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Regulation of RUNX proteins by long non-coding RNAs and circular RNAs in different cancers

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ABSTRACT

RUNX proteins have been shown to behave as "double-edge sword" in wide variety of cancers. Discovery of non-coding RNAs has played linchpin role in improving our understanding about the post-transcriptional regulation of different cell signaling pathways. Several new mechanistic insights and distinct modes of cross-regulation of RUNX proteins and non-coding RNAs have been highlighted by recent research. In this review we have attempted to provide an intricate interplay between non-coding RNAs and RUNX proteins in different cancers. Better conceptual and mechanistic understanding of layered regulation of RUNX proteins by non-coding RNAs will be helpful in effective translation of the laboratory findings to clinically effective therapeutics.

1. Introduction

We have witnessed milestone achievements ranging from single-gene to genome-wide scales and from basic cell biology to clinical genetics. With the increasing arsenal of anticancer agents, improving preclinical models and the breakthroughs in high-throughput technologies, there have been groundbreaking discoveries in the field of cancer biology. In recent years, we have witnessed unprecedented progress in non-coding RNA research [1–10]. Structural, biochemical and molecular methodologies have contributed to piecing together the puzzle of how RUNX proteins work and how they contribute to carcinogenesis and metastasis. In this review, we will touch on the latest findings related to the push and pull between non-coding RNAs and RUNX proteins and how these interactions regulate carcinogenesis and metastasis [11–15]. Thus, lncRNAs and circRNAs may represent fast-evolving tools, which contextually add greater than ever complicated regulatory tiers to signaling cascades. LncRNAs and circRNAs play contributory role in shaping the signaling networks, both as backups of transcriptional control and as feedback or feed-forward devices that confer robustness to the output of cellular signaling. In this mini-review, we will attempt to provide an overview of the most recent developments in the regulation of RUNX proteins by lncRNAs and circRNAs in different cancers. We have divided this multi-component review into different sub-sections. We will first provide an overview of different RUNX proteins in various cancers. In the later sections, we will discuss how lncRNAs and circRNAs modulate RUNX proteins in wide variety of cancers. The main aim of this review is to mechanistically analyze how various lncRNAs and circRNAs control the expression of different RUNX proteins to inhibit or promote cancer.

1.1. Overview of RUNX proteins

RUNX1: Tartrate-resistant acid phosphatase (TRAP/ACP5) played central role in lung carcinogenesis (He 16). RUNX1 transcriptionally upregulated ACP5 (Fig. 1). ACP5 overexpression in 95C cells led to an increase in the phosphorylated levels of ERK/MAPK, whereas inhibition of ACP5 caused marked reduction in the phosphorylated levels of ERK/MAPK. Tumors derived from ACP5- overexpressing-95C cells were larger in size in xenografted mice (He [16]).

FUBP1 (Far upstream binding protein-1) worked synchronously with

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RUNX1 and transcriptionally upregulated c-KIT (Fig. 1) (Debaize [17]). Upregulation of c-KIT made cancer cells more resistant to the c-KIT inhibitors (Debaize [17]).

RUNX1 binding sites are present within promoter region of ZEB1 (Hong [18]). RUNX1 transcriptionally repressed ZEB1 (Fig. 1). Invasive potential of RUNX1 overexpressing-MCF10AT1 and MCF10CA1a cells was noted to be significantly reduced. Tumors derived from RUNX1-overexpressing-MCF10CA1a were found to be smaller in size (Hong [18]).

RUNX2: RUNX2 transcriptionally upregulated OPN/SPP1 (Osteopontin) (Fig. 1) (Villanueva [19]). Enforced expression of RUNX2 potently enhanced the secretion of osteopontin in conditioned media. Moreover, pre-incubation of G292 cells with conditioned media from RUNX2-overexpressing-G292 cells led to an increase in their ability to adhere to pulmonary endothelial cells. Lung colonization rates as well as number of pulmonary metastatic nodules were found to be reduced in mice transplanted with RUNX2-silenced-SaOS-2 cells (Villanueva [19]).

RUNX2 transcriptionally upregulated ITGA5 (Integrin α5) in breast cancer cells (Fig. 1) (Li [20]). RUNX2-overexpressing-breast cancer cells are prone to metastasize to bone. RUNX2 knockdown caused marked reduction in the chemotactic movement of MDA-MB-231 cells towards MG63 osteoblast-like cells. Whereas, RUNX2 overexpression led to an increase in the chemotactic movement of MDA-MB-231 and T47D cells towards MG-63 cells. RUNX2 enhanced the adhesive ability of cancer cells with MG-63 but knockdown of ITGA5 severely reduced the adhesive ability. RUNX2-overexpressing-MDA-MB-231 cancer cells invaded the bone marrow of tumor-bearing mice. Whereas, inhibition of Integrin-α5 considerably reduced the accumulation of RUNX2-overexpressing cancer cells in the bone marrow (Li [20]).

Levels of RUNX2 were found to be reduced in SET7/9-depleted MCF-7 cells and MDA-MB-231 cells (Si [21]). TRIM21 physically interacted with SET7/9 and marked it for degradation. Tumor growth was noted to be significantly reduced in the mice orthotopically implanted with SET7/9-silenced MDA-MB-231 cells. Collectively, these findings suggested that SET7/9 stimulated the expression of RUNX2. However, TRIM21 served as a tumor suppressor and interfered with SET7/9-mediated increase in the expression of RUNX2 (Si [21]).

MPZL2 (Myelin protein Zero-like-2) and EPAS1 (Endothelial PAS domain protein-1) played central role in metastasis (Yi [22]). Binding of RUNX2 to the upstream distal region of MPZL2 and intronic regions of EPAS1 enhanced their expression. RUNX2 overexpression enhanced the metastasis of Wnt^{low} cells but knockdown of RUNX2 considerably inhibited metastasizing ability of Wnt^{high} cells (Yi [22]).

RUNX3: Two consensus binding sequences of RUNX3 are present within AKT1 promoter region (Fig. 1) (Lin [23]) RUNX3 transcriptionally downregulated AKT1 in gastric cancer cells. RUNX3 caused marked reduction in the phosphorylation of AKT1 at Thr-308 and Ser-473. RUNX3 also reduced nuclear accumulation of β-catenin. Collectively, RUNX3 inhibited proliferation of gastric cancer cells through inactivation of AKT1 and β-catenin (Lin [23]).

SMAD3 binding sites are present within promote region of miR-29 b. RUNX3 and SMAD3 worked synchronously and stimulated the expression of a tumor suppressor miR-29b (Fig. 1) (Kong 24). KDM2A (Lysine demethylase 2A) is directly targeted by miR-29 b. miR-29 b reduced the expression of KDM2A and repressed the proliferation potential of gastric cancer cells (Kong [24]).

EZH2 is member of PRC2 (Polycomb repressive complex-2) (Sengupta [25]). EZH2 is a lysine methyltransferase and catalyzes the addition of H3K27me2/me3 (repressive histone marks) to enhance chromatin compactness and consequent transcriptional repression. Elevated levels of H3K27me3 are associated with lower levels of E-cadherin and RUNX3 in aggressive melanoma WM115EZ and WM266-4 cells. Treatment of melanoma cells with GSK126 (EZH2 inhibitor) led to notably reduced levels of H3K27me3. GSK126-mediated EZH2 inhibition reduced H3K27me3 occupancy at the promoter region of RUNX3. Similarly, targeting of EZH2 also caused an increase in the expression of E-cadherin (Sengupta [25]).

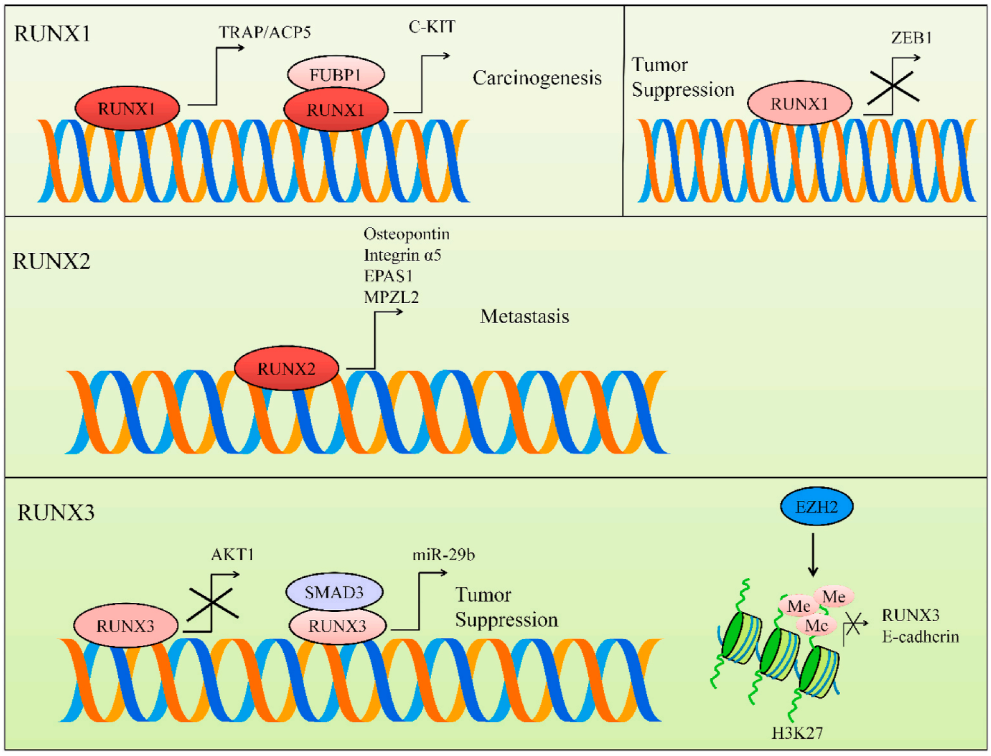

Fig. 1. Regulation of target genes by RUNX proteins. RUNX1 dualistically regulates the expression of target genes. RUNX1 stimulated the expression of TRAP/ACP5 and c-KIT. RUNX1 inhibited the expression of ZEB1. RUNX2 also stimulates the expression of different oncogenes. RUNX3 is involved in transcriptional down-regulation of oncogenes. Moreover, RUNX3 stimulated the expression of tumor suppressor miRNA.

2. Interplay between lncRNAs and RUNX1

2.1. Oncogenic role of RUNX1-IT1

RUNX1-IT1 is transcribed from the intron of RUNX1 (Liu [26]). RUNX1-IT1 stimulated the expression of RUNX1 by promoting the acetylation of H3K27 in the proximal promoter region of RUNX1. RUNX1-IT1 knockdown significantly reduced the levels of H3K27 acetylation in the proximal promoter region of RUNX1. RUNX1-IT1 potentiated the binding of RUNX1 to the promoter region of c-Fos. Relatively fewer cases of intrahepatic metastases were noticed in the mice inoculated with RUNX1-IT1 knockout PANC-1 cancer cells. Importantly, fewer micro-metastatic lesions were noticed on the liver surfaces of mice inoculated with RUNX1-IT1-knockout PANC-1 cancer cells (Liu [26]).

2.2. Tumor suppressive role of RUNX1-IT1

RUNX1-IT1 inactivated Wnt/β-catenin signaling by interfering with miR-632-mediated inhibition of GSK-3β (Sun [27]). Interestingly, cytoplasmic and nuclear levels of β-catenin were noted to be enhanced in RUNX1-IT1-silenced cancer cells. Hypoxia induced an increase in the levels of HDAC3. Hypoxia-driven HDAC3 caused transcriptional repression of RUNX1-IT1. Findings obtained from orthotopic liver tumor models were used to analyze the activity of RUNX1-IT1 on intrahepatic diffusion and pulmonary colonization of HCC. RUNX1-IT1 notably reduced the metastasizing ability of MHCC-97H cells in tumor-bearing mice. Relatively fewer and smaller metastatic nodules were noticed in mice transplanted with RUNX1-IT1 overexpressing cancer cells (Sun [27]).

2.3. LncRNA-mediated activation of RUNX1

RUNXOR is an intragenic lncRNA. It is transcribed from a promoter located upstream of the RUNX1 promoter (Nie [28]). Astonishingly, transcripts from the RUNX1 P1 promoter were found to be significantly increased by RUNXOR. RUNXOR induced an increase in the histone H3K4me3 epigenetic marks in promoter P1 of RUNX1. Collectively, these findings suggested that RUNXOR selectively activated oncogenic RUNX1 from the promoter P1 (Nie [28]).

2.4. Tumor suppressive role of RUNX1

LncRNA-NEF overexpression inhibited the proliferative ability of gastric cancer cells (Wang [29]). LncRNA-NEF knockdown significantly inhibited the expression of RUNX1. In contrast, overexpression of lncRNA-NEF significantly stimulated the expression of RUNX1 (Wang [29]).

LncRNA-H19 RNA is the primary precursor of miR-675. However, miR-675 mediated H19-induced gastric cancer progression (Zhuang [30]). miR-675 directly targeted RUNX1 and promoted carcinogenesis. RUNX1 overexpression counteracted the proliferative potential of cancer cells caused by miR-675 (Zhuang [30]).

Higher expression levels of RUNX1 and LINC00160 were associated with higher overall survival rates in ER + breast cancer patients (Zhang [31]). Higher levels of E2-responsive RUNX1 and LINC00160 in ER^{+} breast cancer patients enhance the rate of sensitivity to endocrine therapies and consequently improvement in the prognostic outcomes (Zhang [31]).

CASC2 served as a tumor suppressive lncRNA and antagonized miR-18a-5p-mediated inhibitory effects on RUNX1. CASC2 and RUNX1 reduced the proliferation potential of multiple myeloma cells (Zhang et [32]).

FENDRR potentiated the expression of RUNX1 by sequestering away miR-18a-5p (Zhang [33]). FENDRR and RUNX1 reduced the proliferation ability of prostate cancer cells (Zhang [33]).

2.5. Oncogenic role of RUNX1

LincRNA-uc002yug.2 promoted the recruitment of splicing factors (MBNL1 and SFRS1) to promoter region of RUNX1 to increase its alternative splicing by the formation of regional RNA duplexes to enhance the generation of RUNX1a (Fig. 2) (Wu [34]). Tumor development started 3 days earlier in mice transplanted with lincRNA-uc002yug.2-expressing Eca-109 cells. Tumors derived from uc002yug.2-silenced Eca-109 cancer cells were smaller in size (Wu [34]).

TTN-AS1 blocked miR-27 b-3p-mediated inhibition of RUNX1 (Chang [35]). Tumors derived from TTN-AS1-silenced U251 glioma cells were smaller in size (Chang [35]).

RUNX1 transcriptionally upregulated an oncogenic lncRNA RNCR3 (Fig. 2) (Xu [36]). RNCR3 abrogated miR-1301-3p mediated tumor suppressive effects by stimulating the expression of AKT1. There was a marked regression of the tumors in mice transplanted with RNCR3-silenced-HCT116 cells (Xu [36]).

There was a direct interaction of RUNXOR with the RUNX1 promoter and enhancer chromatin DNA sequences through its 3′-terminal segment (Wang [37]). 3′ lncRNA interacted inter-chromosomally with many RUNX1 translocation partner chromatin DNAs, thus unraveling the possibility of this lncRNA in chromosomal translocations in the hematopoietic malignancies. Overall, RUNXOR enhanced the recruitment of RUNX1 and EZH2 to the promoter region of RUNX1 (Wang [37]). However, we still have insufficient information about the exact role of this lncRNA-protein complex in the regulation of RUNX1.

2.6. Oncogenic role of LncRNAs and RUNX2

LINC00994 effectively blocked miR-765-3p-mediated inhibition of RUNX2 in pancreatic cancer PANC-1 and AsPC-1 cells. LINC00994 and RUNX2 played central role in carcinogenesis ([38]).

Likewise, TUC338 also potentiated RUNX2 expression by blockade of miR-466 in prostate cancer cells (**Li** [39]).

MANCR (Mitotically associated lncRNA) enhanced proliferation potential of mantle cell lymphoma cells. MANCR antagonized miR-218-mediated targeting of RUNX2 (**Wen** [40]).

DLX6-AS1 inhibited tumor suppressor miR-505-3p and stimulated the expression of RUNX2. DLX6-AS1 and RUNX2 effectively increased proliferative and invasive capacities of breast cancer cells (**Zhao**, [41]).

RUNX2 overexpression significantly upregulated PVT1 levels in colorectal cancer cells (**Chai**, [42]). miR-455 directly targeted RUNX2 in colorectal cancer cells. However, PVT1 prevented miR-455-mediated targeting of RUNX2 (**Chai**, [42]).

Overexpression of lncRNA EPEL and RUNX2 promoted the migration, proliferation, and invasion of gastric cancers (**Fu**, [43]).

CREB1 transcriptionally upregulated HAS2-AS1 (**Tong**, [44]). HAS2-AS1 caused upregulation of RUNX2 by blockade of miR-466. There was a marked reduction in the growth of the tumors in mice transplanted with HAS2-AS1-silenced SKOV3 cancer cells (**Tong**, [44]).

N6-methyladenosine (m6A) is a frequent biochemical modification of lncRNAs. NEAT1-1 interacted with CYCLINL1 through m6A site 4 (**Wen**, [45]). GxxGxG-domain has a functionally distinct role in CDK19. Deletion of GxxGxG domain caused considerable blockade of the interaction between NEAT1-1 and CDK19. CYCLINL1 associated with m6A region of NEAT1-1. NEAT1-1 acted as a bridge for the connection of CDK19 and CYCLINL1. NEAT1-1 WT overexpression increased the levels of RUNX2, but NEAT1-1 m6A site 4-mutation did not enhance the levels of RUNX2. Site 4 of m6A facilitated NEAT1-1-mediated recruitment of CDK9 and CYCLINL1 onto the promoter of RUNX2. NEAT1-1 overexpression led to marked reduction in the survival rates of tumor-bearing mice and also enhanced the metastatic spread to pelvis bone and lung. Additionally, NEAT1-1 WT potently increased flank tumor growth of patient-derived xenografts, but not NEAT1-1site 4 m6A-mutants (**Wen**, [45]).

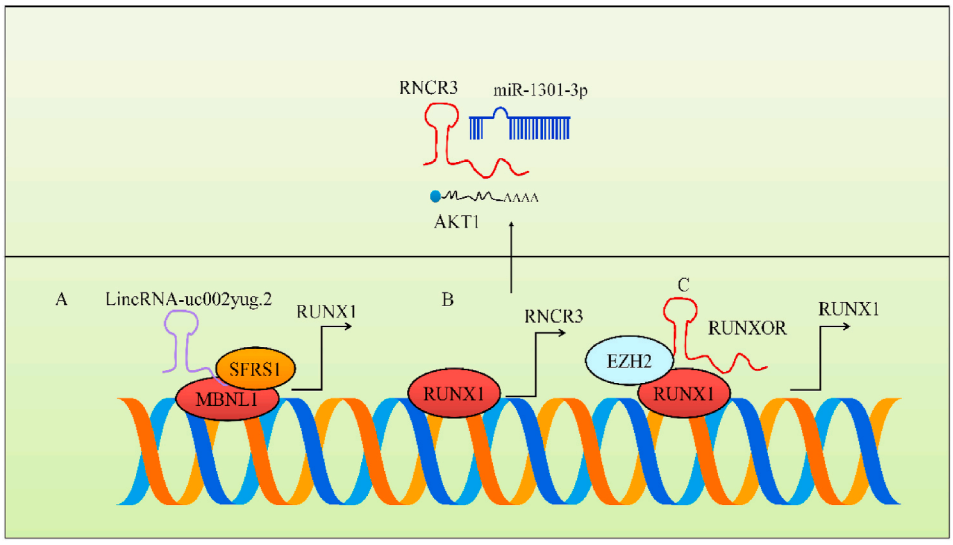

Fig. 2. (A) LincRNA-uc002yug.2 promoted the recruitment of splicing factors (MBNL1 and SFRS1) to promoter region of RUNX1. (B) RUNX1 stimulated the expression of an oncogenic lncRNA (RNCR3). RNCR3 blocked miR-1301-3p mediated targeting of AKT1. (C) EZH2, RUNX1 and RUNXOR bind to the promoter region of RUNX1. However, exact regulation of RUNX1 by this complex is still unknown.

WDR5 is a fundamental member of the histone H3K4 methyltransferase complexes (**Rossi**, [46]). WDR5 promoted H3K4 trimethylation on active promoters and facilitated the recruitment of RNA-Pol-II for transcriptional activation of target genes. RAIN, a novel Enhancer-associated lncRNA not only enhanced the recruitment of RNA-Pol-II on the RUNX2 P2 promoter but also increased the levels of H3K27Ac. Furthermore, l-RAIN caused a significant increase in the levels of H3K4Me3. NELF (Negative elongation factor), a multiprotein complex interacted with the RNA-Pol-II along the gene body and restrained its progression. However, RAIN sequestered away the members of the NELF complex and relieved their inhibitory effects on RNA-Pol–II–mediated elongation. RAIN interacted with NELFe in MDA-MB-231 and TPC1 cancer cells. RAIN silencing led to significant accumulation of NELFe on the transcriptional start site of RUNX2. RAIN restrained the NELFe-induced inhibitory effects on RUNX2 expression. There was a significant upregulation of RUNX2 in NELFe-silenced MDA-MB-231 and TPC1 cancer cells (**Rossi**, [46]).

Collectively, substantial fraction of information has been added into the pool of knowledge related to lncRNA mediated upregulation of RUNX2 to fuel carcinogenesis in wide variety of cancers [47–53].

RUNX2 has also been shown to inhibit the expression of tumor suppressor lncRNAs. RUNX2 and YAP have been shown to bind to the region around the RUNX2 motif and transcriptionally downregulated MT1DP (Metallothionein 1D, Pseudogene) (**Yu** [54]). RUNX2 knockdown caused marked reduction in the occupancy of YAP around the R2 region of MT1DP. RUNX2 and YAP were noticed to be downregulated in FOXA1 knockdown cells. Eukaryotic initiation factor 4E (eIF4E) played an important role in translation of mRNAs. There was a marked increase in the recruitment of eIF4E to FOXA1 mRNA in MT1DP knockdown cells. Tumor growth rates were noted to be reduced in mice inoculated with MT1DP overexpressing Bel-7402 cancer cells. However, these effects could be rescued by simultaneous overexpression of either FOXA1, YAP or RUNX2. Moreover, interestingly, stronger synergistic effects were detected when all three proteins were simultaneously overexpressed in mice model (**Yu** [54]).

2.7. Tumor suppressive role of RUNX3

RUNX3 has been shown to inhibit/suppress carcinogenesis and metastasis. In this section, we will summarize how different lncRNAs inhibit and stimulate the expression of RUNX3 to regulate cancer progression.

HOXD-AS1 worked synchronously with EZH2 and epigenetically inactivated RUNX3 (Fig. 3) (**Zhang** [55]). HOXD-AS1 knockdown not only reduced EZH2 binding but also suppressed H3K27me3 occupancy at promoter region of RUNX3 in A375 and A2058 cells. Tumor growth was drastically reduced in mice injected with HOXD-AS1-silenced A375 cancer cells (**Zhang** [55]).

miR-214-3p, an oncogenic miRNA has the ability to directly target RUNX3 to promote cancer (**Xu** [56]). However, MT1JP interfered with miR-214-3p-mediated targeting of RUNX3. MT1JP overexpression significantly inhibited tumor growth in tumor-bearing mice. MT1JP overexpression increased the expression of RUNX3, Bim and p21 in the tumor tissues of xenografted mice (**Xu** [56]).

Similar findings have been reported in breast cancer cells (**Ouyang** [57]). Importantly, levels of RUNX3 and P21 were noticed to be significantly upregulated, whereas levels of MMP2 and MMP9 were found to be downregulated in MT1JP- overexpressing-Bel-7402 and Huh-7 cancer cells (**Mo** [58]).

HOTAIR overexpression suppressed the levels of RUNX3 in gastric

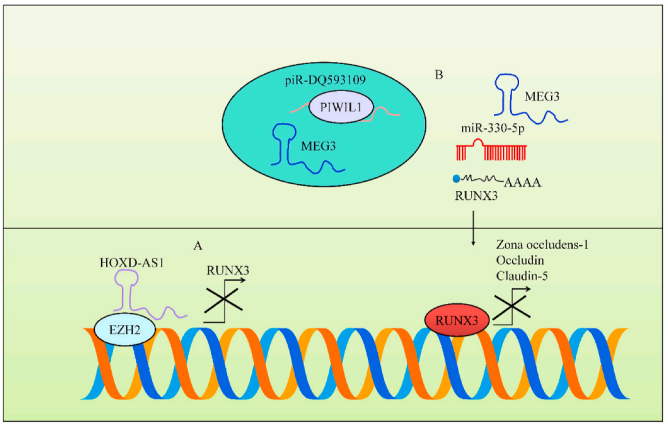

Fig. 3. (A) HOXD-AS1 worked synchronously with EZH2 and epigenetically inactivated RUNX3. (B) PIWI/piRNA complexes are reportedly involved in the degradation of RNAs. piR-DQ593109 binds in a sequence-dependent manner to the MEG3. MEG3 is a tumor suppressor lncRNA and inhibits miR-330-5p-induced targeting of RUNX3. RUNX3 transcriptionally downregulates Zona occludens-1, occludin and claudin-5.

cancer cells (**Xue** [59]). MG132, a ubiquitin–proteasome inhibitor recovered the levels of RUNX3 in HOTAIR-transfected cancer cells. Ubiquitinated levels of RUNX3 were noted to be reduced upon depletion of either Mex3b or HOTAIR in SGC7901 and BGC823 cells. Interaction between RUNX3 and Mex3b was found to be enhanced in HOTAIR-transfected BGC823 and SGC7901 cancer cells. HOTAIR knockdown severely impaired the migratory and invasive capacities of gastric cancer cells (**Xue** [59]).

LINC00657 served as a tumor suppressive lncRNA and inhibited cervical cancer progression (Qin [60]). LINC00657 efficiently abrogated miR-20a-5p-mediated inhibition of RUNX3. RUNX3 transcriptionally upregulated DR5 and potentiated LINC00657-mediated tumor suppressive effects (**Qin** [60]).

Blood-tumor barrier (BTB) strictly reduces the transportation of chemotherapeutic drugs to the glioma microenvironment (**Shen** [61]). PIWI-interacting RNA (piRNA) is a class of small RNAs. Studies have shown that piRNAs bind to PIWI molecules for the regulation of cellular mechanisms. PIWIL1 knockdown led to reduction in the levels of Zona occludens-1, occludin and claudin-5. piR-DQ593109 downregulation caused an increase in the permeability of BTB and lowered the levels of occludin, claudin-5 and Zona occludens-1. PIWI/piRNA complexes are reportedly involved in the degradation of RNAs. piR-DQ593109 binds in a sequence-dependent manner to the MEG3. Degradation of MEG3 by the PIWIL1/piR-DQ593109-mediated silencing complexes enhance the carcinogenesis. MEG3 blocked miR-330-5p-mediated targeting of RUNX3 (Fig. 3). RUNX3-binding sites are present within promoter regions of Zona occludens-1, occludin and claudin-5. Importantly, RUNX3 transcriptionally downregulated Zona occludens-1, occludin and claudin-5. RUNX3 increased the permeability of BTB and inhibited Zona occludens-1, occludin and claudin-5 (**Shen** [61]).

3. Interplay between CircRNAs and RUNX proteins

3.1. Oncogenic role of RUNX1 and circular RNAs

circ_0000512 antagonized miR-296-5p-mediated targeting of RUNX1 in colorectal cancer cells (Wang [62]). Downregulation of miR-296-5p or overexpression of RUNX1 caused reversal of the anti-proliferative and pro-apoptotic effects caused by knockdown of circ_0000512 in CRC cells. circ_0000512 knockdown enhanced miR-296-5p levels in excised tumor tissues of xenografted mice. circ_0000512 knockdown resulted in a decrease of RUNX1 levels in the tumor tissues (Wang [62]).

CircMUC16 potentiated the expression of RUNX1 by sequestering away miR-199a-5p (Gan [63]). RUNX1 stimulated circMUC16 expression. CircMUC16 directly associated with ATG13 and stabilized its expression. circMUC16 inhibition caused a marked reduction in the levels of ATG13, whereas ectopic expression of circMUC16 promoted ATG13 levels. circMUC16 silencing resulted in the suppression of pelvic peritoneal invasion (Gan [63]).

3.2. Tumor suppressive role of RUNX1 and circular RNAs

circFAT1(e2) interfered with miR-548gmediated targeting of RUNX1 (**Fang** [64]). Moreover, circFAT1(e2) interacted with YBX1 in the nucleus and interfered with YBX1-mediated upregulation of EGFR, CDC25A and c-Met. There was a marked reduction in the growth of the tumors in mice transplanted with circFAT1(e2)-overexpressing MGC-803 cancer cells (**Fang** [64]).

3.3. Oncogenic role of RUNX2 and circular RNAs

CircRNAs and RUNX2 have been reported to fuel carcinogenesis. This section mainly deals with the positive relationship between circRNAs and RUNX2 to promote cancer progression.

hsa_circ_0000144 interfered with miR-217-mediated inhibition of RUNX2 (**Huang** [65]). Knockdown of hsa_circ_0000144 significantly delayed the growth of tumors in xenografted mice (**Huang** [65]).

circRNA_102272 served as a sponge for miR-326 and potentiated the expression of RUNX2 (**Guan** [66]). Importantly, tumor volume and weight in the circRNA_102272 knockdown groups were significantly suppressed. Moreover, intraperitoneally injected cisplatin caused inhibition of the volume and weight of the tumors in mice inoculated with circRNA_102272 knockdown cancer cells (**Guan** [66]).

3.4. Tumor suppressive role of RUNX3 and circular RNAs

RUNX3 mediated tumor suppressive effects have also been investigated in recent years. Certain circRNAs have been shown to stimulate the expression of RUNX3 to inhibit cancer progression and tumor development in preclinical models.

hsa_circ_0000673 overexpression inhibited the proliferative and invasive capacity of gastric cancer cells (Chang [67]). hsa_circ_0000673 downregulation promoted the proliferation and invasion of gastric cancer cells. hsa_circ_0000673 antagonized miR-532-5p-mediated targeting of RUNX3. hsa_circ_0000673 increased the levels of RUNX3 and E-cadherin in BGC823 and AGS cancer cells. Tumors developed from has_circ-0000673-overexpressing AGS cancer cells were smaller in size in tumor-bearing mice (Chang [67]).

circLARP4 effectively blocked miR-761-mediated targeting of RUNX3 (Chen [68]). Increased levels of p53 and p21 in circLARP4-overexpressing MHCC97L cancer cells were abolished after knockdown of RUNX3. Tumors derived from circLARP4-overexpressing-MHCC97L cancer cells were smaller in size. Higher levels of RUNX3, p53 and p21 were noticed in the tumors derived from circLARP4-overexpressing-MHCC97L groups (Chen [68]).

circREPS2 efficiently blocked miR-558-induced targeting of RUNX3 (**Guo** [69]). RUNX3 exerted repressive effects on Wnt/β-catenin signaling in gastric cancer cells. Wnt/β-catenin pathway was significantly inhibited in RUNX3-expressing-BGC-823 and SGC-7901 cells, resulting in a significant reduction in nuclear accumulation of β-catenin. RUNX3 significantly inhibited the transcriptional activity of Wnt/β-catenin signaling cascade (**Guo** [69]).

4. Concluding remarks

The regulation of the RUNX family by non-coding RNAs is a surprisingly unexplored field and needs detailed research. Astonishingly, RUNX genes illuminate an exciting fact that disruption of cell-fate determination can have an etiological role in carcinogenesis and metastasis, but with a more intricate and multifaceted set of consequences than previously surmised for the ‘simple’ tumor suppressors or oncogenes. These puzzling complexities highlight opportunities and threats for therapeutic targeting of RUNX, which might have unintended and unexpected consequences. It is safe to conclude that a fool-proof and comprehensive understanding of the intricate interplay between non-coding RNAs and RUNX factors will be essential if scientists aim to harness rapidly evolving knowledge of this gene family for further beneficial advancements in cancer therapeutics.

Declaration of competing interest

I declare on the behalf of all authors that none of the authors have any conflict of interest.

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