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Mini-Review

Regulation of Kisspeptin mediated signaling by non-coding RNAs in different cancers: the beginning of a new era

Ammad Ahmad Farooqi[1*], Rukset Attar[2], Behnaz Bageshlooyafshar[3], Uteuliyev Yerzhan Sabitaliyevich[4], Sadykov Bolat Nurmurzayevich[5], Armida Bakhytbekovna Yelekenova[6], Uzay Gormus[7]

[1] Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan
[2] Department of Obstetrics and Gynecology, Yeditepe University, Turkey
[3] Department of Animal Science, Faculty of Agricultural Science and Natural Resource, University of Gonbad Kavous, Gonbad-e Kavus, Golestan, Iran
[4] Kazakhstan Medical University "KSPH", Kazakhstan
[5] City Clinical Hospital No.5 in Almaty, Kazakhstan
[6] Department of Obstetrics and Gynecology, Astana Medical University, Kazakhstan
[7] Department of Medical Biochemistry and Biophysics, Division of Biochemistry, Karolinska Institutet, Stockholm, Sweden

Correspondence to: Ammadfarooqi@rlmclahore.com

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Abstract: Kisspeptin-driven intracellular signaling has captured enormous attention because of its central role in cancer onset and progression. Wealth of information has helped us to develop a better understanding of the critical roles of Kisspeptin-mediated signaling in different cancers. However, astonishingly, we have not yet drilled down deep into the mysterious aspects associated with non-coding RNA mediated regulation of Kisspeptin-driven signaling. Therefore, in this mini-review, we will comprehensively analyze available evidence related to miRNAs and long non-coding RNAs (LncRNAs) and their ability to modulate Kisspeptin-mediated signaling. There are visible knowledge gaps about interplay between non-coding RNAs and Kisspeptin-mediated signaling. It will be appropriate to say that we have just started to scratch the surface of an entirely new regulatory layer of Kisspeptin-mediated transduction cascade. Mechanistically, it has been revealed that inhibition of Kisspeptin mediated signaling activated and stimulated the entry of NFκB into the nucleus to stimulate expression of proteins which can sequentially inactivate tumor suppressor miRNAs. miRNAs have also an instrumental role in regulation of proteins which post-translationally modify and inhibit KISS1 expression. It is becoming progressively more understandable that LncRNAs act as miRNA sponges and protect oncogenic mRNAs. However, these facets are also incompletely investigated. Identification of LncRNAs which interfere with Kisspeptin-mediated pathway either through acting as miRNA sponges or working with methylation-associated machinery will be helpful in sharpening the resolution of the pixels of the regulatory network which shapes Kisspeptin-mediated signaling.

Key words: Kisspeptin; Cancer; Apoptosis; miRNA; Signaling.

Introduction

KISS1R (GPR54), a $G\alpha_{q/11}$-coupled GPCR has emerged as an important and versatile regulator of reproductive axis. Structural studies have shown that Kisspeptins (KPs) encoded by the KISS1 gene interacted with KISS1R. KPs (10, 13, 14 and 54 amino acids) are biologically active endogenous ligands having the ability to interact with G-protein-coupled receptor (GPR54) and transduce the signals intracellularly (1). Our rapidly evolving knowledge has helped us to conceptualize central role of Kisspeptin-mediated signaling in carcinogenesis (2, 3, 4, 5).

Excitingly, accumulating evidence has also allowed us to unravel previously unexplored interplay between non-coding RNAs and kisspeptin-driven signaling. In this review we have specifically addressed the facets related to regulation of kisspeptin-mediated signaling by non-coding RNAs. We have partitioned this multi-component review into positive and negative regulation of kisspeptin-mediated signaling. Lastly, we have comprehensively interpreted scattered pieces of information about integral role of non-coding RNAs in regulation of kisspeptin-mediated signaling.

Kisspeptin signaling as negative regulator of cancers

Conditionally replicative adenovirus with enhanced infectivity encoding KISS1 was engineered and used effectively against brain-invading metastatic clones of MDA-MB-231 and CN34 BCa cells (6).

SMAD ubiquitin regulatory factor-1 (SMURF1), a HECT-type E3 ubiquitin ligase has been shown to negatively regulate Kisspeptin-driven signaling (7). SMURF1 overexpression promoted BCPAP and K1 cell viability, migratory, invasive and proliferation abilities. SMURF1 negatively regulated the protein level of KISS1 in thyroid TPC-1 and SW579 cancer cells. SMURF1 promoted the ubiquitination of KISS1 in

thyroid TPC-1 and SW579 cancer cells. Overexpression of SMURF1 dose-dependently reduced KISS1 protein levels (7). Furthermore, SMURF1 overexpression enhanced the ubiquitination of KISS-1. More importantly, KISS1 overexpression inhibited the NF-κB signaling pathway in thyroid cancer TPC-1 and SW579 cells (7).

Melatonin inhibited breast cancer cell invasiveness mainly through GATA3-dependent KISS1 expression. Melatonin stimulated expression of KISS1 by enhancing the binding of GATA binding protein 3 to binding sites in promoter region of KISS1 (8).

Kisspeptin exerted its suppressive effects on the metastatic abilities of cancer cells via an EIF2AK2-mediated pathway (9). Rho proteins bind to and activate RHO-associated coiled-coil-containing protein kinase (ROCK1 and ROCK2), which further phosphorylate target proteins, LIMK1/2 and MLC. Kisspeptin induced an increase in the phosphorylation of the downstream mediators of RhoA (MLC and cofilin). Notably, inhibition of EIF2AK2 did not prevent the activation of RhoA in LoVo cells. However, inhibition of ROCK prevented EIF2AK2 phosphorylation. Kisspeptin prevented the development of LoVo-derived lung metastasis in nude mice, while inhibition of EIF2AK2 severely abrogated the inhibitory effects of kisspeptin on the metastatic capabilities of LoVo cells (9).

Kisspeptin signaling as positive regulator of cancers

ABCG2/BCRP (breast cancer resistance protein) and receptor tyrosine kinase AXL have recently been reported to be overexpressed and played central role in development of resistance against doxorubicin (10). Doxorubicin accumulation was drastically reduced in KISS1R-overexpressing SKBR3 cancer cells. Use of inhibitors of drug efflux transporters or KISS1R antagonists restored sensitivity to doxorubicin (Blake, 2017). Pharmacological inhibition of KISS1R resulted in reduction of BCRP mRNA levels in MDA-MB-231 cells. KISS1R signaling induced transcriptional upregulation of AXL via binding of a transcription factor, SP-1 (10). Overall these findings clearly suggested that KISS1R played instrumental role in development of chemoresistance in breast cancer cells via upregulation of AXL and BRCP/ ABCG2.

KISS1R signaling stimulated fibulin-3 in ERα-negative BCa cells. KP-10 induced an increase in the level of fibulin-3 in KISS1R-expressing SKBR3 cells and potentiated secretion of fibulin-3. KP-10 did not stimulate MMP-9 activity in fibulin-3 depleted cells (11). Metastatic spread to the lung was considerably reduced in mice injected with fibulin-3-silenced MDA-MB-231 cells (11).

EVI1 has recently been reported to transcriptionally upregulate KISS1. KISS1 overexpression also induced migration in EVI1 knockdown MDA-MB-231 BCa cells (12).

In the upcoming section, we will specifically focus on emerging evidence related to regulation of Kisspeptin mediated signaling by non-coding RNAs in different cancers.

Regulation of Kisspeptin-mediated signaling by miRNAs and long non-coding RNAs

Explosion of discoveries revolving around non-coding RNAs has enabled us to develop a better understanding of the underlying mechanisms of carcinogenesis, drug resistance and metastasis. Highly sophisticated scientific evidence has unraveled molecular mechanisms associated with miRNA biogenesis and regulation of target genes in different cancers. In this section, we have set spotlight on the miRNAs and LncRNAs which have been shown to modulate Kisspeptin-driven signaling axis in different cancers.

miR-199b

Transfection of miR-199b mimics into SW480 and SW620 cells markedly reduced proliferation and metastasizing abilities (13). miR-199b repressed the metastasizing potential of tumor cells in xenografted mice. Detailed mechanistic insights revealed that CREB (c-AMP response element-binding protein), a transcriptional factor upregulated the expression of KISS1. However, SIRT1 (Sirtuin-1) de-acetylated it and prevented CREB mediated upregulation of KISS1 (13) (figure 1). miR-199b has been shown to directly target SIRT1 in colorectal cancer cells (13). Henceforth, miR-199b overexpression exerted repressive effects on SIRT1 and potentiated CREB-triggered upregulation of KISS1 in colorectal cancer cells.

miRNA-199 family has also been shown to target Integrin-α3 in bladder cancer cells (14). miR-199b-5p overexpression suppressed cellular migration of HCC cells and inhibited tumor metastasis in xenografted mice (15).

Regulation of TCF21 by miR-21

TCF21 worked synchronously with E12, a TCF3 isoform and TCF12 and transcriptionally upregulated KISS1 in C8161 cells (16) (figure 1). There are direct pieces of evidence which have highlighted regulation of TCF21 by non-coding RNAs. TARID (for TCF21 antisense RNA inducing demethylation) is reportedly involved in stimulation of transcription of TCF21 (17). Likewise, LINC00163, another long non-coding RNA positively regulated TCF21 expression (18).

TCF21 silencing resulted in downregulation of KISS1 in Caki-1 cells (19). MiR-21 directly targeted TCF21 in Caki-1 cells. KISS1 overexpression inhibited invasive potential of Caki-1 cells (19). Overall these findings provided evidence that miR-21 mediated targeting of TCF21 resulted in suppression of KISS in renal cell carcinoma cells.

Inhibition of KISS1 resulted in downregulation of miR-200

It has previously been convincingly revealed that WASF3 knockdown induced upregulation of KISS1 in cancer cells (20). Moreover, stapled peptides, known as WASF helix mimics exerted inhibitory effects on WASF3. KISS1 levels were found to be considerably enhanced in stapled peptides treated-MDA-MB-231 and PC3 cells (21). KISS1 inhibition or downregulation re-

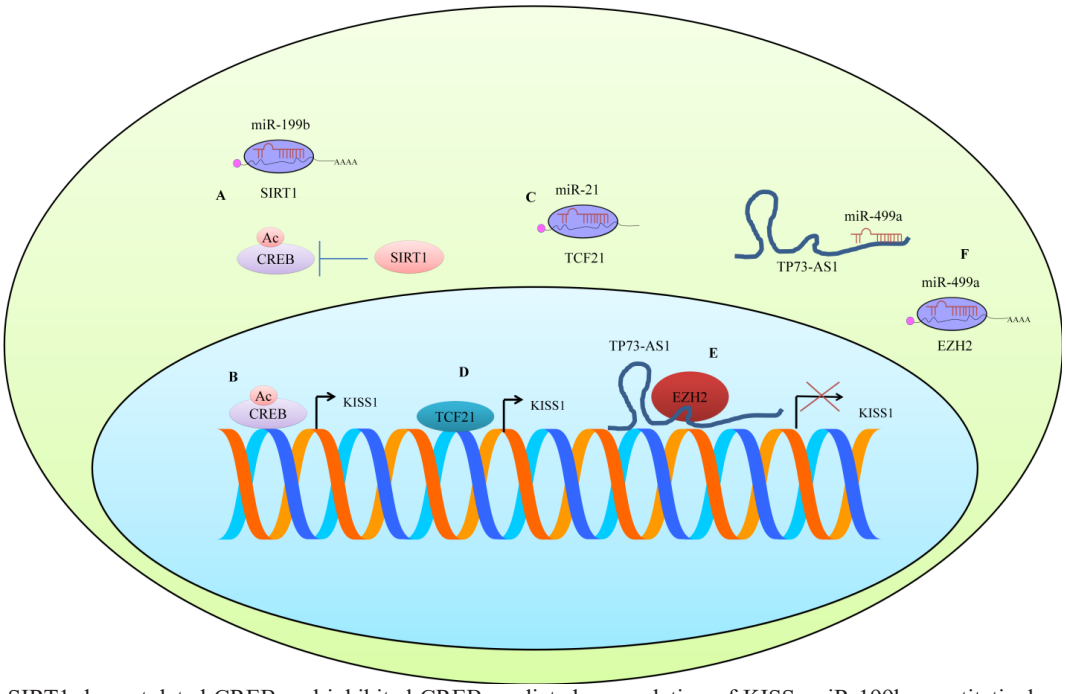

Figure 1. (A-B) SIRT1 de-acetylated CREB and inhibited CREB mediated upregulation of KISS. miR-199b quantitatively controlled SIRT1 and enabled CREB mediated stimulation of KISS1. (C-D) TCF21 transcriptionally upregulated KISS1. However, miR-21 mediated targeting of TCF21 severely repressed TCF21-driven upregulation of KISS1. (E-F) TP73-AS1 worked harmoniously with EZH2 and transcriptionally repressed KISS1. TP73-AS1 sequestered EZH2-targeting miR-499a away and potentiated EZH2 expression.

sulted in increased nuclear accumulation of NFκB (22). Furthermore, NFκB triggered upregulation of ZEB1. ZEB1 transcriptionally repressed E-cadherin and tumor suppressor miRNAs. miR-200 promoter contained paired binding sites for ZEB. Expectedly ZEB1 transcriptionally downregulated miR-200 and promoted metastasizing potential of breast cancer cells (22). Triacetyl resveratrol has been shown to stimulate the expression of miR-200 in pancreatic cancer cells (23).

Certain hints have surfaced which pinpointed towards miRNA regulation of WASF3 in different cancers. miR-217 and miR-218 directly targeted WASF3 in different cancers and repressed proliferation and metastasizing abilities of osteosarcoma and gastric cancer cells (24, 25).

Long non-coding RNA mediated control of KISS1

Long non-coding RNAs (LncRNAs) have been shown to pleiotropically modulate wide ranging signaling pathways. However, surprisingly, regulation of Kisspeptin mediated signaling by LncRNAs has been insufficiently explored. Recently emerging scientific evidence has substantiated critical role of LncRNAs in different cancers. Series of high-quality researches have unveiled that LncRNAs worked synchronously with EZH2 to transcriptionally regulate expression of target genes. LncRNAs strategically engaged tumor suppressor miRNAs and sequestered oncogenic mRNAs away.

EZH2, a catalytic subunit of PRC2 (polycomb repressive complex-2) transcriptionally repressed myriad of target genes mainly through methylation of lysine 27 of histone 3 (H3K27).

TP73-AS1, a long non-coding RNA worked in an orchestrated manner with EZH2 and transcriptionally repressed KISS1 (26) (figure 1). It has recently been revealed that TP73-AS1 sequestered away EZH2-targeting miRNA. miR-499a was noted to directly target EZH2 but TP73-AS1 interacted with miR-499a and protected EZH2 from targeting (27).

TP73-AS1 acted as a miRNA sponge and sequestered miR-490-3p away from TWIST1 in breast cancer. However, inhibition of TP73-AS1 potentiated miR-490-3p mediated targeting of TWIST1 (28).

Concluding remarks

Detailed mechanistic insights have helped us to develop a better knowledge about central role of kisspeptin mediated signaling in different cancers. More importantly, kisspeptin-driven pathway has been shown to dualistically regulate carcinogenesis. Confluence of information suggested that kisspeptin-mediated cascade exerted repressive effects on NFκB and consequently inhibited NFκB-target genes. Transcriptional regulation of Kisspeptin by different proteins is also very essential and future studies must converge on detailed analysis of epigenetic modifications associated with kisspeptin and its receptor in different cancers. However, we cannot overlook lack of available evidence related to crosstalk of kisspeptin-mediated signaling with various transduction cascades. There are many pathways which are deregulated in cancers and it will be paramount to identify the crosstalks of kisspeptin-mediated signaling proteins with Wnt/β-catenin, SHH/GLI, TGF/SMAD, Notch, JAK-STAT in various types of cancers.

Regulation of kisspeptin-mediated signaling by non-coding RNAs is providing new momentum to explore a phenomenon which has started to attract attention of researchers. Although we have witnessed developments in this area of research but these characterized non-coding RNAs can be considered as "tip of iceberg", as most non-coding RNAs have not been investigated with reference to kisspeptin-mediated signaling. It seems

clear that there is a layered regulation of Kisspeptin mediated signaling. Myriad of transcriptional factors inactivate and stimulate expression of Kisspeptin and its receptor. Therefore, some of the key questions which need extensive research are tightly interconnected with identification of miRNAs and LncRNAs which regulate these transcriptional factors. Furthermore, LncRNA have been shown to work harmoniously with epigenetic-modifying machinery to regulate expression of different genes. It needs to be investigated how different LncRNAs modulate expression of Kisspeptin and its receptor. Although we have seen that LncRNA work with EZH2 and inactivate KISS1, however, further studies are necessary for a better analysis of LncRNAs which negatively regulate KISS1.

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