Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Review

Interplay of long non-coding RNAs and TGF/SMAD signaling in different cancers

Ammad Ahmad Farooqi[1*], Rukset Attar[2], Muhammad Zahid Qureshi[3], Sundas Fayyaz[4], Muhammad Imran Sohail[5], Uteuliyev Yerzhan Sabitaliyevich[6], Sadykov Bolat Nurmurzayevich[7], Armida Yelekenova[8], Ilhan Yaylim[9], Nada Alaaeddine[10]

[1] Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan
[2] Department of Obstetrics and Gynecology, Yeditepe University Hospital, Istanbul, Turkey
[3] Department of Chemistry, GCU, Lahore, Pakistan
[4] Laboratory for Translational Oncology and Personalized Medicine, Rashid Latif Medical College, Lahore, Pakistan
[5] Department of Zoology, GCU, Lahore, Pakistan
[6] Kazakhstan Medical University "KSPH", Kazakhstan
[7] City Clinical Hospital No.5 in Almaty, Kazakhstan
[8] Department of Obstetrics and Gynecology, Astana Medical University, Kazakhstan
[9] Department of Molecular Medicine, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey
[10] Laboratoire d'immunologie cellulaire et moleculaire, Centre hospitalier de l'universite de Montreal, Tour Viger, 900 rue Saint-Denis, Montreal, Montreal H2X0A9, Quebec, Canada

Correspondence to: ammadfarooqi@rlmclahore.com

Received November 8, 2018; **Accepted** December 6, 2018; **Published** December 31, 2018

Doi: http://dx.doi.org/10.14715/cmb/2017.64.15.1

Abstract: Based on the exciting insights gleaned from decades of ground-breaking research, it has become evident that deregulated signaling pathways play instrumental role in cancer development and progression. Interestingly discovery of non-coding RNAs has revolutionized our understanding related to transcription, post-transcription and translation. Modern era has witnessed landmark discoveries in the field of molecular cancer and non-coding RNA biology has undergone tremendous broadening. There has been an exponential growth in the list of publications related to non-coding RNAs and overwhelmingly increasing classes of non-coding RNAs are adding new layers of complexity to already complicated nature of cancer. Regulation of TGF/SMAD signaling by miRNAs and LncRNAs has opened new horizons for therapeutic targeting of TGF/SMAD pathway. In this review we have set spotlight on central role of LncRNAs in modulation of TGF/SMAD pathway. Major proportion of the available evidence is underlining positive role of LncRNAs in contextual regulation of TGF/SMAD pathway. LncRNAs are vital to these regulatory networks because they provide a background support to make the TGF/SMAD mediated intracellular signaling more smooth or make transduction cascade more flexible in response to cues from extracellular environment. Therefore, in accordance with this notion, MALAT1, OIP5-AS1, MIR100HG, HOTAIR, ANRIL, PVT1, AFAP1-AS1, SPRY4-IT, ZEB2NAT, TUG1 and Lnc-SNHG1 have been reported to positively regulate TGF/SMAD signaling. In this review, we have focused on the regulation of TGF/SMAD signaling by LncRNAs and how these non-coding RNAs can be therapeutically exploited. Short-interfering RNA (siRNA) and natural products are currently being tested for efficacy against different LncRNAs. Nanotechnological strategies to efficiently deliver LncRNA-targeting siRNAs are also currently being investigated in different cancers.

Key words: Cancer; TGF; SMAD; Signaling; LncRNA; MALAT1; HOTAIR; ANRIL.

Introduction

TGF-β (Transforming growth factor-β) superfamily of ligands has attracted substantial attention because of its linchpin role in myriad of cellular mechanisms ranging from development to pathogenesis (1). Since the discovery of the prototypic member, TGF-β, we have witnessed groundbreaking discoveries which have helped us to put together missing pieces of an incomplete jig-saw puzzle and enabled us to unravel how this pathway played central role in cancer development and progression (2). Binding of ligand to type-II and type-I receptors, ligand-hetero-tetrameric receptor complex transduced the signals intracellularly through downstream transcriptional factors SMADS. Strategically, SMAD protein family is characterized categorically into three groups: R-SMAD (SMAD1,-2,-3 and SMAD8), co-SMAD (SMAD4), and inhibitory-SMADs (SMAD6,-7). Structural and biochemical studies have shown that receptor-regulated SMADS are phosphorylated by type-I receptors. Phosphorylated SMADs interacted with SMAD4 and moved into the nucleus. SMADs associated with characteristically unique transcription factors and co-regulators to modulate the expression of target genes (3).

Data obtained through high-throughput technologies has provided a finer resolution of non-coding RNAs and it is now evident that different classes of regulatory noncoding RNAs, which include microRNAs (miRNAs, ~21 nucleotides) and long noncoding RNAs (lncRNAs, >200 nucleotides) are spatio-temporally expressed in developmental-, cell-type and tissue-specific manner and strategically regulate myriad of biological processes (4,5). The accelerating pace with which both intergenic

and genic lncRNAs have been discovered and annotated has added substantial fraction of new information (6).

There has been a paradigm shift in our understanding related to TGF/SMAD signaling and its central role in regulation of cancer development and progression. TGF/SMAD signaling has been extensively investigated but most research efforts in this field have been focused on protein regulators, leaving big knowledge gaps about role of lncRNAs in regulation of TGF/SMAD pathway. In this review, we discuss most recent evidence related to lncRNA mediated regulation of TGF/SMAD signaling in different cancers.

There are some high-quality reviews which highlight regulation of signaling pathways by LncRNAs (7,8,9,10). However, we have specifically focused on regulation of TGF/SMAD signaling by LncRNAs.

MALAT1: Guardian Angel for TGF/SMAD Signaling

Wealth of information has enabled us to categorize wide ranging LncRNAs on the basis of positive or negative regulation of TGF/SMAD signaling.

MARCH7 (Membrane-associated RING-CH finger protein-7), a member of the MARCH family of membrane-bound E3 ubiquitin ligases played central role in ovarian cancer progression. Tumor growth was drastically reduced in mice xenografted with MARCH7 silenced SKOV3 cells (Hu et al, 2015). MALAT1 has been shown to function as a ceRNA (competitive endogenous ribonucleic acid) in context of sponging miR-200a away from MARCH7 in ovarian cancer cells. MiR-200a notably downregulated MALAT1 and MARCH7 (11). Silencing of MARCH7 or MALAT1 induced upregulation of miR-200a. Chromatin immunoprecipitation assay has provided evidence of positioning of SMAD3 to the site present within promoter region of MALAT1. Ectopically expressed MARCH7 promoted TGF-β-triggered autophagic response, migratory and invasive potential of A2780 cells, while MARCH7 silencing markedly reduced TGF-β mediated autophagic response, migratory and invasive potential of SKOV3 cells. Furthermore, luciferase reporter assays of TGF-β/SMAD2/3 cascade demonstrated augmented activities in ovarian cancer A2780 cells that ectopically expressed MARCH7 (11). Co-immunoprecipitation assays verified that MARCH7 interacted with TGFBR2. TGFBR2 levels were notably enhanced in ovarian cancer cells which ectopically expressed MARCH7. Overall the findings clearly suggested that TGF-β/SMAD pathway promoted cancer through upregulation of MALAT1 (12). MALAT1 interacted with miR-200a and interfered with miR-200 mediated targeting of MARCH7 (shown in fig.1). MARCH7 further promoted TGF-β/SMAD signaling to enhance migration of ovarian cancer cells.

In another study it has been shown that miR-124 considerably reduced the luciferase activities of wild-type MALAT1 but luciferase activities of mutant MALAT1 remained unchanged (13). TGF-β induced upregulation of MALAT1 in nasopharyngeal carcinoma. Whereas, miRNA-124 overexpression exerted repressive effects on MALAT1 expression. Furthermore, MALAT1 knockdown strikingly reduced the activation of TGF-β pathway. Accordingly, proliferative and invasive potential of MALAT1 silenced NPC cells was also reduced. Levels of SMAD2/3, p-SMAD2/3 and SMAD4 were reduced in miR-124 overexpressing NPC cells (13).

MicroRNA-145 directly targeted TGFBR2 and SMAD3 (14) (shown in fig.1). MALAT1 knockdown led to increased DICER expression which highlighted that endogenous MALAT1 repressed miR-145 partially by downregulation of DICER which consequently interfered with miR-145 maturation. MiRNAs activated RNA-induced silencing complex (RISC) to silence complementary target mRNAs. MALAT1 had a putative binding site for miR-145 therefore, miR-145 recruited MALAT1 into the RISC for degradation (14). Western blot analysis provided clear evidence that Ago2 antibody-coated magnetic beads pulled down the Ago2 protein from cellular lysates. Likewise, QRT-PCR analysis revealed higher MALAT1 and miR-145 levels in the Ago2 precipitates (14). Many questions remain unaddressed with regard to regulation of DICER. These findings have unveiled exciting strategy used by MALAT1 to inhibit maturation of miR-145. It will be important to see if MALAT1 mediated inhibition of DICER also interfered with maturation of different SMAD pathway-targeting miRNAs.

SMAD4 is directly targeted by miR-205 in osteosarcoma (15). However, MALAT1 acted as a sponge and sequestered miR-205 away from SMAD4 (shown in fig.1). MALAT1 effectively promoted cellular proliferation through suppression of miR-205 and upregulation of SMAD4 in osteosarcoma (15).

It seems clear that MALAT1 has a key role in promoting TGF/SMAD signaling and it strategically inhibits negative regulators of TGF/SMAD signaling.

OIP5-AS1

OPA-interacting protein 5 antisense transcript 1 (OIP5-AS1) promoted cancer via sequestration of SMAD-pathway targeting miRNAs (16).

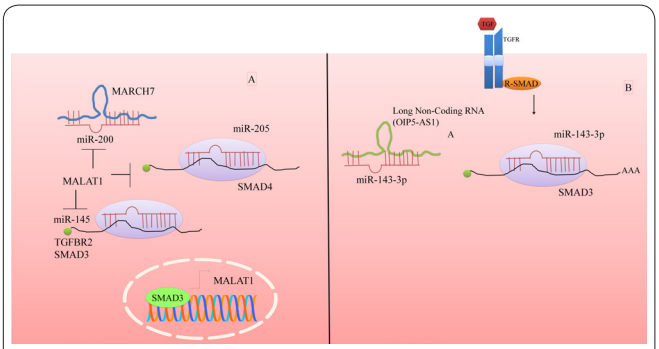

Figure 1. TGF/SMAD mediated upregulation of MALAT1 to potentiate TGF/SMAD signaling. miRNA sponges are RNA transcripts which contain high-affinity binding sites that interact with and sequester specific miRNAs to prevent their interaction with their target mRNAs. MALAT1 tactfully interfered with TGF/SMAD-targeting miRNAs. miR-205, miR-200 and miR-145 have been shown to negatively regulate TGF/SMAD pathway. However, TGF/SMAD pathway-stimulated MALAT1 potentiated SMAD signaling via sequestering these miRNAs away from SMADs and TGF-receptor. (B) miR-143-3p has been shown to directly target SMAD3 but OIP5-AS1 sequestered miR-143-3p away from SMAD3.

LINP1

LncRNA in nonhomologous end joining (NHEJ) pathway 1 (LINP1) was found to be inhibited by TGF-β1 (17). LINP1 knockdown induced a mesenchymal phenotype, weak adhesive properties and a spindle-shaped morphology. LINP1 overexpressing A549 cells demonstrated stronger adhesive properties, accompanied by a decrease in N-cadherin, SNAIL and vimentin and a simultaneous increase in E-cadherin. LINP1 has SMAD4 binding sites (shown in figure.2). Mutation in the SMAD4-binding sites severely impaired the ability of TGF-β1 to repress LINP1 (17).

MIR100HG

TGF-β induced upregulation of long non-coding RNA (MIR100HG) in PANC-1 cells. MIR100HG also acted as a tri-cistronic host gene as it harbored miRNA-100, miRNA-125b, and let-7a (18). Mechanistically it was shown that downregulation or inhibition of SMAD2 and SMAD3 significantly reduced miR-125b and miR-100 levels, and drastically abrogated the ability of TGF-β to stimulate their expression. Additionally, MIR100HG represented only transcript regulated by TGF-β present within its related topologically associated domain (TAD) which pinpointed towards ability of SMAD2/3 to interact here to stimulate transcription of MIR100HG. Mesenchymal-to-epithelial transition (MET) was induced upon inhibition of these miRNAs in mesenchymal-like PDAC cells (18). Expectedly, tumor sphere formation was more pronounced in miR-100 or miR-125b overexpressing BxPC-3 cells (18).

HOTAIR

Cancer-associated fibroblasts (CAFs) have been shown to promote EMT. HOTAIR (HOX transcript antisense RNA) is involved in facilitating H3K27 trimethylation to epigenetically inactivate tumor suppressors by recruiting EZH2 (enhancer of zeste homolog-2) (19). Conditioned media from CAFs contained high concentrations of TGF-β1. TGF-β1 was noted to stimulate HOTAIR expression in breast cancer cells. Expectedly, p-SMAD2, p-SMAD3 and p-SMAD4 were noted to be considerably enhanced in CAF-conditioned media and TGF-β1-treated cancer cells. SMAD2, 3, and 4 have been shown to bind directly to the promoter region of HOTAIR and analysis of promoter region using PROMO and JASPAR revealed different SMAD-binding sites within HOTAIR promoter region (19). CDK5RAP1 (CDK5 Regulatory subunit-associated protein-1) and EGR-1 were found to be epigenetically modified in HOTAIR expressing breast cancer cells. Promoter regions of EGR-1 and CDK5RAP1 were highly enriched with H3K27-trimethylation marks. To verify instrumental role of HOTAIR in cancer progression, sh-HOTAIR-transfected MDA-MB-231 cells and CAFs were co-injected into the nude mice. HOTAIR inhibition drastically reduced CAF-triggered tumor growth and lung metastases in mice (19). Overall these findings clearly suggested that CAFs induced HOTAIR upregulation in breast cancer cells and epigenetically modified various genes to promote metastasis.

ANRIL

ANRIL (Antisense noncoding RNA in the INK4 locus) was noted to be frequently overexpressed in prostate cancer and inhibition of ANRIL exerted inhibitory suppressive effects on proliferation and migration of prostate cancer cells (20). Interestingly, TGF-β1 and p-SMAD2 levels were significantly reduced while p-SMAD7 levels were found to be considerably enhanced in ANRIL silenced prostate cancer cells. Knockdown of ANRIL increased let-7a expression. It was surprising to note that inhibition of let-7a reactivated TGF-β1/SMAD signaling cascade in prostate cancer cells (20). Data suggested that ANRIL promoted TGF/SMAD signaling through inhibition of let-7a in prostate cancer cells. These aspects might be helpful in dissecting detailed mechanism used by ANIRL to promote TGF/SMAD pathway.

However, surprisingly in thyroid cancer, ANRIL inhibited the expression of tumor suppressor gene p15INK4b through inhibition of TGF-β/SMAD signaling cascade (21). ANRIL reduced p15INK4b through inhibition of TGF-β/SMAD signaling and promoted invasion and metastasis of thyroid cancer cells. Most importantly, number of lung metastatic nodules was significantly lower in mice injected with ANRIL silenced TPC-1 cells (21).

PVT1

PVT1 knockdown exerted repressive effects on levels of mesenchymal markers including Slug, Snail, β-catenin, vimentin and N-cadherin (22). Importantly, levels of p-SMAD2/SMAD3 were reduced in PVT1 knockdown pancreatic cancer cells but astonishingly, SMAD4 was found to be considerably enhanced (22).

PVT1 overexpression severely abrogated apoptosis in cisplatin-sensitive cancer cells (23). Cisplatin sensitivity was restored after knockdown of PVT1 in cisplatin-resistant cancer cells. Phosphorylated-SMAD4 was notably increased in PVT1 knockdown SKOV-3/DDP and A2780/DDP cells but mRNA levels of SMAD4 remained unchanged in PVT1 silenced ovarian cancer cells (23).

AFAP1-AS1 (Actin filament associated protein 1 antisense RNA-1)

AFAP1-AS1 (actin filament associated protein 1 antisense RNA-1) played central role in tongue squamous cell carcinoma (24). SMAD2 levels were dramatically reduced in AFAP1-AS1 silenced CAL-27 cells. Furthermore, tumor growth was significantly reduced in mice subcutaneously injected with AFAP1-AS1 silenced CAL-27 cells (24).

SPRY4-IT

SPRY4-IT (SPRY4-intronic transcript-1), another long non-coding RNA also effectively promoted TGF/SMAD signaling in thyroid cancer cells. Levels of p-SMAD2/3 and TGF-β1 were markedly reduced in SPRY4-IT-silenced thyroid cancer cells (25). These findings should also be tested in mice by inoculation of

SPRY4-IT-expressing cancer cells to substantiate cancer promoting role of SPRY4-IT.

ZEB2NAT

Conditioned medium from CAFs markedly enhanced migratory and invasive potential of bladder cancer cells (26). ZEB2NAT, an antisense transcript to ZEB2 gene was considerably upregulated in cancer cells treated with TGFβ1. Reduced levels of E-Cadherin were noticed in ZEB2NAT overexpressing cancer cells. Reduction in level of E-Cadherin is a hallmark feature of epithelial to mesenchymal transition (26). Findings suggested that TGFβ1 induced upregulation of ZEB-2NAT in bladder cancer cells.

Taurine-up-regulated gene 1 (TUG1)

Taurine-up-regulated gene 1 (TUG1) also promoted TGF/SMAD signaling in pancreatic cancer cells (27). TUG1 overexpression promoted SMAD2 and SMAD3 phosphorylation but levels of p-SMAD2 and p-SMAD3 were reduced in TUG1 silenced cancer cells. Levels of TGF-β and TGFR were also found to be increased in TUG1 overexpressing cancer cells (27).

Lnc-SNHG1

Ectopic expression of lnc-SNHG1 induced an increase in proliferation, migration, and invasive potential of cancer cells (28). Lnc-SNHG1 overexpression markedly inhibited the expression of miRNA-302/372/373/520 (miRNA-pool) in pituitary tumor cells (invasive phenotype). Furthermore, upregulation of TGFBR2 and RAB11A (RAS-associated protein-11A) was noticed in lnc-SNHG1 overexpressing cells. It is relevant to mention that TGFBR2 and RAB11A are post-transcriptionally controlled by miR-302/372/373/520 (28). Findings clearly suggested that lnc-SNHG1 activated RAB11A/Wnt/β-catenin and TGFBR2/SMAD3 cascades in pituitary tumor cells mainly through sponging miR-302/372/373/520.

SNHG7 knockdown in osteosarcoma cell lines SaOS2 and MG63 induced re-expression of tumor suppressor miR-34a (29). Tumor growth was significantly reduced in mice xenografted with SNHG7 silenced MG63cells. Expectedly, TGF-β1-induced EMT was not observed in SNHG7-silenced osteosarcoma cells (29).

NORAD

NORAD is a cytoplasmic lncRNAs and strategically modulates nuclear transport of SMAD complexes (30). Nuclear accumulation of p-SMAD2 and p-SMAD3 were reduced in NORAD-depleted cancer cells. SMADs are shipped to the nucleus by importin proteins. NORAD interacted with importin-7 and importin-β1 and facilitated nuclear distribution of SMAD proteins. Co-immunoprecipitation assays indicated that NORAD knockdown partially impaired structural association between importin-β1 and SMAD3 in TGF-β-treated A549 cells (30).

LINC01186 was significantly downregulated in A549 cells treated with TGF-β1 (31). Mechanistically

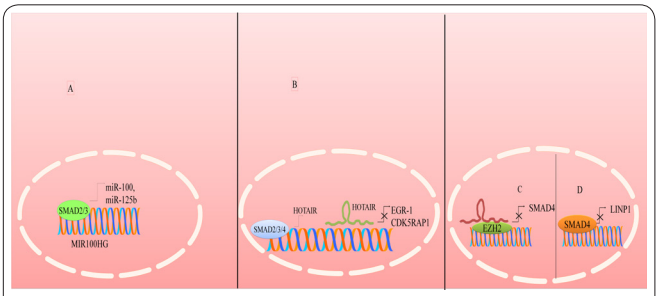

Figure 2. (A) SMAD2/3 mediated upregulation of miR-100 and miR-125b. These miRNAs are present in MIR100HG. (B) SMAD2/3/4 transcriptionally upregulated HOTAIR. HOTAIR worked synchronously with epigenetic machinery to repress EGR-1 and CDK5RAP1. (C) AWPPH worked with EZH2 to repress SMAD4. (D) SMAD4 transcriptionally downregulated LINP1.

it was shown that SMAD3 transcriptionally repressed LINC01186. ChIP-Seq data analysis provided evidence of SMAD3 binding to specific sequence of LINC01186. LINC01186 knockdown decreased epithelial markers and enhanced mesenchymal markers in lung cancer cells (31).

AWPPH worked synchronously with EZH2 and epigenetically inactivated SMAD4 in bladder cancer cells (32). Histone tri-methylation at 27th lysine residue (H3K27me3) provides clue of epigenetic inactivation. SMAD4 had tumor suppressive role in bladder cancer but AWPPH promoted cancer through inhibition of SMAD4 (shown in fig.2) (32).

Conclusion

Experimental validation of newly identified LncRNAs in cancer cell lines and xenografted mice is really necessary. Therefore, closing this gulf between mapped and experimentally validated lncRNAs has helped in developing a better understanding of critical role of LncRNAs in different cancers. Over the timeline of last 15 years, firstly through microarray screens and afterwards through RNA sequencing technologies, a large number of lncRNAs have been annotated in different cancers. Recent technological developments have certainly revolutionized annotation methodologies. Third-generation sequencing technologies have helped us to comprehensively read entire RNA or cDNA molecules.

Keeping in view, rapidly upgrading list of newly discovered LncRNAs and complexity of cell signaling, it is critically challenging to identify lncRNAs carrying functional domains (or aptamers) that interact with corresponding binding partners. Because of extra-ordinary advancements in the scientific technologies, RNA-Immunoprecipitation (RIP) and Cross-Linking Immunoprecipitation (CLIP) are the two highly acclaimed and fundamental approaches for analysis of RNA-protein interactions. Therefore, this intermeshed network of miRNAs, LncRNAs and their target molecules can be disentangled by use of RNA precipitation and RIP or CLIP which will greatly assist in the identification of specific binding partners. In particular, RNA precipitation combined with high-throughput mass spectrometry and RIP/CLIP combined with deep sequencing will prove to be helpful in exploring central role of LncRNAs in cell signaling. Additionally, rapidly broadening

landscape of LncRNAs needs to be therapeutically exploited. Even though there are stumbling blocks associated with oligonucleotide-based therapies, but excitingly we have witnessed encouraging results in context of oligonucleotide design and many of the chemically modified analogues have shown promising results in preclinical trials. Particularly, it is important to note that single-stranded oligonucleotides such as antagoNATs are advantageous mainly because of their systemic administration as they can be systemically administered and do not need delivery systems. In January 2013, Mipomersen, an antisense oligonucleotide targeting the mRNA for apolipoprotein-B was approved by FDA for treatment of homozygous familial hypercholesterolaemia. However, it was not critically acclaimed by a European Medicines Agency panel.

Interdisciplinary researchers are making worthwhile efforts to design and develop efficient oligonucleotide-based therapies. Reducible cationic nanogels based on functionalized low-molecular-weight poly(glycidyl methacrylate) (PGMA) is an effective delivery system for MALAT1-targeting siRNA (33). Recently, tumor-targeting and BBB-crossing immunoliposome has been reported to efficiently deliver MALAT1-targeting siRNA (34). Moreover, bioactive molecules from natural sources are currently being tested for efficacy against LncRNAs. Nimbolide was noted to exert repressive effects on HOTAIR (35). Attempts are also being made to identify natural products which can abrogate LncRNA and protein interactions (36).

There is a need to design result-oriented preclinical trials to properly observe efficacy of LncRNA-targeting therapies.

References

1. Schmierer B, Hill CS. TGFbeta-SMAD signal transduction: molecular specificity and functional flexibility. Nat Rev Mol Cell Biol. 2007 Dec;8(12):970-82.

2. Lönn P, Morén A, Raja E, Dahl M, Moustakas A. Regulating the stability of TGFbeta receptors and Smads. Cell Res. 2009 Jan;19(1):21-35.

3. Ikushima H, Miyazono K. TGFbeta signalling: a complex web in cancer progression. Nat Rev Cancer. 2010 Jun;10(6):415-24.

4. Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer. 2018 Jan;18(1):5-18.

5. Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs. Nature. 2012 Feb 15;482(7385):339-46.

6. Matsui M, Corey DR. Non-coding RNAs as drug targets. Nat Rev Drug Discov. 2017 Mar;16(3):167-179.

7. Tang Y, He Y, Zhang P, Wang J, Fan C, Yang L, Xiong F, Zhang S, Gong Z, Nie S, Liao Q, Li X, Li X, Li Y, Li G, Zeng Z, Xiong W, Guo C. LncRNAs regulate the cytoskeleton and related Rho/ROCK signaling in cancer metastasis. Mol Cancer. 2018 Apr 4;17(1):77.

8. Janakiraman H, House RP, Gangaraju VK, Diehl JA, Howe PH, Palanisamy V.The Long (lncRNA) and Short (miRNA) of It: TGFβ-Mediated Control of RNA-Binding Proteins and Noncoding RNAs. Mol Cancer Res. 2018 Apr;16(4):567-579.

9. Lin C, Yang L. Long Noncoding RNA in Cancer: Wiring Signaling Circuitry. Trends Cell Biol. 2018 Apr;28(4):287-301.

10. Peng WX, Koirala P, Mo YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene. 2017 Oct 12;36(41):5661-5667.

11. Hu J, Zhang L, Mei Z, Jiang Y, Yi Y, Liu L, Meng Y, Zhou L, Zeng J, Wu H, Jiang X. Interaction of E3 Ubiquitin Ligase MARCH7 with Long Noncoding RNA MALAT1 and Autophagy-Related Protein ATG7 Promotes Autophagy and Invasion in Ovarian Cancer. Cell Physiol Biochem. 2018;47(2):654-666.

12. Hu J, Meng Y, Yu T, Hu L, Mao M. Ubiquitin E3 ligase MARCH7 promotes ovarian tumor growth. Oncotarget. 2015 May 20;6(14):12174-87.

13. Du M, Chen W, Zhang W, Tian XK, Wang T, Wu J, Gu J, Zhang N, Lu ZW, Qian LX, Fei Q, Wang Y, Peng F, He X, Yin L. TGF-? regulates the ERK/MAPK pathway independent of the SMAD pathway by repressing miRNA-124 to increase MALAT1 expression in nasopharyngeal carcinoma. Biomed Pharmacother. 2018 Mar;99:688-696. doi: 10.1016/j.biopha.2018.01.120.

14. Xiang Y, Zhang Y, Tang Y, Li Q. MALAT1 Modulates TGF-β1-Induced Endothelial-to-Mesenchymal Transition through Downregulation of miR-145. Cell Physiol Biochem. 2017;42(1):357-372.

15. Li Q, Pan X, Wang X, Jiao X, Zheng J, Li Z, Huo Y. Long noncoding RNA MALAT1 promotes cell proliferation through suppressing miR-205 and promoting SMAD4 expression in osteosarcoma. Oncotarget. 2017 Sep 6;8(63):106648-106660.

16. Chen X, Xiong D, Yang H, Ye L, Mei S, Wu J, Chen S, Shang X, Wang K, Huang L. Long noncoding RNA OPA-interacting protein 5 antisense transcript 1 upregulated SMAD3 expression to contribute to metastasis of cervical cancer by sponging miR-143-3p. J Cell Physiol. 2018 Oct 20.

17. Zhang C, Hao Y, Wang Y, Xu J, Teng Y, Yang X. TGF-β/SMAD4-Regulated LncRNA-LINP1 Inhibits Epithelial-Mesenchymal Transition in Lung Cancer. Int J Biol Sci. 2018 Sep 7;14(12):1715-1723.

18. Ottaviani S, Stebbing J, Frampton AE, Zagorac S, Krell J, de Giorgio A, Trabulo SM, Nguyen VTM, Magnani L, Feng H, Giovannetti E, Funel N, Gress TM, Jiao LR, Lombardo Y, Lemoine NR, Heeschen C, Castellano L. TGF-β induces miR-100 and miR-125b but blocks let-7a through LIN28B controlling PDAC progression. Nat Commun. 2018 May 10;9(1):1845.

19. Ren Y, Jia HH, Xu YQ, Zhou X, Zhao XH, Wang YF, Song X, Zhu ZY, Sun T, Dou Y, Tian WP, Zhao XL, Kang CS, Mei M. Paracrine and epigenetic control of CAF-induced metastasis: the role of HOTAIR stimulated by TGF-ß1 secretion. Mol Cancer. 2018;17(1):5.

20. Zhao B, Lu YL, Yang Y, Hu LB, Bai Y, Li RQ, Zhang GY, Li J, Bi CW, Yang LB, Hu C, Lei YH, Wang QL, Liu ZM. Overexpression of lncRNA ANRIL promoted the proliferation and migration of prostate cancer cells via regulating let-7a/TGF-β1/ Smad signaling pathway. Cancer Biomark. 2018 Feb 14;21(3):613-620.

21. Zhao JJ, Hao S, Wang LL, Hu CY, Zhang S, Guo LJ, Zhang G, Gao B, Jiang Y, Tian WG, Luo DL. Long non-coding RNA ANRIL promotes the invasion and metastasis of thyroid cancer cells through TGF-β/Smad signaling pathway. Oncotarget. 2016 Sep 6;7(36):57903-57918.

22. Zhang X, Feng W, Zhang J, Ge L, Zhang Y, Jiang X, Peng W, Wang D, Gong A, Xu M. Long non-coding RNA PVT1 promotes epithelial-mesenchymal transition via the TGF-β/Smad pathway in pancreatic cancer cells. Oncol Rep. 2018 Aug;40(2):1093-1102.

23. Liu E, Liu Z, Zhou Y, Mi R, Wang D. Overexpression of long non-coding RNA PVT1 in ovarian cancer cells promotes cisplatin resistance by regulating apoptotic pathways. Int J Clin Exp Med. 2015 Nov 15;8(11):20565-72. eCollection 2015.

24. Wang ZY, Hu M, Dai MH, Xiong J, Zhang S, Wu HJ, Zhang SS, Gong ZJ. Upregulation of the long non-coding RNA AFAP1-AS1 affects the proliferation, invasion and survival of tongue squamous cell carcinoma via the Wnt/β-catenin signaling pathway. Mol Cancer. 2018 Jan 8;17(1):3.

25. Zhou H, Sun Z, Li S, Wang X, Zhou X. LncRNA SPRY4-IT was concerned with the poor prognosis and contributed to the progression of thyroid cancer. Cancer Gene Ther. 2018 Feb;25(1-2):39-46.

26. Zhuang J, Lu Q, Shen B, Huang X, Shen L, Zheng X, Huang R, Yan J, Guo H. TGFβ1 secreted by cancer-associated fibroblasts induces epithelial-mesenchymal transition of bladder cancer cells through lncRNA-ZEB2NAT. Sci Rep. 2015 Jul 8;5:11924.
27. Qin CF, Zhao FL. Long non-coding RNA TUG1 can promote proliferation and migration of pancreatic cancer via EMT pathway. Eur Rev Med Pharmacol Sci. 2017 May;21(10):2377-2384.
28. Wang H, Wang G, Gao Y, Zhao C, Li X, Zhang F, Jiang C, Wu B. Lnc-SNHG1 Activates the TGFBR2/SMAD3 and RAB11A/Wnt/β-Catenin Pathway by Sponging MiR-302/372/373/520 in Invasive Pituitary Tumors. Cell Physiol Biochem. 2018;48(3):1291-1303.
29. Deng Y, Zhao F, Zhang Z, Sun F, Wang M. Long Noncoding RNA SNHG7 Promotes the Tumor Growth and Epithelial-to-Mesenchymal Transition via Regulation of miR-34a Signals in Osteosarcoma. Cancer Biother Radiopharm. 2018 Jul 10.
30. Kawasaki N, Miwa T, Hokari S, Sakurai T, Ohmori K, Miyauchi K, Miyazono K, Koinuma D. Long noncoding RNA NORAD regulates transforming growth factor-β signaling and epithelial-to-mesenchymal transition-like phenotype. Cancer Sci. 2018 Jul;109(7):2211-2220.
31. Hao Y, Yang X, Zhang D, Luo J, Chen R. Long noncoding RNA LINC01186, regulated by TGF-β/SMAD3, inhibits migration and invasion through Epithelial-Mesenchymal-Transition in lung cancer. Gene. 2017 Apr 15;608:1-12.
32. Zhu F, Zhang X, Yu Q, Han G, Diao F, Wu C, Zhang Y. LncRNA AWPPH inhibits SMAD4 via EZH2 to regulate bladder cancer progression. J Cell Biochem. 2018 Jun;119(6):4496-4505.
33. Li RQ, Wu W, Song HQ, Ren Y, Yang M, Li J, Xu FJ. Well-defined reducible cationic nanogels based on functionalized low-molecular-weight PGMA for effective pDNA and siRNA delivery. Acta Biomater. 2016 Sep 1;41:282-92.
34. Kim SS, Harford JB, Moghe M, Rait A, Pirollo KF, Chang EH. Targeted nanocomplex carrying siRNA against MALAT1 sensitizes glioblastoma to temozolomide. Nucleic Acids Res. 2018 Feb 16;46(3):1424-1440.
35. Sophia J, Kowshik J, Dwivedi A, Bhutia SK, Manavathi B, Mishra R, Nagini S. Nimbolide, a neem limonoid inhibits cytoprotective autophagy to activate apoptosis via modulation of the PI3K/Akt/GSK-3β signalling pathway in oral cancer. Cell Death Dis. 2018 Oct 23;9(11):1087.
36. Pedram Fatemi R, Salah-Uddin S, Modarresi F, Khoury N, Wahlestedt C, Faghihi MA. Screening for Small-Molecule Modulators of Long Noncoding RNA-Protein Interactions Using AlphaScreen. J Biomol Screen. 2015 Oct;20(9):1132-41.