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Review Article

Interplay between JAK/STAT pathway and non-coding RNAs in different cancers

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A B S T R A C T

Progress in the identification of core multi-protein modules within JAK/STAT pathway has enabled researchers to develop a better understanding of the linchpin role of deregulated signaling cascade in carcinogenesis and metastasis. More excitingly, complex interplay between JAK/STAT pathway and non-coding RNAs has been shown to reprogramme the outcome of signaling cascade and modulate immunological responses within tumor microenvironment. Wealth of information has comprehensively illustrated that most of this complexity regulates the re-shaping of the immunological responses. Increasingly sophisticated mechanistic insights have illuminated fundamental role of STAT-signaling in polarization of macrophages to M2 phenotype that promotes disease aggressiveness. Overall, JAK/STAT signaling drives different stages of cancer ranging from cancer metastasis to the reshaping of the tumor microenvironment. JAK/STAT signaling has also been found to play role in the regulation of infiltration and activity of natural killer cells and CD4/CD8 cells by PD-L1/PD-1 signaling. In this review, we have attempted to set spotlight on regulation of JAK/STAT pathway by microRNAs, long non-coding RNAs and circular RNAs in primary tumors and metastasizing tumors. Therefore, existing knowledge gaps need to be addressed to propel this fledgling field of research to the forefront and bring lncRNAs and circRNAs to the frontline of clinical practice. Leveraging the growing momentum will enable interdisciplinary researchers to gain transition from segmented view to a fairly detailed conceptual continuum.

1. Introduction

Cancer is a multifaceted and genomically complex disease. It has now been convincingly revealed that wide ranging mechanisms particularly, genetic/epigenetic mutations, resistance against different therapeutics and loss of apoptosis efficiently promoted the onset and progression of cancer. Data obtained through high-throughput technologies has not only sharpened the resolution of signaling landscapes but also highlighted spatio-temporally controlled nature of the cellular pathways. Increasingly it is being realized that dysregulations of spatio-temporally controlled intracellular signaling cascades are central drivers of cancer progression. Signaling cascades modulate different molecular activities through multiple effectors and also by crosstalks with other transduction cascades. JAK/STAT mediated signaling has gained considerable appreciation [1]. Rapidly emerging experimental evidence has started to shed light on the principal role of JAK/STAT signaling in regulation of carcinogenesis and tumor microenvironment.

High-throughput experimental studies have facilitated a comprehensive characterization of the components and pathogenesis of JAK-STAT pathway in different cancers. These mechanisms are relevant in a particular context and the interaction networks are large and complex [2,3]. A sophisticated understanding of JAK-STAT cascade has provided mechanistic insights into the intracellular signaling stimulated by the cytokines. Upon the binding of extracellular ligands to the native receptor, Janus kinases (JAKs) initiate tyrosine phosphorylation of the receptors and trigger the recruitment of STAT proteins [4–6]. Consequently, phosphorylated-STATs undergo dimerization and accumulate in the nucleus to regulate specific transcriptional gene networks.

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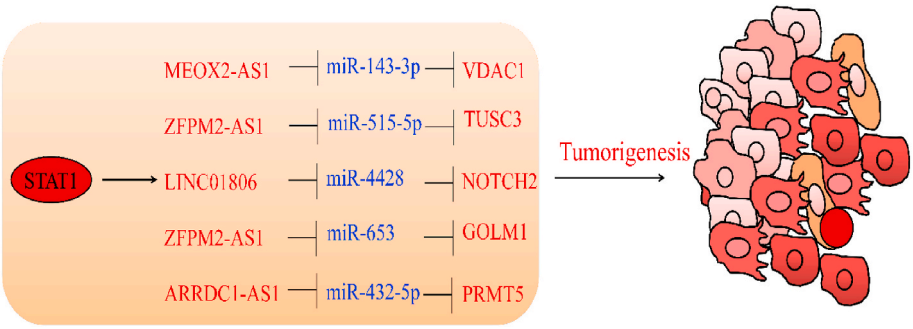

Fig. 1. STAT1-controlled lncRNAs promoted tumorigenesis mainly through upregulation of oncogenes.

Once viewed simplistically as an intermediate between DNA and protein, a renaissance in RNA structure and functions has paradigmatically shifted our understanding about the central role of non-coding RNAs in carcinogenesis and metastasis. Although characteristically unique features of the biogenesis of miRNA and functions were revealed early on, recent years have mechanistically unraveled fundamental information related to the molecular and structural dynamics of core miRNA machinery [7–9]. More importantly, modern research has illuminated how miRNA substrates and targets are selected from the transcriptome and how lncRNAs and circRNAs interact with miRNAs for the regulation of cell signaling pathways.

Central role of JAK/STAT signaling has been comprehensively investigated in cancer progression, epithelial-to-mesenchymal transition and how metastatically competent cancer cells invade and form secondary tumors in distant organs. However, discovery of non-coding RNAs has revolutionized our understanding about interplay between non-coding RNAs and JAK/STAT pathway in molecular oncology. These interactions seem to be more sophisticated than previously surmised and mechanistically modulate cancer progression, infiltration of natural killer cells and $CD4^+$/$CD8^+$ in tumor microenvironment as well as tumor-associated macrophages. Moreover, how cancer cells evade apoptotic cell death by inducing exhaustion of T cells is also a fascinating facet of the interplay between non-coding RNAs and JAK/STAT pathway. Furthermore, non-coding RNAs have also been shown to promote immunosuppressive microenvironment by polarization of macrophages principally through activation of STAT pathway. Therefore, in this review, we have put together different proof-of-concept studies related to interplay between non-coding RNAS and JAK/STAT pathway for the regulation of carcinogenesis, how cancer cells evade apoptotic death and how tumor microenvironment is shifted from immunostimulatory to immunosuppressive state for the progression of cancer.

2. Regulation of JAK/STAT pathway by long non-coding RNAs

Genome-wide sequencing has paved the way for the discovery of thousands of long non-coding RNA (lncRNA) loci in the human genome [10–13]. LncRNA complexes formed by various molecular interactions exert robust gene regulatory effects. Competing endogenous RNAs (ceRNAs) have been reported to demonstrate unique ability to bind competitively with microRNAs (miRNAs) and sequester/sponge miRNAs from their target transcripts consequently interfering with the inhibition or degradation of target transcripts induced by miRNAs. In the upcoming section, we have provided mechanistic information about

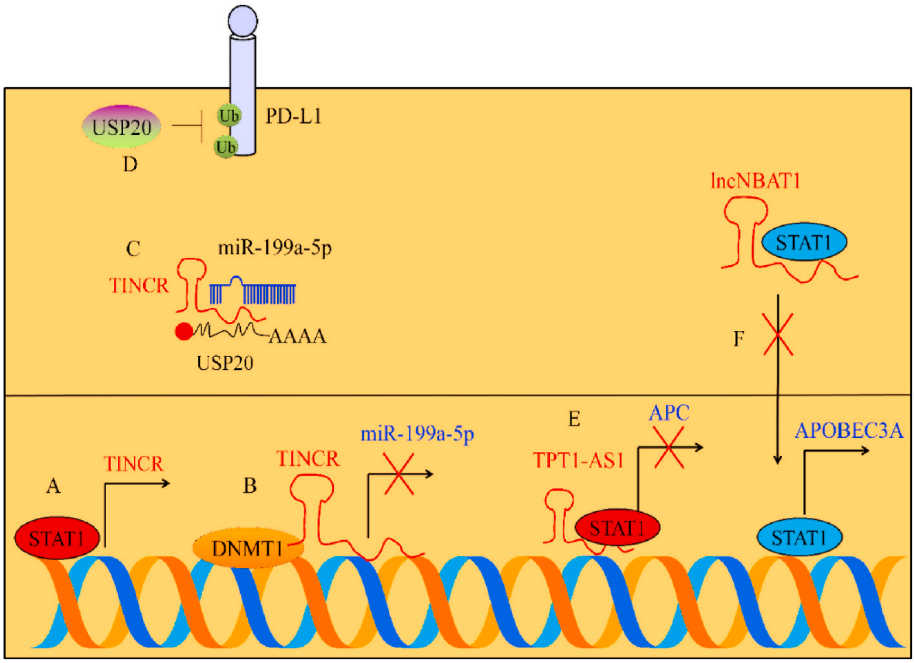

Fig. 2. (A–D) STAT1 stimulates TINCR. Importantly, TINCR works with DNMT1 and epigenetically represses miR-199a-5p. TINCR also interferes with miR-199a-5p-mediated targeting of USP20. Consequently, USP20 deubiquitinates PD-L1. (E) TPT1-AS1 recruits STAT1 to transcriptionally repress APC (Adenomatous polyposis coli). (F) lncNBAT1 interacts with STAT1 to prevent its enrichment at the promoter region of APOBEC3A.

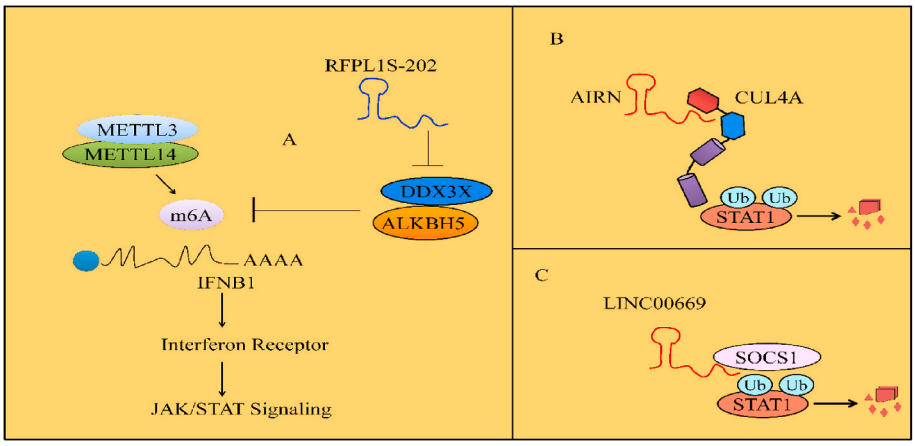

Fig. 3. (A) METTL14 promotes the binding of METTL3 to IFNB1. METTL3/METTL14 regulates m6A modifications. However, DDX3X and ALKBH5 work synchronously and demethylate IFNB1. RFPL1S-202 interacts with DDX3X and impairs ALKBH5-mediated demethylation of IFNB1. (B) AIRN stabilizes STAT1 by inhibition of CUL4A-mediated degradation of STAT1. (C) LINC00669 inhibits SOCS1-mediated STAT1.

lncRNA-mediated regulation of JAK/STAT pathway.

3. Transcriptional regulation of oncogenic lncRNAs by STAT1

STAT1 has been reported to transcriptionally activate MEOX2-AS1 (Fig. 1). VDAC1 allows the passage of nucleotides, metabolites and ions across the outer mitochondrial membrane. Mechanistically, MEOX2-AS1 sponges miR-143-3p and potentiates the expression of VDAC1. Experimental mice subcutaneously injected with MEOX2-AS1-silenced-HeLa cells presented evident regression of the tumor growth [14].

STAT1 transcriptionally upregulates ZFPM2-AS1 in thyroid cancer cells (Fig. 1). Importantly, ZFPM2-AS1 interfered with miR-515-5p-mediated targeting of TUSC3 in 8505C and SW579 cells. miR-515-5p suppressed proliferation and invasive properties of thyroid cancer cells by inhibition of TUSC3 [15].

STAT1 transcriptionally stimulates DLEU2 in gastric cancer cells. DLEU2 inhibited miR-23b-3p-mediated targeting of NOTCH2 and activated NOTCH signaling pathway [16].

STAT1 also activated NOTCH pathway by transcriptional upregulation of LINC01806. Importantly, LINC01806 also acted as a sponge for miR-4428 and interfered with miR-4428-mediated targeting of NOTCH2. There was an evident regression of the tumors developed from LINC01806-silenced NSCLC cells. However, acceleration in tumor growth was noted when NSCLC cells were co-transfected with miR-4428 antagomirs or overexpression of NOTCH2 [17].

Transcriptional upregulation of LINC00504 is also controlled by STAT1. TAF15 functions as an RNA-binding protein and stabilizes mRNAs. LINC00504-mediated TAF15 induced stability of CPEB2. Expression levels of CPEB2 mRNA were found to be reduced in LINC00504 knockdown or TAF15 depleted breast cancer cells treated with actinomycin D. Collectively, these findings indicated that stability of CPEB2 was evidently reduced upon the depletion of LINC00504 or TAF15 [18].

TINCR (Tissue differentiation inducing non-protein coding RNA), a long non-coding RNA recruited DNMT1 and promoted epigenetic inactivation of miR-199a-5p. TINCR served as a molecular sponge for miR-199a-5p and stimulated the expression of USP20 (Ubiquitin-Specific Protease 20). USP20 removes ubiquitin peptides from PD-L1 and enhances its stability (Fig. 2). STAT1 stimulates the expression of TINCR in IFNγ-treated cancer cells [19].

STAT1 stimulates ZFPM2-AS1 (ZFPM2 antisense RNA-1) in HCC cells. ZFPM2-AS1 efficiently inhibits miR-653-mediated targeting of GOLM1 (Golgi Membrane Protein 1) (Fig. 1). ZFPM2-AS1- depletion caused remarkable shrinkage of the tumors in mice subcutaneously implanted with ZFPM2-AS1-silenced-HepG2 cells [20].

STAT1 activated LINC01160 and potently enhanced malignancy phenotype of nasopharyngeal carcinoma cells [21].

STAT1 transcriptionally activates ARRDC1-AS1 (ARRDC1 antisense RNA 1) and promotes carcinogenesis. ARRDC1-AS1 acted as a sponge for miR-432-5p and relieved inhibitory effects of miR-432-5p on PRMT5. ARRDC1-AS1 knockdown severely impaired the migratory and invasive abilities of U251 and LN229 cells [22].

Wnt/β-catenin pathway pays role in carcinogenesis [23,24]. STAT1 mediated upregulation of lncRNAs efficiently promoted Wnt/β-Catenin signaling in ovarian cancer and glioma [25,26]. STAT1 transcriptionally upregulates LINC00467 in lung cancer cells. LINC00467 works synchronously with EZH2 and epigenetically inactivates Dickkopf-1 (DKK1). DKK1 is an inhibitor of Wnt signaling pathway and suppresses cancer progression. However, LINC00467 promotes Wnt/β-catenin signaling and fuels carcinogenesis [27].

4. Interaction of STAT1 with lncRNAs in transcriptional regulation of target gene networks

TPT1-AS1 recruits STAT1 to transcriptionally repress APC (Adenomatous polyposis coli) (Fig. 2). APC has the ability to reduce cancer stemness of colorectal cancer stem cells. However, STAT1-mediated transcriptional repression of APC potently enhanced the stemness of colorectal cancer stem cells by the activation of Wnt/β-catenin [28].

lncNBAT1 interacts with STAT1 to prevent its enrichment at the promoter region of APOBEC3A (Apolipoprotein B mRNA editing enzyme catalytic subunit-3A) thus inhibiting the expression of APOBEC3A (Fig. 2). Downregulation of APOBEC3A efficiently induced resistance against methotrexate in DLBCL cells. There was a considerable increase in the methotrexate sensitivity and tumor shrinkage in mice inoculated with lncNBAT1-knockdown HBX-expressing SUDHL-4 cells [29].

RUNX1-IT1, an oncogenic lncRNA is involved in cancer progression [30]. Nucleosome remodeling and histone deacetylase (NuRD) complex is involved in the regulation of gene expression. GPX1 (Glutathione Peroxidase 1) is negatively regulated by STAT1. STAT1 works with RUNX1-IT1/NuRD complex and represses the expression of GPX1. Decrease in the levels of GPX1 leads to an increase in ROS levels to further activate NF-κB pathway. Use of entinostat (HDAC1 inhibitor) and antisense oligonucleotides against RUNX1-IT1 synergistically reduced the metastatic nodules in the abdomens of mice implanted with OVCA429 cells [31].

5. N6-methyladenosine (m6A) of LncRNAs and regulation of JAK/STAT signaling

N6-methyladenosine (m6A) is the most common mRNA modification. The discovery of m6A, a predominantly internal epigenetic modification of mRNAs, heralded the breakthroughs in the field of epitranscriptomics. Studies have shown that deletion of the m6A 'writer' METTL3 or 'reader' YTHDF2 resulted in a significant increase in the stability of mRNA transcript. RFPL1S-202 has been shown to interact with DDX3X protein. DDX3X interacted with m6A RNA demethylase ALKBH5 and subsequently caused the removal of the m6A modification (Fig. 3). ALKBH5 depletion reduced the production of nascent IFNB1 mRNA while depletion of m6A writer METTL14 exerted opposite effects. m6A levels of IFNB1 were found to be greatly increased in DDX3X-silenced SKOV3 cells. Secretion of IFNβ was also noticed to be decreased significantly in DDX3X-silenced SKOV3 cells [32]. RFPL1S-202 inhibited the metastasis by reducing the levels of p-STAT1 and IFN inducible genes.

Intraperitoneal injections of lipopolysaccharides enhanced tumor growth in orthotopic liver cancer models. Expression levels of PD-1 and PD-L1 were noted to be upregulated in hepatoma tissues of mice injected with lipopolysaccharides [33]. PD-L1 is expressed on the surface of tumor cells and tumor-associated-macrophages. PD-L1 binds to PD-1 on activated cytotoxic T lymphocytes and inhibits the activation of T cells. In METTL3/14 target mRNAs and lncRNAs with HuR-binding sites, when an m6A base is positioned in closer position to the HuR-binding site, m6A promotes the binding of ELAVL1/HuR to the mRNA or lncRNA. Growing evidence suggested that METTL3 played a central role in introducing m6A onto nascent transcripts co-transcriptionally, while METTL14 supported the binding of METTL3 to the target mRNAs. METTL14 overexpression caused a significant rise in the levels of PD-L1 in Huh7 cells. m6A methylation is introduced by methyltransferases and ELAVL1/HuR stabilizes m6A-containing lncRNAs. ELAVL1/HuR provides stability to MIR155HG. MIR155HG interfered with miR-223-mediated inhibition of STAT1. Consequently, STAT1 moves into the nucleus and stimulates the expression of PD-L1 [33].

5.1. LncRNAs mediate stability of oncogenic STAT1

CUL4A (Cullin 4A) is an E3 ubiquitin ligase. CUL4A ubiquitinated STAT1 and tagged it for degradation. LncRNA AIRN interfered with CUL4A-mediated ubiquitination of STAT1 in HCC cells (Fig. 3). Tumor growth was found to be significantly reduced in mice inoculated subcutaneously with AIRN-silenced-HepG2 cells [34].

SOCS1 triggers ubiquitin-proteasome-mediated degradation of STAT1. LINC00669 stabilizes STAT1 by blockade of SOCS1 mediated ubiquitination and degradation (Fig. 3). Importantly, accelerated degradation of STAT1 was noted in LINC00669-depleted cells. Tumor growth regression reported in mice xenografted with LINC00669-deficient CNE-2 cells was reversed completely in the recipient experimental mice injected with SOCS1 and LINC00669 double knockdown cells [35].

PMSB8-AS1 is involved in the progression of cancer [36]. PMSB8-AS1 interfered with miR-382-3p-mediated targeting of STAT1. Evidence suggests that STAT1 transcriptionally upregulates PD-L1. PSMB8-AS1 significantly promoted the apoptotic death of $CD8^+$ T cells and decreased the activity of $CD8^+$ T cells [37].

PTPN11 is a ubiquitous protein tyrosine phosphatase that dephosphorylates different proteins in cell signaling cascades. PRPF19 (Pre-mRNA-processing factor 19), a U-box-containing E3 ubiquitin ligase forms a complex with its specific substrates for ubiquitination. LINC00673 promotes the association between PRPF19 and PTPN11 and enhances PRPF19-mediated ubiquitination and degradation of PTPN11. LINC00673 overexpression increases the levels of p-STAT1, as well as STAT1-dependent increase in the levels of interferon-response genes. However, ectopic expression of PTPN11 severely abrogated STAT1-mediated upregulation of target genes. Growth rates of tumor xenografts were found to be considerably reduced in mice inoculated with LINC00673-overexpressing-BXPC-3 and CFPAC-1 cells [38].

6. Double-edge role of STAT1 signaling in the regulation of immunosuppressive tumor microenvironment

Evidence suggests that different oncogenic lncRNAs are involved in the transformation of macrophages into M2-phenotype by inactivation of STAT1-driven signaling.

PVT1, an oncogenic lncRNA efficiently induces immunosuppressive microenvironment. PVT1 transcriptionally downregulates STAT1 but simultaneously enhances the expression of CX3CL1 in U87 and U251 glioblastoma cells. CX3CL1 induced transformation of macrophages into M2 phenotype [39]. Pharmacological targeting of PVT1 will be helpful in inhibition of M2 macrophages in the immunosuppressive microenvironment.

LncRNA-HOXC-AS2 is also involved in the transformation of macrophages to M2 phenotype. HOXC-AS2 interacts with STAT1 and impairs STAT1 mediated conversion of M2 macrophages to M1 phenotype. SOCS1 is a negative regulator of STAT1 signaling. SOCS1 is expressed in HOXC-AS2-expressing macrophages. However, there is a decline in the levels of SOCS1 in HOXC-AS2-silenced macrophages [40].

It is important to mention that apart from unique ability of STAT1 signaling in the inhibition of polarization of macrophages to M2 phenotype, certain clues have emerged which highlight central role of STAT1 in polarization of macrophages to M2 phenotype.

Studies have shown that different types of cells are present within the tumor microenvironment. These include the antitumor CTLs and TH1 cells and the pro-tumor type 2 helper T (TH2) and regulatory T (Treg) cells. CTLs and TH1 cells are more sensitive to tumor-mediated AICD (activation induced cell death) as compared to TH2 and Treg cells. Evident increase in susceptibility of CTLs and TH1 cells to undergo AICD is mainly because of overexpression of NKILA (NFκB-interacting lncRNAs). STAT1 plays oncogenic role and simulates the expression of NKILA. Therefore, NKILA silencing in CTLs or TH1 cells protects them from AICD and increases their accumulation in tumor tissues in immunocompromised mice [41].

7. Interplay between lncRNAs and STAT2 promotes carcinogenesis

STAT2 has an oncogenic role in different cancers. As there is limited evidence about the interplay between STAT2 and lncRNAs, we have presented an overview of oncogenic role of lncRNAs and STAT2 in different cancers.

DLX6-AS1 sponges away miR-506-3p and potentiates the expression of STAT2. There is a considerable retrogression of the tumor mass in mice subcutaneously inoculated with DLX6-AS1-silenced-SK-N-SH cells [42].

STAT2 transcriptionally upregulates linc02231 and promotes cancer progression. Linc02231 interferes with miR-939-5p-mediated targeting of hnRNPA1. Mechanistically, hnRNPA1 prevents the maturation of ANGPTL4 (angiopoietin-like protein 4) in colorectal cancer cells. There was a significant shrinkage in the transplanted tumor tissues after linc02231 knockdown [43].

8. Regulation of STAT3-driven signaling by LncRNAs

B cells are antigen-presenting cells and play significant role in tumor microenvironment. B cells have been found to frequently overexpress PD-L1. HOTAIR was found to be enriched in the exosomes secreted by colorectal cancer cells. HOTAIR was transported to the B cells through exosomal uptake. HOTAIR upregulates PD-L1 expression in B cells mainly through inhibition of ubiquitin-mediated degradation of PKM2. PKM2 increases STAT3-mediated transcriptional activation of PD-L1.

There is an evident increment in the tumor-infiltrating PD-L1+ B cells in xenografted mice [44]. HOTAIR-overexpressing PD-L1+ B cells efficiently induce exhaustion of $CD8^+$ T cells and promote tumor progression. Overall, STAT3-mediated upregulation of PD-L1 in B cells is necessary for the inactivation and exhaustion of $CD8^+$ T cells.

AC093818.1 is involved in transcriptional upregulation of PDK1 by directing the recruitment of transcriptional factors. AC093818.1 binds to transcriptional factors STAT3 and SP1 and promotes transcriptional activation of PDK1.There was a significant increase in the levels of vimentin, MMP-2, and MMP-9 in the liver and lung tissues of experimental mice implanted with AC093818.1-overexpressing-MKN28 cells [45].

NCAPD3 is one of the non-SMC regulatory subunits of Condensin II and promotes the progression of prostate cancer. Levels of STAT3 and E2F1 were found to be enhanced in NCAPD3-expressing prostate cancer cells. STAT3 and E2F1 stimulate the expression of EZH2 whereas, STAT3 transcriptionally activates MALAT1 in prostate cancer cells. NCAPD3 overexpression fuels the growth of prostate cancer cells, while NCAPD3 knockdown impairs the proliferation and invasion of prostate cancer cells [46].

MALAT1 works synchronously with EZH2 and induces trimethylation on histone H3 lysine27 (H3K27me3) for transcriptional repression of VHL. Importantly, levels of EZH2 and H3K27me3 were noticed to be suppressed in MALAT1-silenced HNSCC cells. Moreover, levels of functionally active STAT3 and AKT were found to be enhanced in EZH2-expressing cancer cells. VHL targeted β-catenin and NF-κB for degradation. Intratumoral injections of MALAT1 siRNAs efficiently induces regression of the tumors in mice inoculated with SCC15 cells. Furthermore, targeted inhibition of MALAT1 markedly impaired the lymph node metastases of xenografts. Subsequently, intratumorally injected siMALAT1 severely suppressed the levels of MALAT1, EZH2, p-AKT and p-STAT3 in SCC15 xenografts [47]. Leucine-rich pentatricopeptide repeat-containing (LRPPRC), an RNA-binding protein has been found to be frequently overexpressed in many tumors. DANCR efficiently stabilizes IL-11, CCND1 and PLAU mRNAs in an LRPPRC-dependent manner. Levels of p-JAK2 and p-STAT3 were reported to be suppressed in DANCR-knockdown cancer cells, whereas these levels were reported to be increased in DANCR-overexpressing cancer cells. Additionally, LRPPRC knockdown abrogated STAT3-driven downstream pathway activated by overexpression of DANCR in bladder cancer cells. Essentially, the volume of popliteal lymph nodes was palpably smaller in DANCR-silenced- rodent models but significantly larger in size in DANCR-overexpressing rodent models [48]. Collectively, these findings indicated that DANCR potently enhanced the stability of oncogenes mainly through LRPPRC. Moreover, DANCR activated JAK2/STAT3 pathway for the stimulation of MMP9. Therefore, DANCR induced activation of different pathways for progression of cancer.

TINCR simulates the expression of EGFR by acting as a ceRNA to sponge miR-503-5p. TINCR also works synchronously with DNMT1 and epigenetically inactivates miR-503-5p. Furthermore, TINCR activated JAK2/STAT3 pathway in breast cancer cells. STAT3 thus transcriptionally upregulates TINCR and promotes breast cancer. Use of EGFR-inhibitor (gefitinib) combinatorially and synergistically impaired tumor growth in mice inoculated with TINCR knockdown-4T1 cancer cells [49].

9. STAT3 regulates the expression of tumor suppressor and oncogenic lncRNAs

There is a gradual increase in our understanding about STAT3-regulated lncRNAs and how these lncRNAs further modulate target genes by working with epigenetics-associated machinery as well as serving as sponges for miRNAs.

GAS5, an lncRNA is transcriptionally upregulated by STAT3. PDCD4 (Programmed Cell Death 4) is negatively regulated by miR-21 in cervical cancer cells. GAS5 impairs miR-21-mediated targeting of PDCD4. Tumors derived from GAS5 overexpressing-SiHa cells were smaller in size and importantly cisplatin administration further reduced the tumor volume [50].

STAT3-induced upregulation of lncRNA CASC11 promotes the migration, invasion and metastasis of hepatocellular carcinoma cells. CASC11 works synchronously with EZH2 and epigenetically represses PTEN in HCC cells. As PTEN negatively regulates PI3K/AKT signaling in HCC cells, therefore downregulation of PTEN leads to activation of PI3K/AKT signaling [51].

STAT3 transcriptionally activates HOXD-AS1. HOXD-AS1 knockdown significantly inhibited migratory and invasive properties of HCC cells. HOXD-AS1 blocks miR-130a-3p-mediated targeting of SOX4 in HCC cells. Consequently, SOX4 triggers the expression of EZH2 and MMP2. There was a considerable reduction in the number of metastatic lung nodules in mice inoculated with HOXD-AS1-knockdown Huh7 cells [52].

10. LncRNAs activate STAT3 signaling and induce polarization of M2 macrophages

linc00514 overexpressing breast cancer cells induced an increase in the levels of CD163 and CD206 in THP-1 derived macrophages. linc00514 promotes phosphorylation of STAT3 and consequently, STAT3 mediates upregulation of Jagged1. Essentially, Jagged1 is a ligand for Notch receptor mediated signaling. Moreover, Notch signaling has been shown to stimulate the expression of interleukin-6. Accordingly, it was shown that activation of Notch signaling induced an increase in the secretion of interleukin 4 and interleukin-6 from breast cancer cells [53]. Collectively, these findings clearly suggested that linc00514 overexpressing breast cancer cells not only gained metastasizing potential but also induced polarization of macrophages to M2 phenotype.

KLHDC7B-DT, another long non-coding RNA has been shown to trigger the expression and secretion of interleukin-6. Thus, interleukin-6 interacts with its receptor and induces intracellular activation of STAT3 signaling in pancreatic cancer cells. Moreover, interleukin-6 also activates STAT3 signaling in macrophages and induces M2 polarization [54].

Exosomes are highly efficient delivery vesicles. Exosomes are loaded with different proteins and non-coding RNAs and demonstrated extraordinary ability to transform recipient cells [55,56]. Exosomes secreted by cancer cells are loaded with lncRNAs. These exosomes are taken up by macrophages and payload is transferred to the macrophages.

HEIH, an oncogenic lncRNA is rich in exosomes secreted by HCC cells. HEIH-loaded exosomes are taken up by macrophages. HEIH acts as a sponge and interferes with miR-98-5p-mediated targeting of STAT3. Resultantly, HEIH mediated increase in STAT3 is necessary for the polarization of macrophages to M2 phenotype [57].

Exosomes secreted by clear cell renal cell carcinoma (ccRCC) are rich in AP000439.2 exosomes loaded with AP000439.2 are taken up by macrophages. AP000439.2 interacts with STAT3 in the nucleus and activates it. Additionally, NF-κB pathway was also found to be activated in AP000439.2-overexpressing macrophages. AP000439.2-depleted exosomes reduced tumor growth primarily through repolarization of macrophages from M2 to M1 phenotype [58]. LncARSR-loaded exosomes secreted by RCC cells induced M2 phenotype. miR-34/miR-449 mediated targeting of STAT3 prevented polarization of macrophages. However, LncARSR interferes with miR-34/miR-449-mediated targeting of STAT3 in macrophages and induces polarization of macrophages to M2 phenotype [59]. PTPRD (Protein Tyrosine Phosphatase Receptor type-D) induce de-phosphorylation of STAT3 in macrophages. miR-19b-3p-loaded exosomes are taken up by macrophages and induce polarization. miR-19b-3p directly targets PTPRD and triggers the activation of STAT3. Functionally active STAT3 stimulates the expression of LINC00273. Moreover, LINC00273-loaded exosomes secreted by

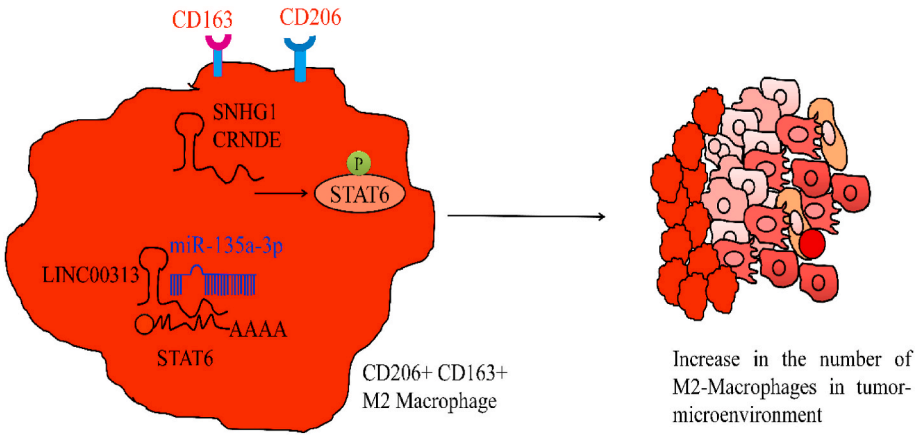

Fig. 4. Oncogenic lncRNAs promote the polarization of M2-macrophages. LINC00313 interfered with miR-135a-3p-mediated targeting of STAT6. Moreover, SNHG1 and CRNDE promote STAT6 activation.

macrophages are taken up by lung cancer cells. In lung cancer cells, LINC00273 promotes NEDD4-mediated ubiquitination and degradation of LATS2. Loss of LATS2 prevents YAP phosphorylation and degradation. Therefore, YAP accumulates in the nucleus and transcriptionally upregulates RBMX. RBMX is involved in the exosomal packaging of miR-19b-3p into LUAD cell-derived exosomes [60].

As c-Myc transcriptionally upregulates interleukin-6 in gastric cancer cells, LOC339059 structurally interacts with c-Myc and downregulates interleukin-6. Decrease in the levels of interleukin-6 also exerts inhibitory effects on interleukin-mediated JAK/STAT3 signaling and consequent suppression of PD-L1. Moreover, polarization of macrophages into M2 phenotype was also effectively reduced [61].

Exosomes secreted by pancreatic cancer cells also induce polarization of macrophages to M2 phenotype. FGD5-AS1 promotes invasion and metastasizing properties of pancreatic cancer cells when co-cultured with macrophages [62].

11. Regulation of oncogenic STAT5 by LncRNAs

In this section, we have summarized how tumor suppressor and oncogenic lncRNAs regulate the oncogenic activity of STAT3.

Oncogenic LncRNAs: SALIS (Suppression of Apoptosis by LINC01186 Interacting with STAT5A) is an oncogenic lncRNA. SALIS interacted with STAT5a and caused transcriptional repression of caspase-7 and IGFBP3. SALIS overexpression considerably promoted tumor growth and triggered the formation of palpable tumor xenografts [63].

TLX1NB (T cell leukemia homeobox 1 neighbor) also promoted colorectal cancer. TLX1NB overexpression enhanced the phosphorylation of STAT5A but TLX1NB knockdown suppressed the phosphorylation of STAT5A. Moreover, the inhibition of STAT5A phosphorylation led to reversal of TLX1NB overexpression-induced increase in the invasive and migratory properties of HCT116 cells. There was an evident reduction in pulmonary metastatic nodules in experimental mice injected with TLX1NB-silenced-SW620 cells. Levels of p-STAT5A were found to be suppressed in the metastatic nodules from mice injected with TLX1NB-silenced-SW620 cells [64].

lncRNA PVT1 stabilizes STAT5B by suppression of the ubiquitination and enhances STAT5B-mediated transcriptional gene networks during carcinogenesis. In the nucleus, STAT5B transcriptionally activates lncRNA PVT1 and promotes tumor growth [65].

STAT5A transcriptionally upregulates LINC01198. Moreover, LINC01198 interacted with DGCR8 and stabilized DGCR8. Moreover, DGCR8 produces an oncogenic miRNA profile that promotes proliferation of glioma cells [66].

LINC01410 is an oncogenic lncRNA and physically interacts with STAT5 in gallbladder cancer cells. STAT5 activates oncogenic ErbB signaling cascade. There is a considerable increase in the metastatic nodules on the surface of livers and lungs of mice intrasplenically injected with LINC01410 over-expressing GBC-SD cells [67].

Tumor suppressor LncRNAs: Imatinib induced apoptotic death in lncRNA-IUR1-expressing-K562 cells. LncRNA-IUR1 inhibits STAT5-mediated transcriptional activation of GATA3. Furthermore, GATA3 promotes transformation of leukemic cells by driving MYC activity. There was a notable increase in the tumor development in mice inoculated with lncRNA-IUR1 knockdown-cells. Depletion of murine lncRNA-IUR1 in ABL-transformed cells promoted the leukemogenesis in experimental models [68].

WDFY3-AS2 interfered with miR-2355-5p-mediated targeting of SOCS2. Importantly, SOCS2 inactivated JAK2/STAT5 signalling pathway and suppressed the proliferation and invasive potential of EC9706 and TE1 cells [69].

12. Oncogenic lncRNAs activate STAT6 signaling and reshape tumor microenvironment by polarization of macrophages

STAT6 stimulates the expression of SOX21-AS1 and SOX21. Essentially, SOX21-AS1 interferes with miR-576-5p-mediated targeting of SOX21 and promotes pancreatic cancer. USP10 is a deubiquitinase and potently deubiquitinates different proteins. SOX21-AS1 works synchronously with USP10 and stabilizes SOX21 by deubiquitination. There is a remarkable impairment in the growth rate of the tumor mass in mice subcutaneously inoculated with SOX21-AS1-silenced-PANC-1 and SW1990 cancer cells [70].

Exosomal secretions from cancer cells promoted the polarization of M2-macrophages. LINC00313-loaded exosomes secreted by cancer cells are taken up by macrophages. LINC00313 potentiates the expression of STAT6 mainly through the blockade of miR-135a-3p-mediated targeting of STAT6 (Fig. 4). LINC00313 knockdown caused an increase in the levels of M1 markers (iNOS and CD86) and decreased the levels of M2 markers (CD206 and CD163). The number of CD206+, CD163+ M2 cells was found to be reduced in LINC00313 knockdown cells. Intra-tumoral injections of GW4869 (pharmacological inhibitor of exosomal release) efficiently impaired tumor growth. Importantly, LINC00313 overexpression stimulated tumorigenesis, while LINC00313 knockdown suppressed tumor growth [71].

LncRNA-SNHG1 has a central role in the polarization of M2 macrophages. Intriguingly, STAT6 signaling centrally steers the polarization of macrophages to M2 phenotype. Phosphorylated levels of STAT6 were found to be reduced in SNHG1-silenced cells (Fig. 4). Inhibition of lncRNA-SNHG1 led to significant reduction in the number of F4/80+CD206+ macrophages. Furthermore, silencing of lncRNA-SNHG1 in

the macrophages inhibited pro-angiogenic and pro-tumorigenic effects of M2-like polarized macrophages [72].

CRNDE overexpression induces an increase in the level of CD163, while downregulation of CRNDE causes significant reduction in the levels of CD163. JAK1/STAT6 signaling induces M2 polarization of macrophages. Notably, CRNDE overexpression enhances the levels of JAK1 and STAT6 and promotes the phosphorylation of STAT6 (Fig. 4). Moreover, levels of angiogenesis-related proteins (VEGFR2, NOTCH1 and Dll4) were also noticed to be upregulated in HUVECs co-cultured with CRNDE-overexpressing macrophages [73]. Collectively, these findings indicated that CRNDE not only promoted M2 polarization but also stimulated the proliferation of a network of tumor blood vessels in tumor-bearing mice. Moreover, lncRNA-MM2P also promotes macrophage-mediated tumorigenesis, tumor growth and tumor angiogenesis. Knockdown of lncRNA-MM2P inhibited STAT6-induced signaling and suppressed polarization of macrophages to M2 phenotype [74].

13. Interplay between JAK/STAT signaling and circular RNAs

With the rapid breakthroughs in RNA sequencing technologies and bioinformatics, the true abundance of circRNAs was discovered. In 2012, an unexpectedly high frequency of human genes was reported to express “scrambled exons” resulting in circular RNA isoforms [75–86].

14. Regulation of STAT1-mediated control of PD-L1/PD-1 signaling

Cancer cells treacherously escape T-cell-directed cytotoxicities by manipulating the inhibitory programmed cell-death protein 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) immune checkpoints. Importantly, therapeutic antibodies that have been designed against PD-1/PD-L1 axis induce clinically durable responses against different types of cancers. Pioneering studies have improved our understanding about the mechanisms regulating the expression of PD-L1/PD-1 at the transcriptional, post-transcriptional, translational and post-translational levels in cancers. Therefore, antagonistic antibodies designed against inhibitory immune-checkpoint receptor PD-1 or its ligand PD-L1 are currently being used for the treatment of different cancer types and multipronged approaches will synergistically and substantially improve the survival of cancer patients.

IFNγ induces the expression of PD-L1 in HNSCC. Importantly, activities of JAK2 and STAT1 were noted to be enhanced in IFNγ-treated cancer cells. Moreover, circ_0000052 impaired miR-382-3p-mediated targeting of PD-L1. Essentially, PD-L1 was decreased significantly in miR-382-3p-overexpressing cancer cells and circ_0000052 depleted cancer cells [87].

15. Regulation of oncogenic STAT1 by circular RNAs

Exosomes derived from cancer cells are rich in non-coding RNAs. Ovarian cancer-derived exosomes potently promoted the angiogenesis in HUVECs. Exosomes derived from SKOV3 and OVCAR3 cancer cells efficiently enhanced VEGFA expression and angiogenesis. Exosomes rich in circNFIX levels were taken up by HUVECs and consequently stimulated the levels of TRIM44, p-JAK, and p-STAT1. miR-518a-3p directly targeted TRIM44 but circNFIX impaired the tumor suppressive effects of miR-518a-3p. Importantly, TRIM44 overexpression increased the levels of JAK/STAT and VEGFA whereas, inactivation of JAK/STAT pathway led to suppression of VEGFA [88].

circRPPH1 acted as an oncogene and inhibited miR-512-5p-mediated targeting of STAT1. Tumor growth was found to be considerably enhanced in mice xenografted with circRPPH1-overexpressing-MDA-MB-231 cancer cells [89].

miR-195-5p impeded growth of the tumor mass in animal models, whereas upregulation of circRNA NRIP1 effectively promoted tumorigenesis in xenografted mice. CircRNA NRIP1 activated JAK/STAT pathway by interfering with miR-195-5p-targeting activity in papillary thyroid carcinoma cells and tumor tissues. Importantly, levels of p-JAK2 and p-STAT1 were noted to be markedly suppressed in miR-195-5p overexpressing papillary thyroid carcinoma cells and tumor xenografts [90].

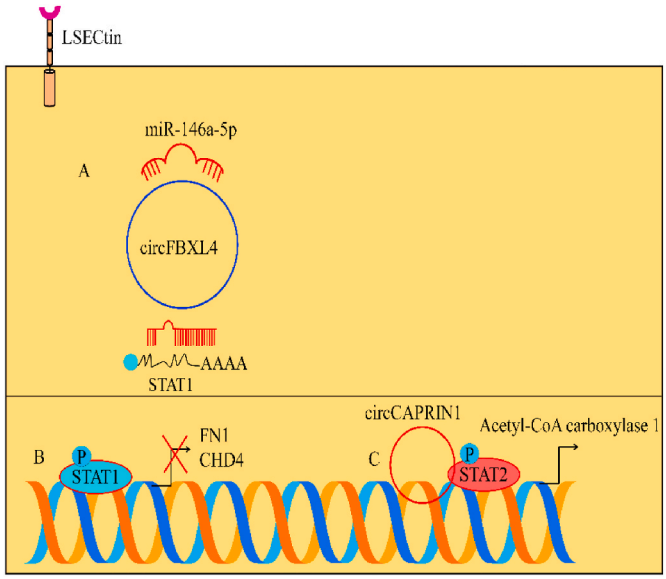

Fig. 5. (A–B) LSECtin reduces the levels of STAT1. CircFBXL4 interfered with miR-146a-5p-mediated targeting of STAT1. LSECtin reduced the levels of CircFBXL4 and STAT1. STAT1 suppression led to an increase in the levels of FN1 and CHD4. (C) circCAPRIN1 interacts with STAT2 and transcriptionally upregulates ACC1.

16. Tumor suppressive role of STAT1

LSECtin (Liver and lymph node sinusoidal endothelial cell C-type lectin) is a 40 kDa type II transmembrane protein. Infiltration of gastric cancer cells occurs through surrounding tissues to lymphatic vessels and reach the lymph nodes during lymphatic metastasis. LSECtin expressed on the surface of lymphatic sinus endothelial cells (LSECs) promotes metastasis of GC cells. Migration of gastric cancer cells was inhibited by LSECtin-blocking antibodies. FN1 (Fibronectin 1) and CHD4 (Chromodomain Helicase DNA Binding Protein 4) have tumor promoting properties. LSECtin triggered the malignant and lymphatic metastases of gastric cancer cells through upregulation of FN1 and CHD4 by interfering with circFBXL4-mediated sequestration of miR-146a-5p. Consequently, blockade of circFBXL4-mediated sponging effects on miR-146a-5p-led to reduction in the levels of STAT1 and subsequent upregulation of FN1 and CHD4 (Fig. 5) [91]. Collectively, these findings indicated that migration and invasion of gastric cancer cells mediated by LSECtin was impaired significantly by overexpression of circFBXL4 or miR-146a-5p depletion. Tumor suppressive circFBXL4 interferes with miR-146a-5p-mediated targeting of STAT1. Consequently, STAT1 moves into the nucleus and transcriptionally represses FN1 and CHD4.

17. Circular RNAs work with STAT2 and promote carcinogenesis

circCAPRIN1 interacted with STAT2 and transcriptionally upregulated acetyl-CoA carboxylase 1 (ACC1) expression (Fig. 5). circCAPRIN1 overexpression resulted in enhanced production of the lipid droplets. circCAPRIN1 knockdown impaired the metastasizing properties of colorectal cancer cells [92].

18. Regulation of oncogenic STAT3 by circular RNAs

CircRPPH1 interfered with miR-296-5p-mediated targeting of STAT3 and promoted the proliferation and invasion of bladder cancer cells. Interaction between circRPPH1 and FUS promoted the nuclear accumulation of p-STAT3. There was a significant reduction in the tumor mass and pulmonary metastasis in different animal models injected with CircRPPH1-silenced bladder cancer cells [93].

CircABCA5 not only interacts with SPI1 for the maintenance of its stability but also promotes its nuclear translocation. SPI1 knockdown severely abolished circABCA5-induced malignancy of gastric cancer cells. SPI1 transcriptionally upregulated IL6 and activated IL6/JAK2/STAT3 pathway in gastric cancer cells.EIF4A3 overexpression upregulated circABCA5 expression, while EIF4A3 knockdown downregulated circABCA5 expression. Half-life of circABCA5 was significantly extended after EIF4A3 overexpression. Importantly, tumors derived from circABCA5-overexpressing MKN-45 cancer cells had a higher volume and weight, while circABCA5-knockdown SGC7901 cancer cells demonstrated remarkably reduced xenograft tumor volume and weight [94].

circFCHO2 promoted the activation of JAK1/STAT3 pathway by interfering with miR-194-5p-mediated targeting of JAK1. Pulmonary metastatic nodules were found to be remarkably reduced in the lung tissues of mice injected with circFCHO2-silenced cancer cells. Moreover, lymphatic metastasis was also reported to be suppressed in mice injected with circFCHO2-silenced cancer cells [95].

CircAHNAK inhibited miR-28-mediated targeting of EIF2B5 (Eukaryotic translation initiation factor 2B). Consequently, EIF2B5 inactivated JAK2/STAT3 pathway. On the contrary, EIF2B5 depletion promotes EMT and activation of JAK2/STAT3 pathway. Mice inoculated with CircAHNAK-silenced cancer cells had the largest tumor sizes and heaviest tumor weights. However, overexpression of circAHNAK retarded tumor growth [96].

Exosomes derived from renal cell carcinoma cells are rich in circSAFB2. These exosomes are taken up by macrophages. Exosomally transmitted circSAFB2 re-shaped signaling landscape in macrophages via regulation of miR-620/JAK1/STAT3 axis. miR-620 is a tumor suppressor and inhibits the expression of JAK1. Exosomally transferred circSAFB2 induced polarization of M2-macrophages by blockade of miRNA-620-mediated targeting of JAK1. JAK1/STAT3 signaling was increased in circSAFB2-overexpressing macrophages. Essentially, co-culture of ACHN cells with macrophages treated with circSAFB2-silenced exosomes demonstrated significant reduction in the metastasizing ability of cancer cells. ACHN cells co-injected with the macrophages pre-treated with circSAFB2-silenced exosomes and miRNA-620 inhibitors displayed evident increase in the metastatic spread [97].

Knockdown of Circ_0005320 resulted in inactivation of p-JAK2 and p-STAT3. However, Circ_0005320 knockdown mediated inactivation of JAK2/STAT3 pathway was re-activated by the introduction of miR-486-3p inhibitors or miR-637 inhibitors in SCC25 and CAL27 cells. Circ_0005320 knockdown caused significant shrinkage in the volume and weight of the tumor mass. Levels of circ_0005320 were reduced, while the levels of miR-637 and miR-486-3p were increased in the tumor tissues of mice inoculated with circ_0005320-silenced cancer cells [98].

circNOLC1 potentiates STAT3 expression by blockade of miR-365a-3p-mediated targeting of STAT3. STAT3 transcriptionally upregulated circNOLC1 and promoted carcinogenesis. Propofol inhibited STAT3-mediated upregulation of circNOLC1. miR-365a-3p mimics repressed sphere forming abilities of MDA-MB-231 and MDA-MB-468 cancer cells [99].

Cancer-associated fibroblasts (CAFs) actively contribute to malignant changes in the stromal microenvironment primarily through extensive secretions of extracellular matrix around tumor cells as well as production of the trophic factors thus promoting formation of the pro-tumorigenic niches. Sibrotuzumab (a humanized monoclonal antibody) previously attracted the attention of researchers because of its ability to effectively target cancer-associated fibroblasts in colorectal cancer patients. However, it is relevant to mention that the unfavorable findings of a clinical trial (phase II) of sibrotuzumab led to the termination of further analysis associated with this inhibitor. It was noted that normal tissue-associated fibroblasts (NFs) transduced with CircCUL2 caused significant increase in the proliferation and invasive abilities of MiaPaCa-2 and PANC-1 cells [100]. Findings suggested that CircCUL2-expressing NFs demonstrated CAF pro-tumorigenic properties, but circCUL2-silenced CAFs failed to exert pro-tumorigenic effects. There was an evident increase in p-STAT3 levels in MiaPaCa-2 and PANC-1 cells treated with conditioned media from circCUL2-expressing-NFs. Treatment of conditioned media from circCUL2-expressing-NFs with neutralizing antibodies against interleukin-6 severely abolished the pro-tumorigenic features of circCUL2-expressing-NFs. Higher metastatic incidence and pulmonary metastatic foci were present in mice co-injected with circCUL2-expressing NFs and pancreatic cancer cells. Notably, addition of a neutralizing antibody against inteleukin-6 to the co-culture systems of circCUL2-expressing NFs and pancreatic cancer cells restricted metastatic spread. Co-injections of MiaPaCa-2 or PANC-1 cells with circCUL2-expressing-NFs into the pancreas of rodent models were used for the analysis of metastasizing properties. Data indicated that circCUL2-transduced NFs potently enhanced the tumorigenesis. Moreover, higher abdominal metastasis rates were observed in mice co-injected with circCUL2-expressing NFs and pancreatic cancer cells, while treatment with anti-IL6 antibodies induced significant regression of the growth of tumor mass as well as abdominal metastasis. CircCUL2 inhibited miR-203a-3p-mediated targeting of MyD88. CircCUL2 overexpression or miRNA-203a-3p inhibition robustly augmented MyD88 and its downstream effectors NF-κB in NFs. Inhibition of MyD88 robustly reversed circCUL2 overexpression-induced increase in the secretion of interleukin-6 from NFs, whereas MyD88 overexpression led to reversal of circCUL2 inhibition-mediated decline in the secretion of interleukin-6 from CAFs [100].

Detailed mechanistic insights suggested that circFAT1 interacted with STAT3 in the cytoplasm and prevented SHP1-induced dephosphorylation of STAT3. STAT3 formed heterodimers with STAT1 and prevented the homodimerization of STAT1 and subsequent STAT1-mediated transcriptional regulation of target gene networks. CXCL9 and CXCL10 promote the accumulation of $CD8^+$ T lymphocytes within tumor tissues. Overall, knockdown of circFAT1 and STAT3 potently enhanced the binding of STAT1 to the promoter regions of CXCL9 and CXCL10. CircFAT1 inhibition and anti-PD1 strongly promoted the accumulation of a high frequency of $CD8^+$ T cells into the tumor microenvironment. Notably, Cytotoxic $CD8^+$ T cells generated Granzyme B to kill tumor cells. CircFAT1 inhibition and anti-PD1 also recruited more Granzyme B expressing $CD8^+$ T cells into tumor tissues. Importantly, tumor growth was reduced in tongues of immunocompetent C57BL/6J mice orthotopically transplanted with CircFAT1-silenced-MOC1 cells [101].

Xenotropic and polytropic retrovirus receptor 1 (XPR1) played central role in the activation of JAK/STAT pathway. circGNB1 blocked miR-515-5p and miR-582-3p-mediated inhibition of XPR1. XPR1 knockdown led to reduction in the levels of Interleukin-6, p-JAK2 and p-STAT3 in GSC27 and U87 cells. IGF2BP3 binds to and maintains the stability of circGNB1 in GSCs. Importantly, half-life of circGNB1 was found to be drastically shortened in IGF2BP3 knockdown GSCs [102].

Biogenesis of circARFGEF2 is considerably activated by alternative splicing factor QKI-5 in $KRAS^{G12D}$ pancreatic ductal adenocarcinoma cells, which recruits U2AF35 to promote spliceosomal assembly. Binding of QKI-5 to the QKI binding motifs and neighboring reverse complement sequences in intron 3 and 6 of ARFGEF2 pre-mRNA facilitated the biogenesis of circARFGEF2. Depletion of U2AF35 markedly hampered QKI-5-induced biogenesis of circARFGEF2. CRISPR/Cas9-mediated knockout of intron 3 and intron 6 in ARFGEF2 pre-mRNA severely hampered QKI-5-driven biogenesis of circARFGEF2. QKI-5

overexpression led to a significant increase in the lymph node metastasis of $KRAS^{G12D}$ PDAC cells, while circARFGEF2 inhibition remarkably reduced these effects. Moreover, circARFGEF2 inhibition significantly reduced the microlymphatic vessel density induced by QKI-5 overexpression. Additionally, QKI-5 greatly enhanced the metastatic spread of cancer cells to peripancreatic lymph nodes and increased the number of metastatic lymph nodes in orthotopically xenografted PDAC models. CircARFGEF2 interfered with miR-1205-mediated targeting of JAK2. CircARFGEF2 overexpression robustly supported the metastases of popliteal lymph nodes and increased the microlymphatic vessel densities, while inactivation of JAK2/STAT3 cascade reversed these effects. CircARFGEF2 promoted lymphangiogenesis and metastasis in $KRAS^{G12D}$ PDAC mainly through JAK2-STAT3 cascade [103].

circPAPD4 is a tumor suppressive circular RNA. ADAR1 (Adenosine deaminase acting on RNA) binds to the flanking regions of circPAPD4 in breast cancer cells and reduces its expression. ADAR1 knockdown causes an increase in the levels of circPAPD4. circPAPD4 inhibited miR-1269a-mediated targeting of CREBZF. CREBZF inhibited STAT3 dimerization and consequent STAT3-mediated transcriptional upregulation of ADAR1. Systemically administered CREBZF-mRNA-nanoparticles efficiently enhanced the expression of CREBZF and circPAPD4, reduced ADAR1 levels and significantly impaired the proliferation of CREBZF-null MCF-7 cancer cells [104].

Circ-HSP90A recruited USP30 for the de-ubiquitination and stability of HSP90A protein. There was an evident increase in STAT3-driven cascade in HSP90-overexpressing cancer cells. Circ-HSP90A triggered apoptotic death of $CD8^+$ T cells through PD-L1. circ-HSP90A interferes with miR-424-5p-mediated targeting of PD-L1. Co-culture of circ-HSP90A-depleted cancer cells and $CD8^+$ T cells caused notable decline in apoptotic death of $CD8^+$ T cells [105].

CCCTC binding factor (CTCF) has been reported to transcriptionally upregulate CircSPARC. Importantly, CircSPARC promoted the activation of JAK2 by increasing the expression of JAK2. CircSPARC interfered with miR-485-3p-mediated targeting of JAK2. CircSPARC interacted with FUS and promoted nuclear accumulation of STAT3. FUS knockdown led to suppression of nuclear transportation of STAT3 in circSPARC-overexpressing CRC cells. Importantly, there was a notable reduction in the number of metastatic foci on the surface of the lungs in rodent models injected with circSPARC-silenced-HCT116 cells [106].

circ-E2F3, an oncogenic circRNA inhibits miR-296-5p-mediated targeting of STAT3 in cervical cancer cells. Nuclear levels of STAT3 were found to be enhanced in circ-E2F3-overexpressing-cancer cells. STAT3 induced transcriptional upregulation of cyclin D1 in cancer cells. Tumor growth rates were noted to be markedly hampered in the experimental mice inoculated with Circ-E2F3-silenced-CaSki cells [107].

SIRT1, an NAD + -dependent deacetylase interacted with STAT3 in cancer cells. However, circPTPN22 induced dissociation of STAT3 and SIRT1. CircPTPN22 knockdown greatly enhanced the interaction between STAT3 and SIRT1. There was a substantial increment in the infiltration of $CD8^+$ cytotoxic T cells in the tumor tissues as well as $CD4^+$ T helper cells, γδT cells and natural killer cells in circPTPN22-silenced-group. Tumor progression was noted to be severely impaired in mice xenografted with CircPTPN22-silenced-BxPC-3 cancer cells [108].

CircATP5B blocked miR-185-5p-mediated targeting of HOXB5 in glioma stem cells. Expression of circATP5B was noted to be increased in SRSF1-overexpressing glioblastoma cells. HOXB5 transcriptionally upregulated the expression of SRSF1 (Serine and arginine rich splicing factor-1). HOXB5 also transcriptionally activated interleukin-6 in glioblastoma cells. Interleukin-6 triggered activation of JAK2/STAT3 pathway. There was a significant regression of the tumor mass in circATP5B knockdown group, miR-185-5p mimics group, and circATP5B knockdown combined with SRSF1-overexpressing groups. Whereas, weight of the tumor mass was noted to be increased in HOXB5-overexpressing groups, SRSF1 overexpressing-groups, circATP5B knockdown combined with HOXB5-overexpressing groups as well as miR-185-5p mimics combined with HOXB5-overexpressing groups [109].

circHIF1A not only increased NFIB expression via posttranscriptional regulation but also promoted nuclear translocation of NFIB. CircHIF1A interfered with miR-149-5p-mediated inhibition of NFIB. Importantly, NFIB activated AKT/STAT3 pathway in breast cancer cells. NFIB transcriptionally upregulates FUS in cancer cells. FUS binding region has been identified in 5′ end flanking region of intron of circHIF1A and consequently FUS efficiently promoted the biogenesis of circHIF1A. There is an increment in the tumor mass and metastasizing potential of cancer cells in mice injected with circHIF1A-overexpressing-MDA-MB-231 cancer cells [110].

CircRNA GGNBP2 principally derived from the GGNBP2 gene is upregulated by interleukin-6 [111]. DHX9 (DExH-Box Helicase 9) has a central role in the biogenesis and stability of cGGNBP2. cGGNBP2 encodes a 184 amino acid protein. Levels of cGGNBP2-184aa were found to be enhanced in cGGNBP2-overexpressing cells. Ectopic expression of cGGNBP2-184aa considerably promoted the phosphorylation at Tyrosine-705 of STAT3. There was a significant increase in nuclear accumulation of p-STAT3 (Tyrosine-705) in cGGNBP2-184aa-overexpressing cells. cGGNBP2-184aa knockdown resulted in the inhibition of IL-6-induced activation of JAK-STAT pathway. DNA binding domain of STAT3 interacts with cGGNBP2-184aa. cGGNBP2-184aa overexpression caused remarkable increase in intrahepatic metastases. Administration of STAT3 inhibitors abolished the role of cGGNBP2-184aa in the progression of intrahepatic cholangiocarcinoma. There was a rapid acceleration in tumor growth after administration of interleukin-6, however, treatment with interleukin-6 neutralizing antibodies led to regression of the tumors. Essentially, tumor growth was inhibited significantly by silencing of cGGNBP2 while overexpression of cGGNBP2 triggered acceleration in growth of the tumors. Notably, fewer intrahepatic metastatic foci were observed in the experimental mice orthotopically transplanted with cGGNBP2 knockdown cells into the left lobes of the liver. Whereas, overexpression of cGGNBP2 efficiently promoted intrahepatic metastasis. Likewise, loss of cGGNBP2 severely reduced the formation of pulmonary metastases, whereas ectopic expression of cGGNBP2 promoted pulmonary metastasis. Overall, cGGNBP2 encoded cGGNBP2-184aa facilitated intrahepatic cholangiocarcinoma [111].

Circ_0043800 (circ-STAT3) interfered with miR-29a/b/c-3p-mediated targeting of GLI2 and STAT3. GLI2 transcriptionally upregulates STAT3 and circ-STAT3. There was an evident regression of the tumor in mice xenografted with circ-STAT3-silenced-HB cells [112].

WDR5 is a core subunit of the human MLL1-4 histone H3K4 methyltransferase complexes. WDR5 and EP300/P300 (Histone acetyltransferase p300) bind to the promoter region of circSOD2. WDR5 enhanced H3K4me3 levels and p300 enhanced H3K27ac at the promoter region of circSOD2. circSOD2 inhibits miR-502-5p-mediated targeting of DNMT3a. DNMA3a increased promoter DNA methylation and epigenetically inactivated SOCS3. Epigenetic repression of SOCS3 led to an increase in the activation of JAK2/STAT3 pathway. Consequently, STAT3 transcriptionally upregulates circSOD2 and promotes carcinogenesis [113].

Circ-LRIG3 forms ternary complexes with STAT3 and EZH2 and promotes EZH2-mediated methylation of STAT3. Importantly, methylation of STAT3 further promoted phosphorylation of STAT3. Overexpression of circ-LRIG3 increased methylation and phosphorylation of STAT3, but these effects were almost blocked completely in cells treated with EZH2 siRNAs or selective EZH2 inhibitors. Furthermore, STAT3 transcriptionally upregulates Circ-LRIG3. Tumors derived from circ-LRIG3-overexpressing cancer cells were heavier in weight and larger in volume. Overexpression of circ-LRIG3 substantially enhanced the number of pulmonary metastatic nodules in experimental mice injected with circ-LRIG3-overexpressing HepG2 cells. However, treatment with STAT3 inhibitor (C188-9) interfered with circ-LRIG3 overexpression-mediated increase in the multiplicity of lung metastatic nodules [114].

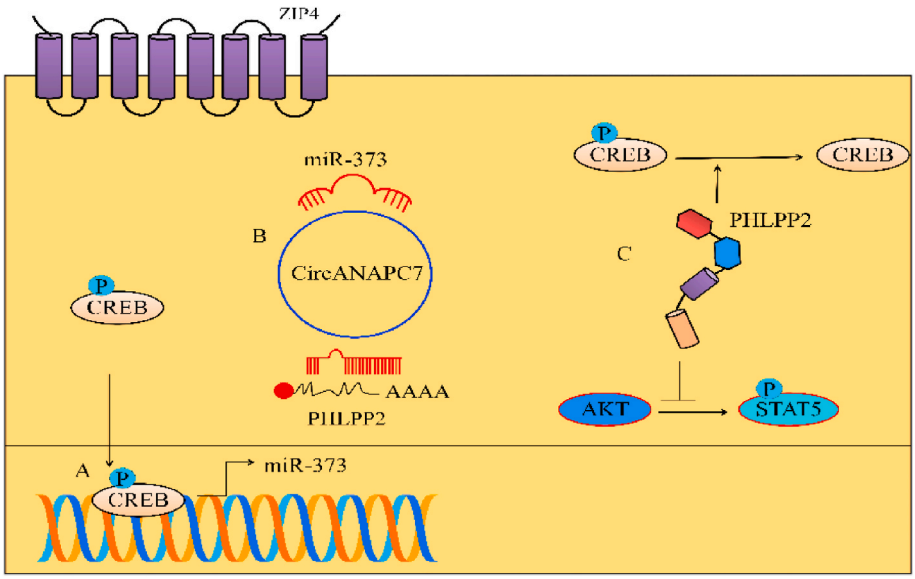

Fig. 6. ZIP4 is a plasma membrane transporter. ZIP4 activates zinc-dependent transcriptional factor CREB and stimulates CREB-mediated upregulation of miR-373. miR-373 directly targets PHLPP2. However, CircANAPC7 potentiates the expression of PHLPP2 by inhibition of miR-373-mediated targeting of PHLPP2. PHLPP2 is a phosphatase and removes phosphate group from CREB. PHLPP2 also inhibits AKT-mediated phosphorylation of STAT5.

Warburg effect (aerobic glycolysis) is a hallmark characteristic of cancer cells, in which they consume a large amount of glucose and promote aerobic glycolysis. HK2 is a central regulator in the Warburg effect and plays a key role in aerobic glycolysis. circCUL3 interfered with miR-515-5p-mediated targeting of STAT3. Furthermore, STAT3 transcriptionally stimulates the levels of hexokinase 2 (HK2). Tumors derived from circCUL3-silenced-SGC-7901 cell lines were smaller in size and the levels of STAT3 were found to be markedly reduced [115].

18.1. STAT5

circCDYL stimulates the expression of tumor suppressor PTEN mainly through inhibition of miR-105-5p-mediated targeting of PTEN. Resultantly, PTEN inactivates PI3K/AKT and JAK/STAT signaling cascades in colon cancer cells [116].

SOCS2 negatively regulates JAK2/STAT5 signaling in breast cancer cells. CircNOL10 acts as a molecular sponge for miR-767-5p and potentiates the expression of SOCS2. Tumors developed from CircNOL10-overexpressing-BT-549 cells were smaller in size [117].

miR-373 is regulated by ZIP4 primarily through a zinc-dependent transcriptional factor CREB. PHLPP2 induces dephosphorylation of CREB (Fig. 6). Moreover, PHLPP2 also inhibits AKT-mediated phosphorylation of STAT5. CircANAPC7-interfered with miR-373-mediated targeting of PHLPP2 (Fig. 6). CircANAPC7 overexpression significantly inhibited tumor growth in orthotopic xenograft rodent models [118].

circ_0086722 drives prostate cancer progression by blockade of miR-339-5p-mediated targeting of STAT5A. These findings indicated that miR-339-5p served as a tumor suppressor and inhibited prostate cancer progression [119].

circRNA ZNF292 promoted the activation of p-STAT3 and p-STAT5 in Huh-7 cells. Inhibition of circRNA ZNF292 induced apoptosis in HCC cells [120].

CircRNA transcriptome analysis holds great promise for refinement of our mechanistic understanding related to highly sophisticated complex biological systems, undoubtedly facilitating therapeutics for the prevention of carcinogenesis and metastasis.

19. Concluding remarks

In past few decades, molecular biologists and clinicians have characterized the cellular, molecular and immunological heterogeneities of different cancers. This landscape is sequentially changing with an increasingly sophisticated appreciation of heterogeneity that pharmaceutical targeting of JAK/STAT pathway will be advantageous in effective cancer therapy. Regulation of JAK/STAT pathway by non-coding RNAs has been shown to play a central role in reshaping the tumor microenvironment. This review gives a mechanistic overview of the interplay between non-coding RNAs and JAK/STAT pathway during different stages of cancer. LncRNAs regulated JAK/STAT pathway by different mechanisms and these interactions played a dominant role in the polarization of macrophages to M2 phenotype. Different STAT proteins have also been shown to control the expression of wide ranging lncRNAs. STAT signaling has also been shown to activate PD-L1/PD-1 signaling and consequent loss of the activity of natural killer cells and CD4+/CD8+ T cells. Hence, oncogenic activities of STAT proteins can be pharmaceutically targeted for the inhibition of carcinogenesis and metastasis in tumor-bearing mice. Furthermore, targeting of oncogenic lncRNAs and circRNAs can be valuable for activation of antitumor immunological responses within tumor microenvironment.

CRediT authorship contribution statement

Ammad Ahmad Farooqi: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Abay M. Shepetov:** Writing – review & editing, Writing – original draft, Data curation. **Venera Rakhmetova:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Zharilkassimov Ruslan:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Aigul Almabayeva:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Saniya Saussakova:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Kaini Baigonova:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Kainish Baimaganbetova:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Kalmakhanov Sundetgali:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Gulnara Kapanova:** Formal analysis, Investigation, Writing – review & editing.

Declaration of competing interest

The Authors declare that they do not have any conflict of interest.

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