIL-mediated apoptosis pathway was shown to be sensitive to miR-29, miR-130a, miR-133b, miR-185-5p, miR-221, and miR-222 [124, 125]. Whereas, miR-483-3p displayed a tumor suppressive function in SCC by targeting CDC25A resulting in cell cycle arrest and API5, BIRC5, and RAN leading to pro-apoptotic pathway, which significantly hampered tumor growth of SCC tumorgrafts [126].

Exposure of SCC cells to cisplatin was also leads to a modulation of certain proteins involved in cell cycle arrest or apoptosis ultimately resulting in cell death phenotype. Specific microRNAs, whose transcription is upregulated by p-ΔNp63α, were reported to decrease the levels of CASP2, CASP3, CASP7 and CASP14, PARP8 and PARP11, BMF, DFFA and CDKN1C, while downregulated microRNAs were shown to increase of CASP2, CASP3 and CASP7, BMF, CDKN1B, CDKN1C and CDKN2B, APAF1, DFFA and CHEK1, as shown in Table (Category **C**). Taken together these data strongly support the notion that some of the TP63-regulated microRNAs are likely to contribute to the tumor cell survival and response to chemotherapy alone on in combination with the specific microRNA mimics or inhibitors [50, 53].

6. TP63-DEPENDENT microRNAs AND AUTOPHAGY

Emerging evidence shows that the specific microRNAs are involved in the regulation of autophagy and play a role in modulating the cross talk between autophagy and apoptosis contributing to cancer and tumor cell response to chemotherapy [19, 127-132]. Autophagy is an intrinsic tightly controlled catabolic cellular process in which proteins and organelles are eliminated through delivery to lysosomes, while preserving the cell function and survival [133, 134]. Deregulation of autophagy under stress leading to a malfunction of the autophagic regulatory mechanisms contributes to cancer and tumor cell response to chemotherapy [134-138].

MicroRNAs were shown to modulate numerous signaling intermediates of autophagic pathway (e.g. miR-519a-3p for ATG10, and ATG16L1; miR-101a-3p for ATG4D and RAB5A; miR-17, miR-20, miR-93a and miR-106 for SQSTM1; miR-204 for MAP1LC3; miR-885-3p for ULK2 and ATG16; miR-630 for ATG12 and UVRAG; miR-30a for BECN1; miR-181a-5p for ATG5; miR-630 for ATG12; miR-376b for ATG4C and BECN1; miR-375 for ATG7; miR-374a-5p for ATG4A, ATG5 and UVRAG; miR-34a for ATG9; and miR-130a for ATG2), as reviewed in [19, 127-132].

By inhibiting BECN1, miR-30a leads to the suppression of autophagic phenotype in cancer cells, thereby contributing to cancer progression [128]. ATG4-ATG8 conjunction is a crucial step in the autophagosome biogenesis pathway, thereby underscoring the importance of miR-101a-dependent regulation [129]. SQSTM1 (p62), a multiple domain protein that acts as a signaling hub, was identified as a key target for multiple microRNAs [130]. SQSTM1 can interfere with autophagy via binding to the autophagic regulator ATG8/MAP1LC3. Thus, elimination of SQSTM1 through microRNA modulation may potentially inhibit the proliferation of these tumor cells [130]. MiR-376b was reported to control starvation and mTOR inhibition-related autophagy by targeting ATG4C and BECN1 [131].

Intriguingly, several confirmed targets of microRNAs are also important mediators in the cross regulation between autophagy and apoptosis [19, 127, 132]. For example, the physical interaction between BECN1 and proteins in the anti-apoptotic family (BCL2, MCL1, BCL2L1) is pivotal for the interplay between the autophagic and apoptotic pathways [128, 139-141]. Normally, BECN1 and anti-apoptotic BCL2 proteins can bind to each other to maintain cellular homeostasis [139]. However, upon stress, BECN1 and BCL2 proteins disassociate, thereby promoting autophagy and inhibiting apoptosis, respectively. ATG5, in addition to the promotion of autophagy, enhances susceptibility towards apoptotic stimuli [142]. Enforced expression of *ATG5* renders tumor cells sensitive to chemotherapy, whereas silencing the *ATG5* with siRNA resulted in partial resistance to anticancer drugs. This tumor cell response was associated with calpain-mediated ATG5 cleavage resulting in cytochrome c release and caspase activation suggesting a molecular link between autophagy and apoptosis [143].

Exposure of SCC-11 cells to cisplatin treatment leads to the p-ΔNp63α- dependent modulation of numerous microRNAs potentially implicated in regulation of autophagic signaling intermediates [50, 51, 53]. Although the most of the autophagic proteins appeared to be induced since their corresponding microRNAs are downregulated in SCC-11 cells upon cisplatin exposure, a few proteins are likely to be reduced by upregulated microRNAs (miR-194-3p, miR-297 and miR-630), as reviewed in [50, 51, 53]. However, all protein targets (ATG2B, ATG4A, ATG4C, ATG5, ATG10, ATG12, ATG16L1, DRAM1, GABARAPL1, MAP1LC3B, SQSTM1 and UVRAG1) seem to be affected by both downregulated and upregulated microRNAs (Table, Category **D**),

Table. TP63-regulated microRNAs in Epithelial Cancers

A. Epigenetic Regulation			
MicroRNA (hsa-miR)	**Protein Target**	**Tissues/cells**	**References**
92b-3p	KAT2B, HDAC9	SCC	Ratovitski, in preparation
185-5p	ATF6, DNMT1, SREBF2	SCC	This review
194-5p	KAT6B, SIRT1, ATM	SCC	This review
196-3p	MBD1	SCC	This review
297	SIRT3, DNMT3A, SKP2, ATM	SCC	[52], Ratovitski, in preparation
382-3p	NFYB	SCC	This review
485-5p	KDM4C	SCC	Ratovitski, in preparation
610	ATF5	SCC	This review
630	EZH2, ZBTB2, KAT3B	SCC	[52]
637	ATF3	SCC	This review
885-3p	CARM1	SCC	[52]
920	KAT6B, NFYB	SCC	This review
181a-5p	HDAC4, SIRT1, KAT2B, ATM, TP63	SCC	[52]
374a-5p	SP1, NFYB, CRTC2, KAT2B, ATM, TP63	SCC	[52]
519a-3p	KDM2A, BHLHE41, ATM, TP63	SCC	[52]
29c-3p	SIRT1, HDAC4, KDM2A, DNMT3B	SCC	[74, 75], Ratovitski, in preparation
22-3p	KAT6B, SIRT1, KDM3A, MECP2	SCC	This review
34c-3p	DNMT1	SCC	Ratovitski, in preparation
339-3p	DNMT3B	SCC	This review
203a	NFYA, CITED2, KAT6B, TP63, ATM	SCC	[38, 41, 52], This review
206	CITED, KAT6A	SCC	This review
25-3p	HDAC9	SCC	Ratovitski, in preparation
155-5p	SP3, KDM2A	SCC	This review
148a-3p	DNMT1, DNMT3B	SCC, breast and gastric cancers	[76, 77, 145], This review
101a-3p	EZH2, DNMT3A	SCC	[80, 81], This review
429	CITED2, E2F3, NFYA	SCC	This review
455-3p	KAT2B	SCC	This review
27a-3p	KDM3A, HDAC9, TP53	SCC	Ratovitski, in preparation
183-5p	KDM3A	SCC	This review
362-3p	SIN3A, E2F1	SCC	This review
603	ATM, TP63	SCC	This review

(Table) contd….

B. Cell Metabolism			
MicroRNA (hsa-miR)	**Protein Target**	**Tissues/cells**	**References**
92b-3p	ATOX1	SCC	This review
297	ATP7A	SCC	This review
382-3p	ETNK	SCC	This review
485-5p	ETNK, H6PD	SCC	This review
885-3p	AKT1	SCC	[50]
29c-3p	CPS1, AKT2	SCC	This review
203a	ATP7B, CPS1, FADS1	SCC	This review
18a-5p	CPS1, CPS2 (CAD)	SCC	This review
146b-3p	CPS1	SCC	This review
101a-3p	COX2, AKT1	Gastric cancer, Prostate cancer	[93]
185-5p	SREBF, FADS1, HMGCR	Prostate cancer	[94]
34a	IMPDH	Lung Cancer	[90]
C. Cell Cycle Arrest and Apoptosis			
MicroRNA (hsa-miR)	**Protein Target**	**Tissues/cells**	**References**
92b-3p	CDKN1C	SCC	This review
185-5p	CASP2, CASP14, PARP11	SCC	This review
194-5p	CASP7	SCC	This review
485-5p	PARP8, DFFA	SCC	This review
760	BMF	SCC	This review
885-3p	CASP3	SCC	[50]
519a-3p	CASP2, CDKN2B	SCC	[49, 53]
34c-3p	BMF	SCC	This review
98-5p	CASP3	SCC	[53]
25-3p	CDKN1C	SCC	[53]
155-5p	APAF1	SCC	This review
29c-3p	BMF	SCC	This review
18a-5p	CASP7	SCC	This review
214-3p	DFFA, BCL2, BCL2L2	SCC, cervical cancer	[53, 120], This review
659-3p	CHEK1	SCC	This review
7a-5p	CASP3, XIAP	SCC, cervical cancer	[109], This review
221-3p	CDKN1B	SCC	This review
429	CASP2, CDKN2B, CDK2, BCL2	SCC	[53]
29c-3p	CDK2	SCC	[53]
382-3p	CDK1	SCC	[53]

(Table) contd….

D. Autophagy			
MicroRNA (hsa-miR)	**Protein Target**	**Tissues/cells**	**References**
181a-5p	ATG5	SCC	[52, 53]
374a-5p	ATG4A, ATG5, UVRAG	SCC	[52, 53]
519a-3p	ATG10, ATG16L1, UVRAG	SCC	[52, 53]
22-3p	ATG2B	SCC	This review
34c-3p	ATG4C, DRAM1	SCC	This review
339-3p	GABARAPL1	SCC	This review
203a	ATG2B, GABARAPL1	SCC	[53]
155-5p	GABARAPL1	SCC	This review
485-3p	MAP1LC3B	SCC	This review
214-3p	SQSTM1, ATG12	SCC	This review
183-5p	ATG12	SCC	[53]
98-5p	ATG10	SCC	[53]
27-3p	ATG10	SCC	[53]
603	ATG10	SCC	[53]
630	UVRAG, ATG2B, ATG4C, ATG12	SCC	[52, 53], This review
297	ATG5	SCC	[53]
101a-3p	ATG4D, RAB5A	HCC, breast cancer	[127]
885-3p	ULK2, ATG16	SCC	[51]
93a	SQSTM1		[53]
194-3p	GABARAPL1	SCC	This review

and as reviewed in [50, 51, 53]. Intriguingly, the specific microRNAs were further shown to modulate resistant phenotype of SCC cells *in vitro*, thereby providing groundwork for novel chemotherapeutic venues for head and neck cancer [50, 51, 53].

7. CONCLUSIONS

Accumulating evidence shows that microRNAs, whose transcription is regulated by many transcriptional factors, including TP53 members (TP53, TP63 and TP73) contribute to multiple mechanisms implicated in control of tumor cell homeostasis, proliferation and survival under chemotherapeutic pressure [31, 43]. The diverse actions of these microRNAs affected by TAp63 isoforms and ΔNp63 isoforms complicate the tumor cell response even more. While the former are generally act as pro-apoptotic and tumor suppressive agents, the latter function more as an anti-apoptotic and oncogenic factors. However, p-ΔNp63α occupies a more intermediate niche, since the microRNAs regulated by this transcriptional factor are capable to function in a pro-apoptotic and cell cycle arrest manner, as well as modulate the survival pathway of autophagy, therefore supporting the sensitive response to chemotherapeutic agents (e.g. platinum drugs), as reviewed in [49-53]. Intriguingly, many microRNAs, whose transcription was shown (miR-181a-5p, miR-374a-5p, miR-519a-3p, miR-203a) or predicted to be regulated by TP63 (miR-297 and miR-603), are, in fact, shown [41, 52], or predicted to maintain the feedback control of the TP63 protein levels, as well as likely to modulate the TP63 phosphorylation status via ATM inhibition (Table, Category **A**).

Over recent years, microRNAs have emerged as major players in the complex networks of gene regulation and have been implicated in various aspects of human disease and were designated as one of the key hallmarks of cancer [144]. In addition to oncogenes and tumor suppressor genes, microRNAs and their regulatory networks should be taken into account to understand the complex molecular mechanisms underlying malignant transformation and acquired chemoresistance to anti-cancer drugs. MicroRNAs are important regulators of numerous aspects of metabolic homeostasis, physiology and disease. On one hand, microRNAs were shown or predicted to regulate the transcription and protein levels of numerous transcription factors and epigenetic/chromatin accessory components or signaling proteins involved in regulation of metabolic enzymes and critical

regulators of cell cycle arrest, apoptosis or autophagy [50, 51, 53]. On the other hand, microRNAs could regulate the production of certain metabolites by directly affecting the levels of metabolic enzymes [83, 95]. Therapeutic use of microRNA mimic or inhibitors to suppress certain stages or steps of tumor cell metabolism is likely to lead to new anti-cancer biotherapeutic strategies [28, 83].

CONFLICT OF INTERESTS

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

ATM	=	Ataxia telangiectasia mutated
CDK	=	Cyclin-dependent kinase
DNMT	=	DNA methyltransferase
microRNA	=	miR
p	=	Phosphorylated
RISC	=	RNA-induced silencing complex
SCC	=	Squamous cell carcinoma
SREBF	=	Sterol-regulatory element-binding transcription factor
TA	=	Transactivation
TNF	=	Tumor necrosis factor
TP	=	Tumor protein
TRAIL	=	Tumor necrosis factor related apoptosis inducing ligand
XIAP	=	X-linked inhibitor of apoptosis protein
UTR	=	Untranslated region

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