[Frontiers in Bioscience 17, 2350-2355, June 1, 2012]

Role of miR-155 in breast cancer

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1. ABSTRACT

Breast cancer is the second leading cause of death due to cancer in women. Accumulating evidence shows a correlation between overexpression of miR-155 and breast cancer development. The microRNA (miRNA) encoded by *mir-155* is known to be oncogenic in multiple tumors. This review summarizes the signaling pathways that are regulated by miR-155 in breast cancer and discusses therapeutic possibilities related to miR-155.

2. INTRODUCTION

MicroRNAs (miRNAs) are a class of short single-stranded RNAs. Usually, miRNAs consist of 19–24 nucleotide-long noncoding RNAs that act as important negative regulators of gene expression at the post-transcriptional level (1). The abundance of miRNAs extends their involvement to many human diseases, including cancer. MiRNAs can be classified as tumor suppressors or oncogenes. Many miRNAs are deregulated in tumors compared with the normal tissues, implying that miRNAs may play important roles in tumorigenesis or tumor maintenance (2). There is accumulating evidence for the joint involvement of miRNAs and transcription factors in feedback and feed-forward loops that affect gene regulation networks. RNA polymerase II transcribes miRNAs, and the transcription of miRNAs is regulated by transcription factors (3; 4). The primary transcript (pri-miRNA) is capped and polyadenylated. The nuclear RNase III Drosha and its cofactor DGCR8/Pasha process the pri-miRNA and convert it to a precursor miRNA of 60–70 nucleotides containing a stem-loop structure (5; 6). Exportin-5 exports the precursor miRNA to the cytoplasm where a second RNase III, Dicer, processes the precursor miRNA and releases a mature 22-nucleotide miRNA. The mature miRNA then moves to an RNA-induced silencing complex (RISC) and directs the complex to complementary regions in the 3'-untranslated region (UTR) of target mRNAs, leading to mRNA degradation or translation inhibition. The degree of complementarity between the miRNA and the target mRNA determines the degree of mRNA degradation or translation inhibition (7; 8). Because of different degrees of complementarity, each miRNA may have several hundreds or thousands of target mRNAs (9).

The human microRNA-155 gene *mir-155* is located at B cell integration cluster (BIC), a region within chromosome 21q21.3 (10). MiR-155 was first reported to be upregulated in B-cell lymphomas and chronic lymphocytic leukemia, implicating a role in the oncogenesis of hematopoietic malignancies (11). MiR-155 is also upregulated in a variety of other human cancers, including breast, colon, lung, pancreatic, and thyroid

cancers (12-16). Oncogenic microRNAs that are overexpressed in tumors function mainly *via* repressing the expression of tumor suppressor or tumor suppressor-like genes (17). Accumulating evidence shows that miR-155 is an oncogenic microRNA.

Breast cancer is the second leading cause of cancer death in women. Despite improvements in treatment over the past few decades, there is an urgent need for development of targeted therapies (18). In this review, we summarize the current knowledge of miR-155 with respect to the signaling pathways involved in breast cancer and discuss some issues to be addressed in the future.

3. MIR-155 AND TGF-B SIGNALING

In normal cells, transforming growth factor β (TGF-β) blocks the cell cycle at the G1 stage, giving rise to proliferation inhibition, differentiation, or apoptosis. In transformed cancer cells, the elements of the TGF-β signaling pathway are altered, promoting proliferation in these cancer cells (19). A dramatic characteristic of advanced breast cancer is metastasis, which accounts for the majority of deaths in cancer patients. The most critical step in metastasis is a process known as the epithelial-mesenchymal transition (EMT). In cells undergoing EMT, the loss of epithelial cell adhesion and remodeling of cytoskeletal components is coordinated with an increase in mesenchymal components and the initiation of a migratory phenotype (20). TGF-β has proven to be a key regulator of EMT in late-stage carcinomas, where it promotes invasion and metastasis (21). TGF-β binds to a heteromeric complex of transmembrane serine/threonine kinases, and subsequently activates Smad2 and Smad3. Phosphorylated Smad2/Smad3 associates with Smad4 as a heteromeric complex and translocates to the nucleus. This complex binds directly to Smad-binding elements and associates with a number of transcription factors, coactivators, or corepressors, thus leading to the transcriptional induction or repression of a diverse array of genes. A number of genes that are associated with tumor growth and metastasis have been shown to be directly regulated by this pathway, including the induction of COX2, Slug, Snail, and Twist and the repression of Id2 and Id3 (21).

MiR-155 lies at downstream of the TGF-β signaling pathway. The promoter of *mir-155* is a target of Smad4. MiR-155 is upregulated in normal mouse mammary gland epithelial cells (NMuMG cells) by the TGF-β/Smad4 pathway and mediates TGF-β-induced EMT and cell invasion (22). Ectopic expression of miR-155 in NMuMG cells disrupted proper tight junction formation and promoted cell migration and invasion. Conversely, antagonizing miR-155 in NMuMG cells reduced the occurrence of TGF-β-induced EMT and cell migration and invasion. MiR-155 also directly inhibited the expression of RhoA. RhoA is the prototypical member of the Rho GTPase family and regulates many cellular processes, including cellular adhesion, motility, and polarity. RhoA is an important modulator of cell junction formation and stability. Importantly, miR-155-induced phenotypes are restored by expressing a miR-155-insensitive version of RhoA in miR-155 overexpressing cells. These findings suggest that miR-155 is regulated by the TGF-β/Smad4 pathway and downregulates RhoA protein expression to promote EMT progression. MiR-155 is highly expressed in invasive tumors, but not in noninvasive cancer tissues. Aside from downregulation of RhoA protein expression by miR-155, TGF-β induces the ubiquitination and degradation of RhoA by Smurf1 E3 ligase that is activated by Par6 (23). Thus, TGF-β downregulates RhoA protein at 2 levels: translation and protein degradation.

4. MIR-155 AND JAK-STAT SIGNALING

The JAK-STAT signaling pathway transmits signals from outside the cell, through the cell membrane, and into the cell nucleus. Gene promoters on the DNA are then activated, leading to DNA transcription (24). JAKs, which possess tyrosine kinase activity, bind to some transmembrane cytokine receptors on the interior of the membrane. The binding of ligand to the receptor induces activation of JAKs. With increased kinase activity, they phosphorylate tyrosine residues on the receptor and create sites for interaction with proteins that contain phosphotyrosine-binding SH2 domains. Signal transducers and activators of transcription (STATs) with SH2 domains capable of binding these phosphotyrosine residues are recruited to the receptors and are themselves tyrosine-phosphorylated by JAKs. These phosphotyrosines then afford binding sites for SH2 domains of other STATs, mediating their dimerization. Different STATs form heterodimers or homodimers. Phosphorylated STAT dimers accumulate in the cell nucleus where they bind to DNA and promote transcription of genes responsive to STATs (25). STATs may also be directly tyrosine-phosphorylated by receptor tyrosine kinases such as the epidermal growth factor receptor, as well as by non-receptor tyrosine kinases such as c-Src. Suppressors of cytokine signaling (SOCS) block STAT phosphorylation by binding and inhibiting JAKs or competing with STATs for phosphotyrosine-binding sites on cytokine receptors (26).

The tumor suppressor gene suppressor of cytokine signaling 1 (SOCS1) is an evolutionarily conserved target of miR-155 in breast cancer cells (27). MiR-155 expression is inversely correlated with SOCS1 expression in breast cancer cell lines as well as in a subset of primary breast tumors. Ectopic expression of miR-155 significantly promotes the proliferation of breast cancer cells and the development of tumors in nude mice. In breast cancer cells, RNA interference mediated knockdown of SOCS1 recapitulates the oncogenic effects of miR-155, whereas restoration of SOCS1 expression attenuates the pro-tumorigenesis function of miR-155. Overexpression of miR-155 in breast cancer cells leads to constitutive activation of STAT3 through the JAK-STAT signaling pathway. As inflammation is an important promoter of cancer, and the JAK-STAT signaling pathway is one of the most important inflammatory pathways, JAK-STAT signaling may contribute to inflammation-associated malignancy. Disrupted or deregulated JAK-STAT signaling can also result in immune deficiency syndromes. Stimulation of breast cancer cells by the inflammatory

cytokines IFN-γ and interleukin-6 (IL-6), lipopolysaccharide (LPS), and polyriboinosinic: polyribocytidylic acid (poly (I:C)) significantly upregulates miR-155 expression, suggesting that miR-155 may serve as a bridge between inflammation and cancer.

5. MIR-155 AND FOXO3A SIGNALING

FOXO3a (FKHRL1) is a major member of the forkhead transcriptional factor family (28). Members of this family are characterized by a distinctive forkhead DNA-binding domain, which is negatively regulated by MEK/ERK and Akt/PI3K signaling. Three other FOXO family members exist in humans: FOXO1, FOXO4, and FOXO6 (29). Phosphorylation of these transcription factors gives rise to the translocation of these transcription factors from the nucleus to the cytoplasm and blocks proapoptotic function. Unphosphorylated active FOXO3a resides in the nucleus and induces cell death by upregulating the apoptotic proteins that promote apoptosis (PUMA, Bim, FasL, and TRAIL) and cell cycle arrest (p27 and p21), and downregulating the antiapoptotic proteins (FLIP and Bcl-xL) (30-35). FOXO3a, therefore, acts as a tumor suppressor. Overexpression of FOXO3a inhibits tumor cell growth *in vitro* and tumor size *in vivo* in breast cancer cells. Deregulation of FOXO3a can also play a role in tumorigenesis. Genetic deletion of 3 FOXO alleles (FOXO1, FOXO3a, and FOXO4) generates progressive cancerous phenotypes such as thymic lymphoma and hemangioma (36).

Ectopic expression of miR-155 induces cell survival and chemoresistance to multiple agents, whereas knockdown of miR-155 renders cells susceptible to apoptosis and enhances chemosensitivity. FOXO3a is a direct target of miR-155 (18). MiR-155 directly targets the FOXO3a 3'-UTR at the miR-155-FOXO3a response element to repress FOXO3a protein expression. Introduction of FOXO3a cDNA lacking the 3'-UTR abrogates miR-155-induced cell survival and chemoresistance. Suppression of miR-155 expression with miR-155 anti-miRNA oligonucleotides (ASOs) results in an increase in the expression of FOXO3a protein. Overexpression of miR-155 resulted in repression of FOXO3a protein without changing mRNA levels, suggesting that miR-155 downregulates FOXO3a by translational inhibition, not mRNA degradation. Basal levels of Bim and p27, major downstream targets of FOXO3a, were reduced by stable expression of miR-155 in BT-474 cells, but increased by knockdown of miR-155 in HS578T cells. Expression of miR-155 considerably reduced the effects of doxorubicin on FOXO3a, Bim, and p27 expression and PARP cleavage and apoptosis. In contrast, depletion of miR-155 enhanced doxorubicin-stimulated FOXO3a, Bim, and p27 expression, as well as PARP cleavage and apoptosis. Of 12 cell lines examined, 3 cell lines expressing high levels of miR-155 exhibited undetectable or low levels of FOXO3a. Of 9 cell lines with low levels of miR-155, 8 cell lines expressed high levels of FOXO3a. In 77 human breast cancer specimens and 11 normal breast tissues, upregulation of miR-155 was detected in 55 breast cancers and 1 normal breast tissue. Of the 55 tumors with elevated miR-155, 41 had low levels of FOXO3a, whereas 16 of 22 specimens with downregulated miR-155 presented high levels of FOXO3a, suggesting an inverse correlation of miR-155 and FOXO3a expression in breast cancer. In 38 recurrent breast cancers due to chemoresistance and/or radioresistance after surgical removal, 31 recurrent tumors express elevated miR-155 and low FOXO3a levels, suggesting that miR-155 regulates FOXO3a *in vivo,* and that elevated levels of miR-155 are associated with chemoresistance and/or radioresistance in breast cancer.

6. ROLE OF MIR-155 IN THE SIGNALING OF OTHER MOLECULES

The p53 target gene TP53INP1 is one of the targets of miR-155. MiR-155 targets the 3'- UTR of the TP53INP1 gene (37). TP53INP1 expression was elevated in a majority of the pancreatic carcinoma samples examined and overexpression of TP53INP1 in tumor cells leads to apoptosis and cell cycle arrest. The expression of TP53INP1 is downregulated by expression of miR-155 in pancreatic ductal adenocarcinomas, which occurs early during pancreatic cancer development.

Bone morphogenetic proteins (BMPs) are a group of growth factors that can be classified as cytokines and metabologens (38). BMPs interact with specific receptors on the cell surface, referred to as bone morphogenetic protein receptors (BMPRs). Signal transduction through BMPRs results in the phosphorylation of SMADs, which facilitates active transport of these mediators from the cytoplasm to the nucleus where they bind and activate gene promoters. Cancer often involves misregulation of the BMP signaling system (39; 40). The human herpes virus Epstein–Barr virus (EBV) is a human DNA tumor virus that contributes to lymphoid and epithelial cell malignancies (41) and disrupts BMP signaling. EBV infection induces elevated miR-155 levels, and MiR-155 targets multiple components of the BMP signaling cascade, including SMAD1, SMAD5, HIVEP2, CEBPB, RUNX2, and MYO10. Targeting of these mediators results in the downregulation of BMP2-, BMP6-, and BMP7-induced ID3 expression in the EBV positive B-cell line Mutu I. Further, miR-155 downregulates SMAD1 and SMAD5 expression in the lung epithelial cell line A549, leading to the inhibition of BMP-mediated induction of the cyclin-dependent kinase inhibitor p21. Thus, miR-155 reverses BMP-mediated cell growth inhibition. In addition to those reviewed here, other signaling pathways governing proliferation may also be regulated by miR-155.

7. CONCLUSIONS AND PERSPECTIVE

The present review summarizes the signaling pathways regulated by miR-155 in cancer development, with a focus on metastatic breast cancer. MiR-155 has been identified as an oncogenic miRNA. Several signaling pathways such as TGF-β, JAK-STAT, and FOXO3a pathways are under the control of miR-155 (Figure 1). A miRNA may have several hundreds to potentially thousands of targets, raising the question of whether other

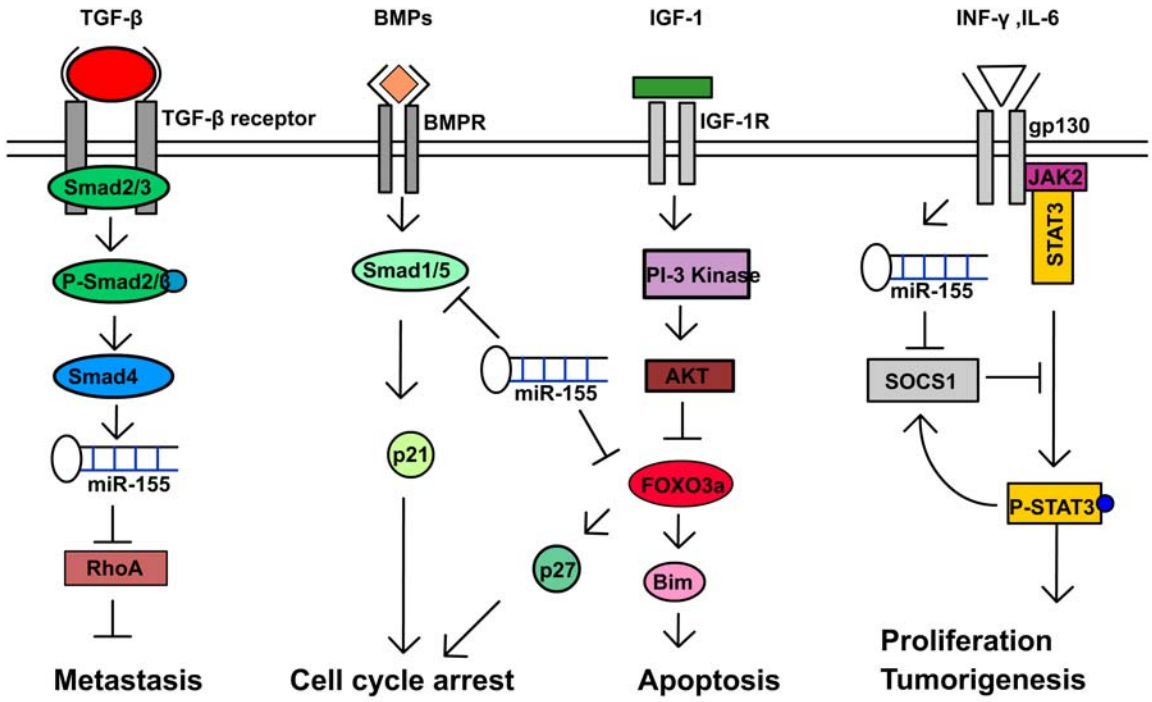

Figure 1. miR-155-mediated pathways in tumor progression and metastasis. The oncogenic miR-155 plays multiple roles in TGF-β, JAK-STAT, and FOXO3a signaling pathways, leading to increased breast cancer cells migration and invasion. In TGF-β signaling pathway, miR-155 targets RhoA to promote EMT and metastasis. In JAK-STAT signaling pathway, miR-155 blocks the negative feedback loop by targeting SOCS1 to promote proliferation and tumorigenesis, suggesting miR-155 may serve as a bridge between inflammation and cancer. In FOXO3a-mediated signaling pathway, miR-155 targets the tumor suppressor of FOXO3a directly, giving rise to downregulation of p27 and Bim which induce cell cycle arrest and apoptosis, respectively. Besides breast cancer metastasis, miR-155 is involved in Lung cancer malignancy. In bone morphogenetic protein (BMP) signaling pathway, miR-155 targets Smad1/5, leading to the inhibition of p21 and the reversal of BMP-induced cell growth inhibition.

signaling pathways involved in carcinogenesis or metastasis are regulated by miR-155. Further investigation will be needed to address this question as a number of signaling pathways could be controlled by miR-155. The downregulation of miR-155 expression in a clinical setting, in conjunction with traditional chemotherapies, has the potential to provide a novel, and possibly specific, way to control the growth of breast cancer cells. Antisense oligonucleotides complementary to the target strand of miRNAs, called anti-miRNA oligonucleotides (AMO or antimirs) or antagomirs (when they are conjugated with cholesterol), can target specific miRNAs, abolishing their function in cultured cells or in mice (42-45). Therefore, an efficacious device for the delivery of AMO or antagomirs will be of great interest.

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Abbreviations: ALI: acute lung injury; ARDS: acute respiratory distress syndrome; PMN: polymorphonuclear neutrophil; PAH: pulmonary artery hypertension; MODS: multiple organ dysfunction syndrome; SIRS: systemic inflammatory response syndrome; Ams: alveolar macrophages; IgSF: immunoglobulin superfamily; ICAM: inter-cellular adhesion molecule; VCAM: vascular cell adhesion molecule; PECAM: platelet/endothelial cell adhesion molecule; MadCAM: mucosal addressin cell adhesion molecule; LPS: lipopolysaccharide; TNF: tumor necrosis factor; IL: interleukin

Key Words: Acute lung injury, Acute respiratory distress syndrome, Polymorphonuclear neutrophil, Review

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