

LncRNAs as Regulators of the STAT3 Signaling Pathway in Cancer

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Abstract

Cancer is a disorder of growth control and cell differentiation caused by the abnormal expression of multiple genes. Long non-coding RNAs (lncRNAs) are critical regulators of numerous biological processes, especially in the development of diseases. Abnormal expression of some lncRNAs causes disease, especially cancer, and disease resistance. lncRNAs may act as oncogenes or tumor suppressors and can be used as diagnostic or prognostic markers, and may also have therapeutic potential in cancer treatment. Studies show that many lncRNAs have different effects on cell activity by regulating multiple downstream targets, such as signaling pathways that are signal transducers and activators of transcription 3 (STAT3). The STAT3 signaling pathway is one of the most critical pathways in developing various diseases, including cancer, which plays a vital role in cellular processes, disease onset and progression, and stem cell regeneration by regulating its target genes. STAT3 has been proven to be an anticancer target in various contexts. Types of genes can activate the STAT3 pathway in cancer. Many lncRNAs have been identified associated with the STAT3 pathway that is upstream or downstream. Oncogenic lncRNAs, including PVT1, HOTAIRM1, and MCM3AP-AS1, increase STAT3 expression, while tumor suppressor lncRNAs, such as TSLNC8, TPTEP1, and DILC decrease STAT3 expression. These lncRNAs can affect STAT3 signaling activity through numerous molecular mechanisms, including sponge of microRNAs, transcriptional activation/inhibition, and epigenetic alterations. Numerous studies show that targeting lncRNAs and molecules associated with the STAT3 signaling pathway are promising therapeutic strategies for various cancers. This review highlighted the mechanisms of the upstream lncRNAs of the STAT3 signaling pathway.

Keywords: STAT3 Transcription Factor, Genetics, Oncogenes, Tumor Suppressor, MicroRNAs

Introduction

Cancer is a genetic disease with unbalanced gene expression, disrupting the gene networks responsible for the cellular identity, growth, and natural differentiation (Cheetham et al., 2013). Numerous studies have shown that defects in the regulation of oncogenes or tumor suppressor genes play an important role in tumorigenesis and cancer progression (Guzel et al., 2020; Prensner and Chinnaiyan, 2011). With the development of modern technology, evidence of genome and transcriptome sequence has been demonstrated that the major part (70%) of gene expression products are non-coding ribonucleotides (ncRNAs) (Zhang et al., 2019b). ncRNA molecules that regulate gene expression are classified into two main groups: short and long

ncRNAs (lncRNA) (Chan and Tay, 2018). Short ncRNAs include piRNAs, siRNAs, miRNAs (Sana et al., 2012). lncRNAs with over 200 ribonucleotides length are the largest class of ncRNAs. The most common lncRNAs are lincRNAs, asRNAs, pseudogenes and circRNAs (Kulczynska and Siatecka, 2016). lncRNAs, as the most important regulators, are involved in many biological processes, especially in cancer progression (Saliani et al., 2021). lncRNAs have different functional mechanisms at the epigenetic, transcriptional, and post-transcriptional levels by regulating multiple downstream targets such as chromatin, proteins, and RNAs (Figure 1) (Do and Kim, 2018). Previous evidence has shown that deregulation of lncRNA expression may lead to several disorders and diseases, including the development of various

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human tumors (Liang et al., 2019; Poursheikhani et al., 2020; Sánchez and Huarte, 2013).

A number of studies revealed that the STAT3 pathway is involved in different types of cancer (de Araujo et al., 2020; Lin et al., 2021; Yang et al., 2005). One of the important strategies to suppress cancers is targeting the STAT3 pathway (Segatto et al., 2018). STAT3 was first discovered in 1994 as a DNA binding protein activated by the EGF and IL-6 (Zhong et al., 1994). Activation of the STAT3 signaling pathway is mediated by growth factor receptors and cytokine receptors such as IL-6 receptor, and non-receptor tyrosine kinases such as EGFR, PDGFR, and SRC (Schroeder et al., 2014). STAT3 is activated through tyrosine and serine phosphorylation via upstream regulators, inducing dimerization of STAT3 molecules (Banerjee and

Resat, 2016). The STAT3 activated dimer is transferred to the nucleus and, with the help of a variety of coactivator proteins, including NCOA/SRC1 α , APE/Ref1, CBP, binds to regulatory regions of genes involved in different phenotypes of cancer cells (Figure 2) (Qin et al., 2019a). Some targeted genes transcribed by STAT3 include *cyclin D1*, *MYC*, *Survivin*, *SOCSSs*, and *MMPs* (Carpenter and Lo, 2014; Johnson et al., 2018). Since the STAT3 signaling pathway regulation can play a pivotal role in controlling various cancers, in this article, we have reviewed the lncRNAs that are related (Figures 3 and 4, Table 1).

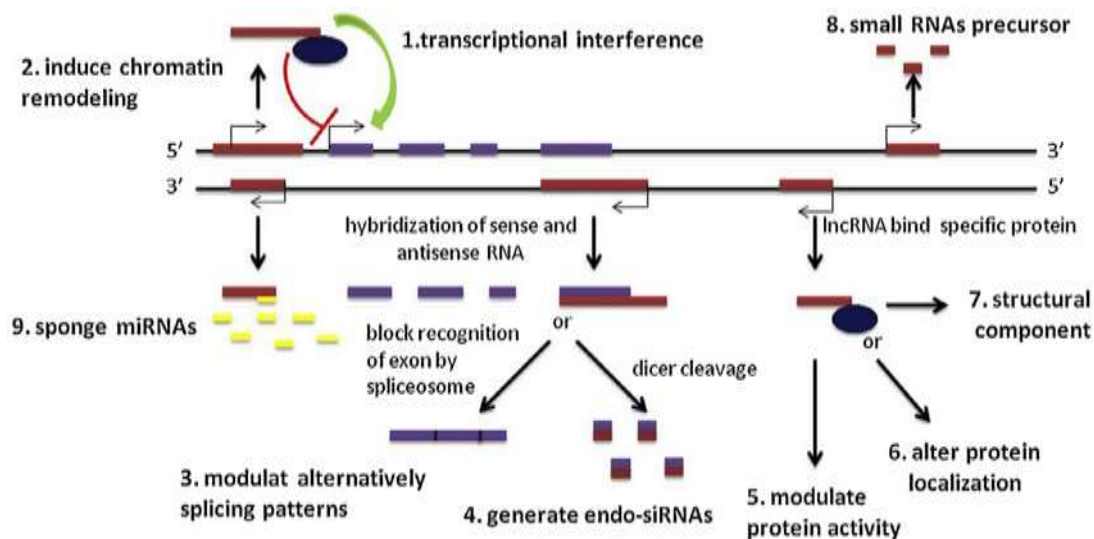


Figure 1. Examples of lncRNAs cellular functions (Shi et al., 2013). They can affect the expression of transcriptional coding genes by chromatin remodeling, negatively (1) or positively (2). Antisense transcripts can be paired with their own specific sense RNAs to alternative forms (3) or endo-siRNA linkages (4). By interacting with proteins, activity (5), their location (6) or even cellular subsets of protein complexes may be affected (7). lncRNAs may process small, single or double stranded RNAs such as endo-siRNAs or miRNAs (8). In addition, they can also act as sponges for miRNAs (9).

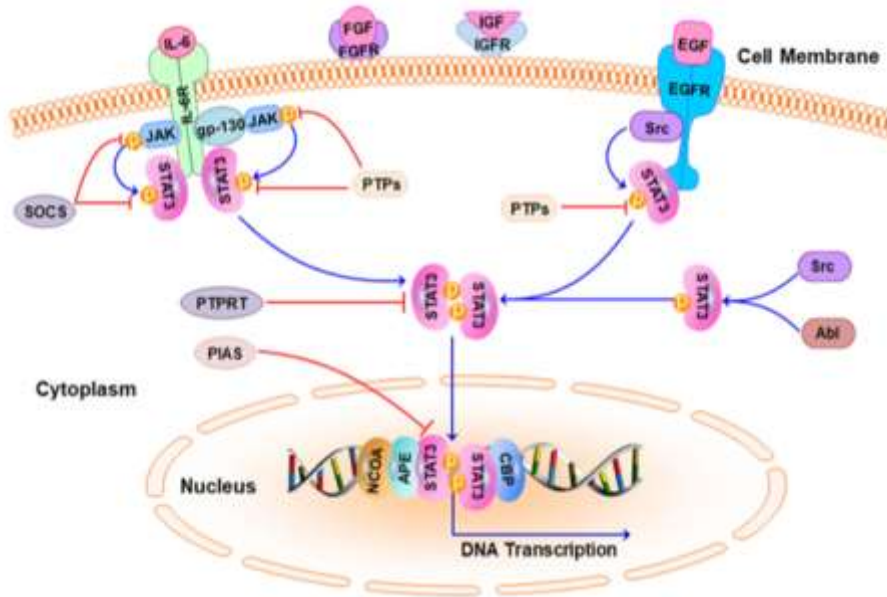


Figure 2. The STAT3 signaling pathway (Qin et al., 2019b).

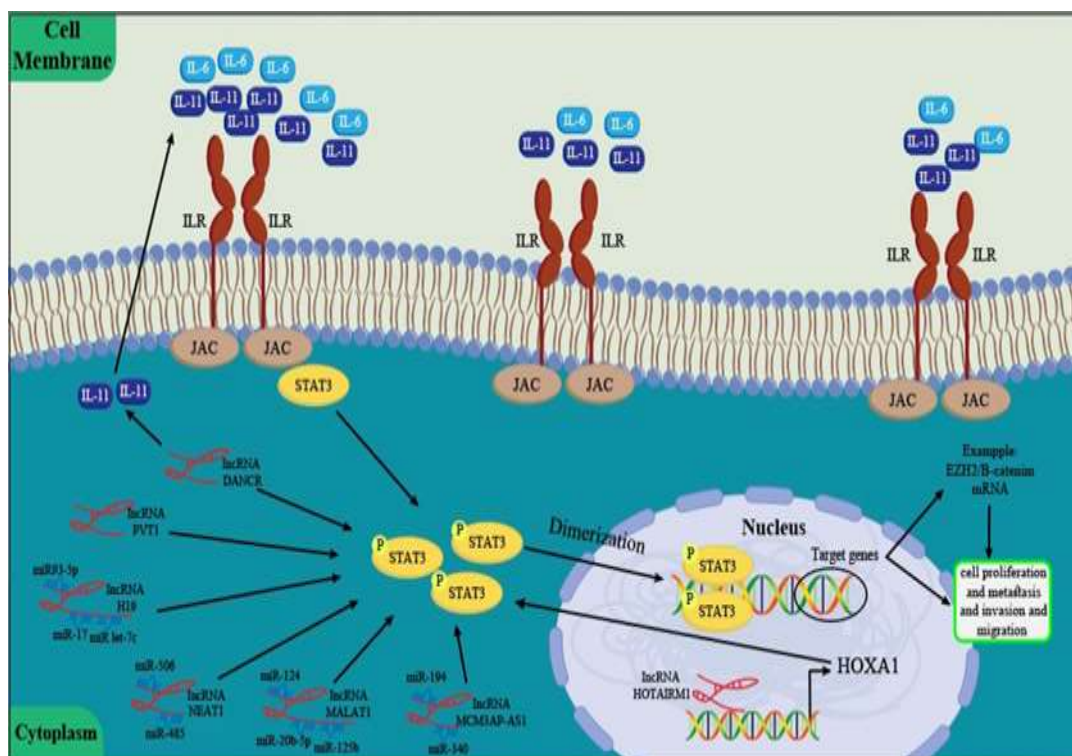


Figure 3. Oncogenic lncRNAs regulate STAT3 signaling pathway.

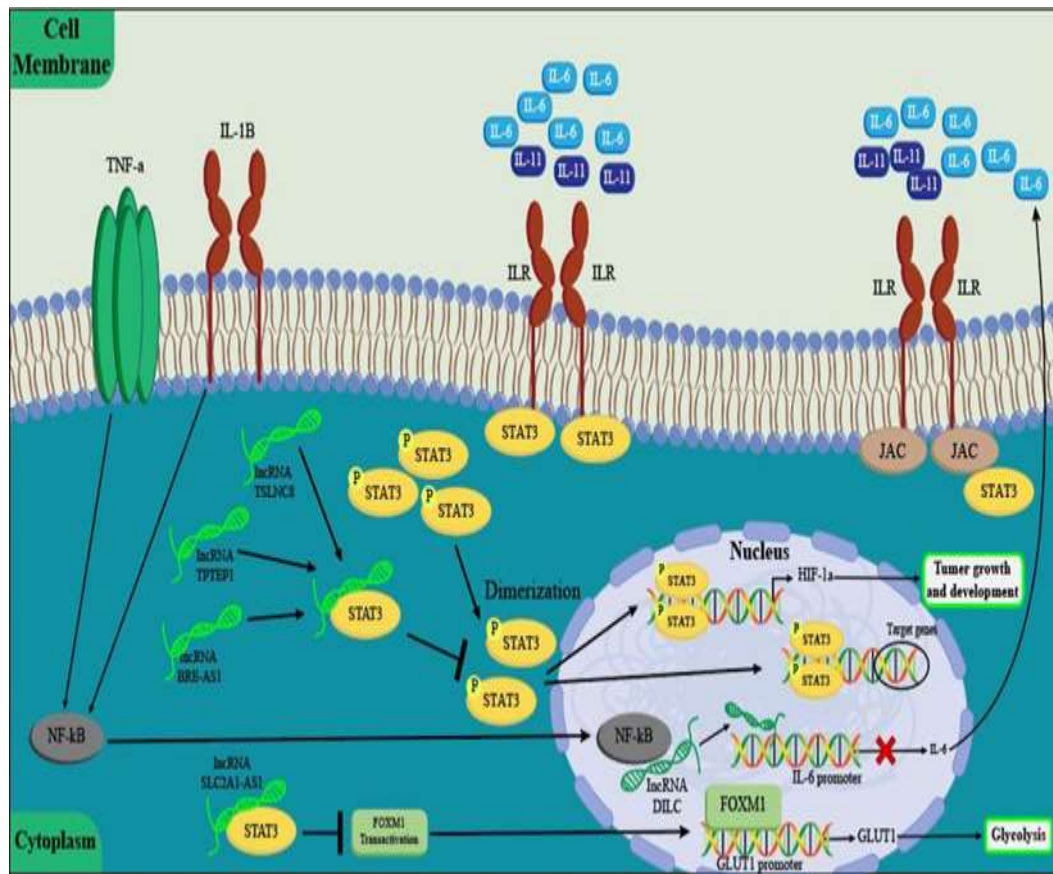


Figure 4. Tumor suppressor lncRNAs regulate STAT3 signaling pathway.

Table 1. lncRNAs that regulate STAT3 pathway

| lncRNA name | Coordinate | Up or down-regulation | Type of cancer | Reference |
|-------------|--------------------------|-----------------------|--|--|
| PVT1 | chr8:127794526-128187101 | up-regulation | Gastric, hepatoblastoma | (Luo and Cao, 2019; Zhao et al., 2020) |
| MCM3AP-AS1 | chr21:46228977-46259390 | up-regulation | Lung, hepatocellular carcinoma (HCC) | (Li et al., 2020; Wang et al., 2019) |
| HOTAIRM1 | chr7:27095647-27100265 | up-regulation | Endometrial, breast, glioblastoma, leukemia | (Díaz-Beyá et al., 2015; Kim et al., 2020; Li et al., 2018a; Li et al., 2019c; Xia et al., 2020; Xie et al., 2021) |
| MALAT1 | chr11:65496266-65509085 | up-regulation | Retinoblastoma, Non-small-cell lung carcinoma (NSCLC), Oral squamous cell carcinoma (OSCC) | (Chang and Hu, 2018; Li et al., 2018b; Wang et al., 2020b) |
| NEAT1 | chr11:65416581-65450093 | up-regulation | Gastric, HCC | (Tan et al., 2019; Zhang et al., 2018b) |

| | | | | |
|-------------------|---------------------------|-----------------|--------------------------|---|
| H19 | chr11:1995129-2001710 | up-regulation | Lung, breast, esophageal | (Chen et al., 2019a; Li et al., 2019a; Liu et al., 2019) |
| DANCR | chr4:52712257-52723623 | up-regulation | Bladder, nasopharyngeal | (Chen et al., 2019b; Zhang et al., 2019c) |
| TSLNC8 | chr8:29667485-29748124 | down-regulation | HCC, lung | (Fan et al., 2019; Zhang et al., 2018a) |
| TPTEP1 | chr22:16601887-16698742 | down-regulation | HCC | (Ding et al., 2019) |
| SLC2A1-AS1 | chr1:42958277-43196506 | down-regulation | HCC | (Shang et al., 2020) |
| BRE-AS1 | chr2:27889455-27891114 | down-regulation | Bladder | (Zhang et al., 2020) |
| DILC | chr13:114239003-114295788 | down-regulation | Bladder, liver | (Gu et al., 2018; Li et al., 2019b; Ma et al., 2019; Wang et al., 2016) |
| GAS5 | chr1:173851284-173869006 | down-regulation | Cervical | (Fang et al., 2020; Yao et al., 2019) |

Oncogenic lncRNAs Regulate the STAT3 Signaling Pathway

lncRNA PVT1

lncRNA PVT1 is a long non-coding RNA transcribed from the human *PVT1* (plasmacytoma variant translocation 1) gene at position chromosome 8:127794526-128187101. lncRNA PVT1 is involved in various mechanisms such as protein interactions, targeting of regulatory genes, increased expression, and competing endogenous RNA (ceRNA) (Onagoruwa et al., 2020). In hepatoblastoma, lncRNA PVT1 is up-regulated and positively associated with progression and metastasis. lncRNA PVT1 activates the transcription of downstream targets involved in cell cycle progression by activating the STAT3 signaling pathway. In addition, selective inhibition of STAT3 by the Stat3 results in loss of lncRNA PVT1 function in the pre-proliferation of hepatoblastoma cells. Due to the association of lncRNA PVT1 with hepatoblastoma malignancy and poor prognosis, it has been suggested to be used as a biomarker to improve classification and help in treatment decisions for hepatoblastoma patients (Luo and Cao, 2019). Also, lncRNA PVT1 plays an important role in regulating angiogenesis and VM formation via the STAT3 signaling pathway in gastric cancer. lncRNA PVT1 interacts directly with the STAT3 transcription activator and activates STAT3 via a stem-loop structure in the region of 850-1770. lncRNA PVT1 increases VE-cadherin, N-cadherin, and Slug proteins expression and decreases E-cadherin expression, which is significantly reversed by inhibiting STAT3. Furthermore, inhibition of

STAT3 reduces the number of VM capillaries promoted by PVT1. Therefore, blocking the lncRNA PVT1/STAT3 axis can be a promising strategy in targeted therapy in gastric cancer patients (Zhao et al., 2020).

lncRNA MCM3AP-AS1

lncRNA MCM3AP-AS1 is an antisense transcript from the *MCM3AP* coding gene, located on chromosome 21:46228977-46259390, identified for the first time in lung cancer (Reymond et al., 2002; Yu et al., 2015). Many mechanisms involved in the development of cancers are affected by lncRNA MCM3AP-AS1, including cell proliferation (Yuan et al., 2016b), tumor angiogenesis (Yang et al., 2017), and cell survival (Zhang et al., 2019a). lncRNA MCM3AP-AS1 mainly functions as an oncogene; nevertheless, in some cases acts as a tumor suppressor (Zhu et al., 2019). lncRNA MCM3AP-AS1 mainly serves as a ceRNA and downregulates tumor suppressor microRNAs such as miR-340, miR-143-3P, miR-194-5P, therefore can restore the oncogenic function of an mRNA targeted molecules. In HCC, miR-340 decreases the activation of the STAT3 signaling pathway by downregulating *JAK1*, reducing the expression of Bcl-2, cyclin D1, and the MMP2 (Li et al., 2020; Yuan et al., 2017). Moreover, miR-194, as a lncRNA MCM3AP-AS1 target, directly acts on *SOCS2* gene transcripts, thereby up-regulated STAT3 signaling pathway. Targeting *SOCS2* by miR-194 reduces oncogenic kinases FLT3 and JAK2 and ultimately increases ERK and STAT3 signaling (Das et al., 2017; Wang et al., 2019).

LncRNA HOTAIRM1

LncRNA HOX antisense intergenic RNA myeloid 1 (*HOTAIRM1*) is located on chromosome 7:27095647-27100265 in the HOXA gene cluster between *HOXA1* and *HOXA2* genes (Zhang et al., 2009). LncRNA HOTAIRM1 has two spliced cytoplasmic isoforms, HM1-3 (775 nucleotides in length) and HM1-2-3 (1044 nucleotides in length), and the un-spliced form HOTAIRM1 mainly was observed in the nucleus (Hamilton et al., 2020). LncRNA HOTAIRM1 was initially identified as an important factor in granulocyte differentiation of human NB4 promyelocytic leukemia (Zhang et al., 2009). LncRNA HOTAIRM1, as an oncogenic, abnormally increases in a type of human tumors. LncRNA HOTAIRM1 and *HOXA1* gene are involved in tumorigenicity of human cancers, including endometrial (Li et al., 2019c), breast (Kim et al., 2020), glioblastoma (Xia et al., 2020; Xie et al., 2021) and leukemia (Díaz-Beyá et al., 2015). LncRNA HOTAIRM1 activates *HOXA1* gene transcription by reducing histone and DNA methylation. Thus, the local epigenetic status of the *HOXA1* gene and its expression is positively regulated by LncRNA HOTAIRM1 (Li et al., 2018a). Up-regulation of *HOXA1* in breast epithelial cancer cells increases the expression of JAK-STAT pathway components (STAT3 and 5B), leading to increased cell proliferation, survival, and oncogenicity. Therefore, LncRNA HOTAIRM1 controls the expression of JAK-STAT pathway components by regulating *HOXA1* expression (Mohankumar et al., 2008).

LncRNA MALAT1

Hence LncRNA MALAT1, first characterized in non-small cell lung cancer (NSCLC), the transcripts called the lung adenocarcinoma associated with metastasis 1. LncRNA MALAT1, also known as nuclear-enriched transcript 2 (NEAT2), with 8.5 kb in length and located on chr11:65496266-65509085 (Sun and Ma, 2019). LncRNA MALAT1 plays an important role in the cell proliferation, cell death, cell cycle, migration, invasion, immunity, angiogenesis and tumorigenesis by regulating numerous signaling pathways such as MAPK/ERK (Chen et al., 2016a; Liu et al., 2018), PI3K/AKT (Dong et al., 2015), WNT/ β -catenin (Liang et al., 2017), NF- κ B (Zhao et al., 2016) and STAT3. miR-124 has been studied in various malignant tumors, including prostate cancer (Lashkarboloki et al., 2020), retinoblastoma (Hu et al., 2018), esophageal squamous cell carcinoma (Li et al., 2019d), and is associated with lncRNAs and STAT3. Overexpression of LncRNA MALAT1 has been

shown in five human NSCLC cell lines, including A549, H23, H522, H1299, and H460. Luciferase reporter assay showed that miR-124 was targeted directly by LncRNA MALAT1 and STAT3. These results were confirmed with *in vitro* analysis in NSCLC cell lines, as the inhibition of LncRNA MALAT1 and miR-124 expression reduced and increased STAT3 expression, respectively. Therefore, the MALAT1/miR-124/STAT3 axis could be a key player in developing NSCLC (Li et al., 2018b). In addition, a positive relationship was reported between MALAT1 and STAT3 in Retinoblastoma (RB) cells. LncRNA MALAT1, by sponging miR-20b-5p, can up-regulate STAT3, increasing proliferation and decreasing apoptosis in RB cells (Wang et al., 2020b). Moreover, high expression of LncRNA MALAT1 and low expression of miR-125b were observed in OSCC cell lines, including Tca8113, SCC-25, CAL-27, and HN5 cells compared to normal human oral cell line Hs680.Tg. At the same time, LncRNA MALAT1 served as a ceRNA and modulated STAT3 expression with sponging miR-125b in OSCC in both *in vitro* and *in vivo*. So, it has been suggested that LncRNA MALAT1 plays an oncogenic role in development and progression of OSCC with a modulating miR-125b/STAT3 axis. Down-regulation of LncRNA MALAT1 induces apoptosis and inhibits cell viability of OSCC cells *in vitro*. Moreover, these findings suggest that LncRNA MALAT1 can be used as a therapeutic target in the early diagnosis and treatment of OSCC (Chang and Hu, 2018).

LncRNA NEAT1

Nuclear paraspeckle assembly transcript 1 (NEAT1) is transcribed from the familial tumor syndrome multiple endocrine neoplasia (*MEN*) type 1 gene located on chr11:65416581-65450093 (Dong et al., 2018). NEAT1 has NEAT1_S and NEAT1_L isoforms, each having a 22741 and 3735 nucleotide length, respectively, with the same transcription start site but different termination points (Ghafouri-Fard and Taheri, 2019). NEAT1 is more concentrated in the nucleus and found in the cytoplasm (van Heesch et al., 2014). Overexpression of LncRNA NEAT1 has been associated with lower survival in several cancer types, such as breast cancer (Shin et al., 2019), glioma (He et al., 2016), ovarian cancer (Chen et al., 2016b), gastric cancer (Fu et al., 2016), bladder cancer (XianGuo et al., 2016). LncRNA NEAT1 have a various role in the stimulation of tumor cells and progression by regulating growth, migration, invasion, metastasis, epithelial-mesenchymal transition, stem cell-like phenotype, chemical

resistance, and radiotherapy resistance, which demonstrates the potential of lncRNA NEAT1 as a diagnostic biomarker and a new therapeutic target (Dong et al., 2018). lncRNA NEAT1 expression is increased in human gastric cancer cells compared to normal gastric cells. Deletion of lncRNA NEAT1 induces the expression of miR-506 and inhibits STAT3. On the other hand, overexpression of lncRNA NEAT1 induces STAT3 expression by suppressing miR-506 expression (Tan et al., 2019). So, miR-506 can directly target STAT3 in GC cells, and lncRNA NEAT1, by sponging miR-506, can regulate the STAT3 pathway indirectly. Therefore, inhibition of lncRNA NEAT1 significantly reduced cell viability, migration and invasion of GC cells *in vitro* (Tan et al., 2019). Moreover, lncRNA NEAT1 serves as a ceRNA of miR-485 in HCC and regulates STAT3 by inhibiting miR-485. Since, lncRNA NEAT1/miR-485/STAT3 axis is involved in migration, invasion, and promotion of viability, it can be used as a biological marker for the diagnosis or therapy of HCC (Zhang et al., 2018b).

LncRNA H19

LncRNA H19 with 2.3 kb length, located on chromosome 11:1995129-2001710 and identified in bladder carcinoma with an oncogenic role for the first time. Nevertheless, there is a controversy about the tumor-suppressing or oncogenic action of lncRNA H19. lncRNA H19, with multiple binding sites of miRNAs, acts as a competitive endogenous RNA (ceRNA) (Alipoor et al., 2020). In esophageal cancer (EC) tissue, the expression level of lncRNA H19 has significantly increased compared to normal tissue. Deleting lncRNA H19 in EC cell lines suppresses cell proliferation, migration, and invasion but increases apoptosis. On the other hand, overexpression of lncRNA H19 in EC cell lines can significantly decrease miRNA let-7c and increase STAT3, EZH2, and β -catenin (Chen et al., 2019a). In lung cancer cells, overexpression of lncRNA H19 increases STAT3 expression via sponging miR-17 (Liu et al., 2019). By sponging miR93-5p, lncRNA H19 can increase STAT3 expression, proliferation, migration and invasion in breast cancer cells (Li et al., 2019a). lncRNA H19 has high diagnostic sensitivity and specificity in breast cancer. On the other hand, anticancer drugs targeting H19 for safer and more effective breast cancer treatment will be introduced soon (Wang et al., 2020a).

LncRNA DANCR

Differentiation Antagonizing Non-Protein Coding RNA (DANCR), which was first discovered as an epidermal cell differentiation inhibitor, is

located on chr4:52712257-52723623 (Zhang et al., 2019c). lncRNA DANCR is an oncogene with various biological processes, including stem cell differentiation and cell proliferation involved in developing different types of tumors (Kretz et al., 2012; Lu et al., 2018; Yuan et al., 2016a). There is a potential relationship between the high expression of lncRNA DANCR and the progression of bladder cancer (BCa). lncRNA DANCR expression is strongly related to pathological staging, grade, and status of LN (lymph node) metastases and enhances metastatic tumor and lymph node growth in bladder cancer via activation of the IL-11-mediated JAK-STAT3 signaling pathway. Silencing lncRNA DANCR dramatically increases cell population in the G0/G1 phase while decreasing cell population in the S phase; in contrast, overexpression of lncRNA DANCR increases cell proliferation and metastasis. So, novel targeted therapies for preventing metastasis in BCa patients with overexpressed DANCR might be used as an anti-IL-11 antibody and STAT3 blocker (Chen et al., 2019b). In Nasopharyngeal carcinoma (NPC), lncRNA DANCR is overexpressed and significantly associated with STAT3 signaling pathway activation. IL-6 dramatically increases lncRNA DANCR expression in both cytoplasm and nucleus. DANCR, by interacting with STAT3, reinforces IL-6 stimulation-induced STAT3 phosphorylation. Hence. There is a positive feedback loop between STAT3 phosphorylation and lncRNA DANCR transcription. Moreover, IL-6-stimulated lncRNA DANCR indirectly binds to the JAK1 via STAT3. Overall, the interaction of lncRNA DANCR with STAT3 through reinforcement of binding JAK1 to STAT3 amplifies IL-6/JAK1/STAT3 signaling for enhancing NPC progression, which recommended a potential target for a new strategy to develop NPC therapies (Zhang et al., 2019c).

Tumor Suppressor LncRNAs Regulate the STAT3 Signaling Pathway

LncRNA TSLNC8

The lncRNA TSLNC8 is located on chr8:29667485-29748124. TSLNC8, also known as LINC00589 (Chen and Yu, 2018). lncRNA TSLNC8 plays as a tumor suppressor in some types of cancer through various processes, including suppression of cell proliferation and facilitation of apoptosis and inactivation of the IL-6/STAT3 signaling pathway. For instance, deletion of lncRNA TSLNC8 is significantly associated with malignancy of hepatocellular carcinoma (HCC). lncRNA TSLNC8 inhibits STAT3 phosphorylation and

transcriptional activity in HCC cells. TSLNC8 has a recognition site at the 748-758nt for the DNA-binding domain of STAT3. It resulted in the reduction of Y705 phosphorylation and an increase of S727 phosphorylation, contributing to the suppressive effects of lncRNA TSLNC8. TSLNC8 controls proliferation, invasion, and metastasis in HCC cells via inactivating the IL-6/STAT3 signaling pathway. lncRNA TSLNC8 may be considered a potential therapeutic target for treatment (Zhang et al., 2018a). In addition, lncRNA TSLNC8 acts as a tumor suppressor in the lung cancer-causing inhibition of HIF-1 protein, along with down-regulation of IL-6 expression and its downstream genes and STAT3 phosphorylation. TSLNC8 can suppress cell proliferation, migration, and invasion and increase apoptosis in lung cancer cells via the IL-6/STAT3/HIF-1 α signaling pathways (Fan et al., 2019).

lncRNA TPTEP1

The transmembrane phosphatase with tensin homolog pseudogene 1 (TPTEP1) is a lncRNA located at chromosomal position 22:16601887-16698742 as a tumor suppressor (Source: GeneCards). lncRNA TPTEP1 has three different variants and is silenced through DNA methylation in various cancers, including kidney, liver, lung, and stomach cancers. So, lncRNA TPTEP1 is expressed when DNA demethylation and deacetylase histone inhibition occurs (Liang et al., 2010). In HCC, lncRNA TPTEP1 directly binds to STAT3 and exerts its suppressive activity by inhibiting STAT3 phosphorylation, homodimerization, and nuclear translocation. Overall, TPTEP1 inhibits the progression of hepatocellular carcinoma cells via the IL-6/STAT3 signaling pathway (Ding et al., 2019).

lncRNA SLC2A1-AS1

lncRNA SLC2A1-AS1 is located on chr1:42958277-43196506 in the human genome and is known as a tumor suppressor. lncRNA SLC2A1-AS1 decrease in HCC cell lines and tissues and associated with non-recurrent survival. lncRNA SLC2A1-AS1 can regulate the abnormal expression of GLUT1 RNA, which has potential effects on the glycolysis process in cancers. Overexpression of lncRNA SLC2A1-AS1 in the nucleus inhibited proliferation and metastasis in HCC by preventing GLUT1 transcription. A suggested molecular mechanism is SLC2A1-AS1 interacts with STAT3 to inhibit FOXM1 activation via STAT3. So, lncRNA SLC2A1-AS1 does not directly regulate the transcriptional activity of GLUT1 but inhibits FOXM1 transcription, which has previously been

identified as an important transcriptional activator of the GLUT1. Inactivation of the FOXM1/GLUT1 axis was shown in HCC cells. Therefore, SLC2A1-AS1 inhibits glycolysis and progression of HCC via the STAT3/FOXM1/GLUT1 axis. These mechanisms highlight the vital role of SLC2A1-AS1 in glycolysis and HCC progression (Shang et al., 2020).

lncRNA BRE-AS1

BRE-AS1 is located on chromosome 2:27889455-27891114 as a non-coding single-stranded RNA with 1659 bp in length. Low expression of lncRNA BRE-AS1 has been shown in bladder cancer tissues. Overexpression of lncRNA BRE-AS1 via suppressing STAT3 phosphorylation reduces cell proliferation and cell cycle transition but increases cell apoptosis *in vitro* and *in vivo* (Zhang et al., 2020).

lncRNA DILC

For the first time, lncRNA DILC was recognized in liver cancer stem cells (LCSCs) by microarray and real-time PCR. The name DILC came from downregulated liver cancer stem cells. lncRNA DILC is located on chromosome 13q34 (chr13:114239003-114295788) with a 2394 bp length (Wang et al., 2016). lncRNA DILC is related to the prognosis in various human diseases, including cancers such as LCSC (Wang et al., 2016) and colorectal (Gu et al., 2018; Li et al., 2019b), bladder (Ma et al., 2019). The IL-6/STAT3 signaling pathway plays an important role in the proliferation of LCSCs; IL-6 transcription is preferentially regulated by NF- κ B, which is overexpression on various stem cells. NF- κ B is usually activated by extracellular inflammatory cytokines such as TNF- α and IL-1 β (Hinohara et al., 2012; Kagoya et al., 2014). Overexpression of lncRNA DILC blocks induction of IL-6 transcription via TNF- α and IL-1 β (NF- κ B). In contrast, decreased lncRNA DILC expression increases IL-6 transcription by TNF- α and IL-1 β . lncRNA DILC suppresses the proliferation of LCSCs by inhibiting the IL-6/STAT3 signaling pathway. This evidence suggests that lncRNA DILC regulates LCSCs by controlling the crosstalk between TNF- α /NF- κ B and IL-6/STAT3 signaling pathways (Wang et al., 2016). Moreover, overexpression of lncRNA DILC in bladder tissue and cell line can suppress bladder cancer by inhibiting IL-6 and STAT3 (Ma et al., 2019). Also, lncRNA DILC is colorectal cancer (CRC) suppressor that can inhibit CRC cell growth and metastasis. DILC suppresses CRC cell progression by inhibiting IL-6 and STAT3 signaling

pathways and is a biomarker for the prognosis of CRC patients (Gu et al., 2018; Li et al., 2019b).

LncRNA GAS5

The lncRNA growth arrest-specific transcript 5 (GAS5), with 630 nucleotides in length, is located on chromosome 1:173851284-173869006. Decreased expression of lncRNA GAS5 has been observed in many human malignancies. Increasing its expression induces apoptosis and inhibits proliferation and metastasis in tumors (Yang et al., 2020). In cervical cancer, lncRNA GAS5 has been shown to affect STAT3 signaling. Phosphorylated-STAT3 is a transcription factor for lncRNA GAS5, which binds to the GAS5 promoter. There are two STAT3 binding sites in the miR-21 enhancer sequence, and in this way, STAT3 directly regulates miR-21 expression (Yao et al., 2019). Several studies have examined the oncogenic role of miR-21 in types of cancers, including colon cancer (Dehghan et al., 2019) and breast cancer (Esmatabadi et al., 2017; Savari et al., 2020). *PDCD4* is the target gene of miR-21 that increases sensitivity to cisplatin. Hence, it is possible that STAT3 regulation and the GAS5/miR-21/PDCD4 axis could have therapeutic potential for cisplatin-based chemotherapy and antitumor functions in cervical cancer (Fang et al., 2020).

Conclusion

The STAT3 signaling pathway is one of the most important pathways involved in types of cancer. LncRNAs can interact with signaling molecules and activate the STAT3 signaling pathway, affecting tumor onset and progression. The interaction between lncRNA, STAT3 signaling, and related molecules leads to the coordination of different cellular processes responsible for cell cycle determination, differentiation, migration, metastasis and drug resistance. Examining the mechanism of lncRNAs in STAT3 signaling helps us identify useful biomarkers for diagnosis and establish effective therapeutic targets for cancer treatment.

Acknowledgments

None.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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