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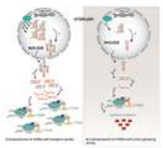

ISSN: 1547-6286 (Print) 1555-8584 (Online) Journal homepage: https://www.tandfonline.com/loi/krnb20

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To cite this article: Arathy S. Kumar, Suresh K. Rayala & Ganesh Venkatraman (2018) Targeting IGF1R pathway in cancer with microRNAs: How close are we?, RNA Biology, 15:3, 320-326, DOI: 10.1080/15476286.2017.1338240

To link to this article: https://doi.org/10.1080/15476286.2017.1338240

RNA BIOLOGY, 2018
VOL. 15, NO. 3, 320–326
https://doi.org/10.1080/15476286.2017.1338240

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REVIEW

Targeting IGF1R pathway in cancer with microRNAs: How close are we?

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ABSTRACT

Cancer of the head and neck are the most common cancers in India and account for 30% of all cancers. At molecular level, it could be attributed to the overexpression of growth factors like IGF1-R, EGFR, VEGF-R and deregulation of cell cycle regulators and tumor suppressors. IGF1-R is an emerging target in head and neck cancer treatment, because of its reported role in tumor development, progression and metastasis. IGF1R targeted agents are in advanced stages of clinical development. Nevertheless, these agents suffer from several disadvantages including acquired resistance and toxic side effects. Hence there is a need for developing newer agents targeting not only the receptor but also its downstream signaling. miRNAs are considered as master regulators of gene expression of multiple genes and has been widely reported to be a promising therapeutic strategy. This review discusses the present status of research in both these arenas and emphasizes the role of miRNA as a promising agent for biologic therapy.

ARTICLE HISTORY
Received 6 March 2017
Accepted 31 May 2017

KEYWORDS
Growth factor receptor signaling; head neck cancer; IGF1R; miR493; miRNA therapy

Introduction

Role of IGF1R signaling in multiple functions including proliferation, differentiation, glucose homeostasis, energy metabolism and its conserved regulatory module is an indication of its importance in coordinating growth, development and metabolism. IGF1 pathway comprise of its ligand- IGF1, respective receptor- IGF1R, ligand binding proteins- IGFBPs, downstream adaptor molecules such Shc and insulin receptor substrate (IRS) −1, −2, −3, and −4 and downstream effectors- AKT1, MAPK, etc. Insulin-like growth factor 1 (IGF-1) is a peptide hormone, functions as the major mediator of growth hormone (GH)-stimulated somatic growth and GH-independent anabolic reactions in most cells and tissues. Circulation of IGF1 in serum is in its bound form to high affinity binding proteins [1]. Synthesis of IGF1 is in 2 different ways- synthesis in the liver and secreted into the blood which is under the control of growth hormones. IGF1 synthesis from peripheral tissues such as bone in autocrine/paracrine manner, which is under the control of growth hormones as well as by factors that are secreted locally by the surrounding cell types. These IGF1 also enter the systemic circulation, which is not under the regulation of GH and hence the regulated secretion of autocrine or paracrine secreted IGF1 and the factors responsible for the secretion needed to be studied and explored more [2].

IGF1R pathway is studied to have a role to play in prenatal and post natal growth in mice and in life span regulation. At the tissue level IGF1R mediated PI3K-AKT and/or ERKs mediates differentiation and also shown to maintain the myocardium and brain. Its role in regulation of vascular homeostasis and endothelial function and reports showed decreased expression of IGF1R increases the fibrosis of kidney disease in mice models [3]. But there are paradoxical results showing IGF1R and longevity in lower animal forms such as C.elegans [4]. IGF1R interaction and cross talk with other growth factor receptors are studied to have a major role in cells; interactions between IR and IGF1R in muscle were found to have significance in glucose homeostasis in mice models [5].

IGF-1 uses its effects via binding followed by the activation of the IGF-1 receptor, which is a tyrosine kinase protein, which is widely distributed and it facilitates circulating IGF-1 to perform the function of balanced growth among multiple tissues and organs. IGF1R consists of 2 half-receptors with an extracellular α-subunit and one transmembrane β-subunit which perform tyrosine kinase activity on binding to the ligand. Receptor has affinity toward the other ligand IGF2 and the ability of IGF1R to form Insulin receptor (IR) and perform the signaling by binding to IGF1/2 makes the signaling complex. Binding of ligand to IGF1R results in the autophosphorylation of IGF1R at tyrosines 1131,1135, and 1136 in the kinase domain of β-subunit of the receptor. This phosphorylation induces further phosphorylation of juxtamembrane tyrosines and carboxyl-terminal serines creating docking sites for proteins including IR substrates 1 to 4 (IRS-1 to IRS-4), and Shc (Src homology and collagen domain protein). Binding of these molecules activates signaling via the phosphatidylinositol-3-kinase (PI3K)-AKT and RAS/RAF/mitogen-activated protein kinase (MAPK) pathways [6].

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IGF1R in cancer: How and why?

Reports of deregulated expression of IGF1R pathway molecules including the receptor and downstream effectors are reported in many cancers as explained below.

Brain tumor

Recent studies on clinical samples showed increased levels of IGF1 as well as IGF-sequestering IGFBP3, IGFBP3-cleaving proteases (MMP and tPA) in CSF and IGF1R was identified as a potential target for clinical trials in high risk medulloblastoma [7]. Expression studies on glioma patient samples shown to have increased expression of IGF1R compares to normal brain tissue [8] and overexpression of IRS1 was reported in both malignant and benign brain tumors [9,10]. The overexpression of IRS1 as well as IRS2 in different cancers including medulloblastoma have reviewed earlier indicating its role in tumorigenesis [11,12]. Validation of genes related to the PI3k/Akt signaling pathway for genetic alteration and aberrant expression in a series of 103 glioblastomas showed overexpression of several genes including IRS2, AKT1 and subunits of Pi3k, but not IRS1 or AKT2 [13].

Head and neck cancer

Validation of IGF1R-α cytoplasmic/membranous overexpression showed it may serve as an independent adverse prognostic factor for recurrence and survival in patients with surgically resected squamous-cell carcinoma of the larynx [14] where a previous study showed IGFBP-3 expression, in a state of co-expression with IGF-1R, can predict poor prognosis in squamous cell carcinoma of the head and neck (SCCHN) patients [15]. Tissue level expression of IGF1R revealed an overexpression in both in primaries and regional lymph nodes of oropharyngeal and nasopharyngeal region [16] and in tongue cancer patients [17], which is capable of transmitting mitogenic signals to the neoplastic cells in response to IGF1. In HNSCC high IGF-1R expression and its association with HPV-negative status, advanced tumor stage and reduced overall and disease-specific survival [18] makes it a promising target for HPV negative HNSCC. In nasopharyngeal carcinoma, overexpression of IRS1 might be closely correlated with lymph node metastasis in NPC and positive expression of IRS-1 is postulated to be used as an independent biomarker for predicting lymph node metastasis of NPC [19] but there are contradicting results showing negative correlation of IRS-1 expression with tumor metastasis both in tissue samples and cell lines of HNSCC [20]. Over expression of IG1R, IRS and MAPK1 was reports in a study where significant number of head and neck cancer patient samples showed the upregulation in tumor compared to the normal counterpart [21].

Breast cancer

Studies on benign and noninvasive breast lesions, IGF-1R expression was slightly increased in lesions that are hormonally driven (such as atypical ductal hyperplasia and columnar cells changes) and was significantly reduced in ER-negative lesions (such as apocrine metaplasia) which may explain partially lower response rate to neo adjuvant chemotherapy in luminal tumors [22]. IGF-1R expression was associated with mammographic breast tissue density in patients aged >40 y and in premenopausal women, IGF-1R overexpression in breast cancer tissue was significantly associated with HER-2 positivity and poor disease free survival (DFS) [23].

In MCF-7 overexpression of IRS1 alone was capable of total loss of estrogen dependence for growth [24] and IRS1 showed a highly significant positive correlation and highly expressed in the less aggressive ductal carcinoma in situ (DCIS) tumors whereas elevated IRS2 expression was associated with high grade invasive ductal carcinomas (IDC) and positive correlation between ERα and IRS1 was hypothesized to respond favorably to chemotherapy [25] and in breast cancer progression [26]. Studies on transgenic mice, overexpression IRS1 and IRS2 in the mammary gland showed progressive mammary hyperplasia, tumorigenesis, and metastasis [27]. Role of IRS proteins in mammary gland development and in its function as well as in tumor formation and metastasis has reviewed earlier [28,29].

Lung cancer

Deregulation in IGF1R pathway and beneficial role of targeting that pathway is reviewed elsewhere [30]. Upregulation and expression of IGF-1 and IGF1R in NSCLC were correlated with tumor progression and patient prognosis [31]. Over expression of IGF1R protein in small cell lung cancer was reported to be correlated with the gene copy number in clinical samples [32] and an independent study on IGF-1R overexpression in squamous cell lung cancer displayed 79.2% of high IGF-1R staining [33]. Another study on NSCLC tissues revealed IGF1R protein expression and mRNA expression is higher in squamous cell carcinomas compared with other histologies which correlated with EGFR expression and high IGF1R gene copy number alone associates with better prognosis in surgically resected NSCLC [34].

Gastrointestinal cancers

Studies on wild type (WT) and pediatric GISTs (gastrointestinal stromal tumors) revealed that IGF1R is amplified and the protein is overexpressed which may be associated with oncogenesis [35] and the overexpression of IGF1R at protein and transcript was tightly SDHB (succinate dehydrogenase) deficiency [36]. Integrative genomic analysis showed enrichment of activation of IGF signaling, including overexpression of IGF2, downregulation of IGFBP3 and allelic losses of IGF2R and the study defined gene signature for IGF-1R activation finally leads to the Proliferation subclass of hepatocellular carcinoma [37]. Over expression of IGF2 as well as IGF1R in protein as well as in RNA level was involved in the pathogenesis of gastric cancer, probably by autocrine/paracrine stimulation of cell growth [38]. In patient samples with colorectal cancer, expression of IGF-1 and IGF-1R seems to increase with tumor size [39]. Expression studies of IGF1R in colorectal cancer patients revealed the fact that functional changes of the IGF-1R expression participate in the maintenance of progression of cancer rather than in its initial development [40].

Bone cancer

Studies on osteosarcoma showed higher mRNA expression and copy number in primary patient samples and xenograft samples compared with corresponding cell lines [41] and the

significant level of expression of IGF1R and the ligands were not correlated with metastatic lesions [42]. Studies on mouse mesenchymal stem cells (MSCs) and in osteosarcoma cells showed a precise regulation of IRS-1 expression level is critical for determining the differentiating capacity of these and that derangement of IRS-1 levels can be a critical step in OS transformation [43]. Genome-wide gene expression data of high-grade osteosarcoma biopsies and cell lines detected an over-representation of IGF1R signaling including downregulation of several IGFBP and further inhibition of IGF1R as well as IR/IGF1R signaling using small molecule inhibitor reduced the phosphorylation of IRS1 [44].

Prostate cancer

Over expression of IGF1R in primary prostate cancer compared with benign prostatic epithelium and the observed increase in IRS-1, a docking protein in IGF1R pathway, in a few sample, highlight the importance of the IGF1R pathway in prostate cancer biology [45]. IGF-1R analysis in PCa cells or clinical samples showed that T2E (MPRSS2-ERG (T2E) fusion protein) expression correlated with higher IGF-1R expression at mRNA and protein levels where ERG acts as a transcriptional activator for IGF1R [46]. Studies on PC cell line showed IGF-1 as a novel survival factor in prostate cancer, which induces a resistance to apoptosis mediated by the expression of the anti-apoptotic proteins Bcl^{-}XL and Mcl^{-}1and is associated with increased phosphorylation of FAK [47]. An independent study on advanced, androgen-independent metastatic PC tumor samples, IGF1R and IRS-1 continued to express during the metastatic development of cancer [45] and in an in vivo study, upregulation of both IGF-I and the IGF1R during progression to androgen-independent growth of tumor was observed [48].

Others

Wilms tumor which is a pediatric metanephric blastema, is observed to have overexpression of IGF1R related to the WT1, Wilms tumor gene product binding to IGF1R promoter [49]. In synovial sarcoma tumors, IGF1R expression check was done using Western blot and reverse transcriptase-PCR and the IGF1R detectable group was associated with a high incidence of lung metastases and high tumor cell proliferative rate, compared with the non-detectable group [50]. Molecular profiling studies on human adrenal tumors validated overexpression of 2 precarious components of the IGF signaling cascade (IGF2 and IGF-1R) and associated activation of the downstream effector, Akt. These results confirming critical role of IGF pathway in ACC pathogenesis [51]. In case of familial pheo/pgl, overexpressed IGF-1R was found to be associated with malignancy and such patients are hypothesized to have an increased risk of metastasis [52]. IGF1R upregulation in bladder cancer compared with non-malignant bladder especially increased transcript level of IGF1R in invasive (T2–4) tumors can relate its contribution to a propensity for invasion [53], but an independent experiment with patient as well as normal subjects showed no difference in free IGF1 level in urine samples [54]. Increased expression of IGF1R as well as IGF1 in chronic lymphocytic leukemia compared with non CLL and the observation that use of TKI, inhibited the several signaling molecules via by blocking IGF1R-mediated signaling, makes this an ideal pathway for CLL treatment in future [55]. In a study on malignant adrenocortical tumor, the IGF1R overexpression was found to be independent of increased gene copy number, IGF1R polymorphisms and the abnormal expression of the microRNAs miR-100, miR-145, miR-375, and miR-126 [56]. Large cohort Genomic characterization of Malignant peripheral nerve sheath tumor (MPNST) identified a significant enrichment of copy number–an important events in the insulin-like growth factor 1 receptor (IGF1R) pathway, including frequent amplifications of the IGF1R gene itself [57]. IRS2 expression studies on a large variety of tumors [58] neurofibromas showed its elevated expression during its the progression to malignant peripheral nerve sheath tumors (MPNSTs) but it does not necessarily correlate with poor survival [59].

miR against IGF1R pathway

Small endogenous, non-coding microRNAs are validated to have significant role in diverse biologic processes which vary from development to different diseases including cancer. Deregulated miR expression was studied extensively in cancer elsewhere [60,61]. The ability of a single miR to regulate expression of multiple mRNAs makes further validation of it in therapy a promising area of research [62]. Independent studies have confirmed different miRs which can target single or multiple molecules in IGF1R pathway [21,63-118]. Existing validated data have shown miRs which can target multiple molecules in IGF1R pathway including IGF1R, which include miR-7, Let-7, miR-493, miR-155, miR-99, miR-145 etc. as shown in Fig. 1.

Perspective

IGF1 pathway has been extensively studied for the identification of deregulated miR which targets the members of this pathway [119]. Microarray as well as qRT- PCR studies have confirmed significant miRs in paired tumor samples as well as in cell lines in different cancer types. Regulation of miR transcription through IGF1R pathway and reciprocal regulation of IGF1R pathway by same miR is an indication of importance of controlled signaling pathways within cells. Reciprocal Regulation of miR and IGF1R pathway have been reported in different studies as miR-1 and Insulin-Like Growth Factor-1 Signal Transduction Cascade through Foxo3a [120], miR-99a via IGF1R/MAPK and IGF1R/AKT signaling [121,122], miR-493 expression through snail [21], miR-122 via C/EBP α [123]. These kinds of experimental evidences indicate the importance of existence miR mediated feedback loops in growth factor mediated signaling and their significance in normal functioning of cells. Use of miRs which can target multiple molecules in IGF1 signaling pathway can be used with successful delivery methods in different cancers where overexpression of multiple pathway molecules are evident and thereby reduce therapeutic resistance. Such therapy will reduce the recurrence of cancer and improve disease free survival of patience.

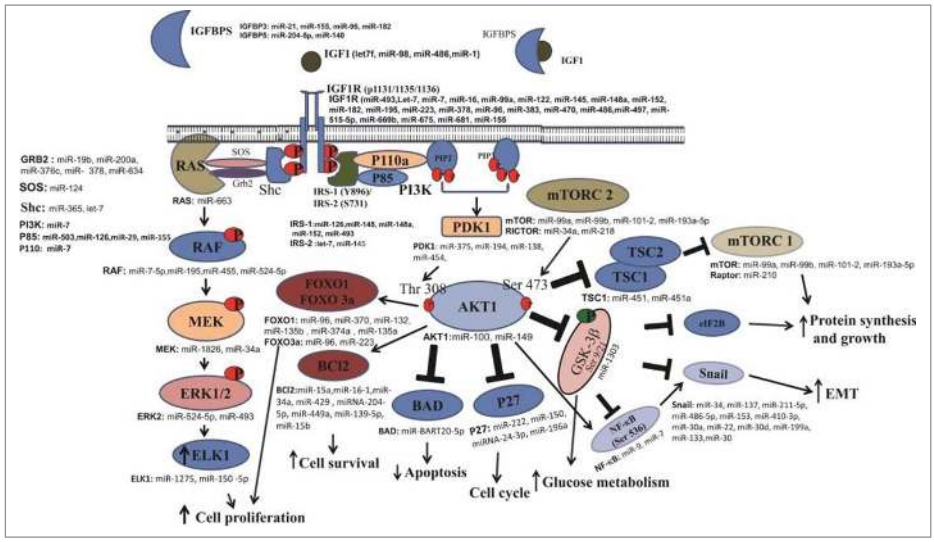

Figure 1. Overview of miRNAs targeting the IGF1R pathway in its entirety.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors would like to acknowledge the support of Prof. S.P.Thyagarajan Dean (Research), Sri Ramachandra University and Dr Solomon FD Paul. Head, Human Genetics, SRU for their constant support and encouragement.

Funding

RSK was supported by a grant from Department of Biotechnology, Ministry of Science & Technology, Govt of India via grant No. BT/PR12930/AGR/36/650/2009. ASK is thankful to Council of Scientific and Industrial Research, Govt of India for research fellowship.

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