Biological Insights
journal home page: www.biologicalinsights.com
ISSN:2456-7604
Biological Insights 1(2016)47-53

Review Article

Molecular Biology, Cell & Tissue Engineering

An insight into oncogenic role of miRNA

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A R T I C L E I N F O

Received 30 May 2016
Revised 14 August 2016
Accepted 23 August 2016

K E Y W O R D S

miRNA
miR-155
miR17-92
miR-221
cancer
oncogenic

A B S T R A C T

The discovery of microRNAs critical role in regulating virtually all biological pathways by reshaping cellular transcriptome and proteome in mammals and other multicellular organisms has revolutionized the way we look at gene regulation. miRNAs can act as oncogenes and are also involved in the downregulation of tumor suppressors within the molecular architecture of gene regulatory networks. Altered miRNAs expression is implicated in the development of several cancers such as hepatocellular carcinoma, colorectal carcinoma, esophageal squamous cell carcinoma, lung cancer, pancreatic cancer, thyroid carcinoma, cervical cancer, breast cancer. In this review, we have given brief insights on the oncogenic role of miR-155, miR-17-92 and miR-221.

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1. Introduction

MicroRNAs (miRNAs) are a recently discovered class of small, non-coding RNAs found in organisms. Around 60% of the discovered human miRNAs are encoded in introns of both protein-coding and non-protein-coding genes. Primary microRNA transcripts are processed co-transcriptionally (Morlando et al. 2008; Scott & Ono 2011). Until recently, the studies on non- coding RNAs and their functions were not given preference considering the fact that they are not converted into the protein and analyzing their functions was a difficult task with no practical utility at that point of time. However, the discovery of miRNAs and their critical role in regulating virtually all biological pathways by reshaping cellular transcriptome and proteome in mammals and other multicellular organisms have revolutionized the way we look at gene regulation. MicroRNAs regulate temporal transitions in gene expression associated with cell fate progression and differentiation throughout development process (Ambros 2011). miR-203 is involved in the development of mammalian skin by promoting differentiation by repressing stemness (Yi & Fuchs 2009; Yi et al. 2008). Early to late developmental transition in retinal progenitors is regulated by three key miRNAs let-7, miR-125,miR-9 and overexpression of these miRNAs can accelerate normal retinal development (La Torre et al. 2013). Expression of miR-223 plays a crucial role in myeloid lineage development in the hematopoietic system and its expression is repressed in multiple tumors including hepatocellular cancer (HCC) and acute myeloid leukemia (Bhattacharya et al. 2016; Yeh et al. 2016). Multiple differentiation pathways such as myogenesis,

cardiogenesis, neurogenesis, and osteogenesis are regulated by miRNAs (Yao 2016). Several studies have reported that expression of miR-16, miR-103, and miR-107 inhibits proliferation of hematopoietic stem cells (HSCs) while expression of miR-128 and miR-181 prevents differentiation of stem cells (Georgantas et al. 2007). An interesting study on miR-26a revealed that miR-26a mainly targeted on GSK3β to activate Wnt signaling for promoting osteogenic differentiation in bone marrow-derived mesenchymal stem cells (BMSCs) whereas it targeted osteogenic transcription factor smad1 to suppress BMP signaling to interfere the osteogenic differentiation in adipose tissue-derived mesenchymal stem cells (ADSCs) demonstrating distinct targeting patterns of miR-26 in BMSCs and ADSCs (Su et al. 2015).Osteoblast differentiation in mouse mesenchymal stem cells was also reported to be inhibited by overexpression of miR-125b (Mizuno et al. 2008).Dysregulated miRNA expression has been associated with several human diseases. In case of Type 2 diabetes patients increased expression of pancreatic miR-375 has been reported due to direct involvement of miR-375 in insulin secretion via targeting myotrophin (MTPN) expression (Li et al. 2010) and glucose homeostasis via targeting phosphoinositide-dependent protein kinase 1 (PDK-1) (El Ouaamari et al. 2008; Delic et al. 2016). Cardiac hypertrophy has been linked to an absence of miR-1, while cardiomyocyte differentiation is regulated by miR-1 through interaction with serum response factor (Sayed et al. 2008). Cardiac Arrhythmogenesis has also been linked to miR-1, as well as miR-133, both acting through the regulation of essential ion channel proteins (Luo et al. 2008). Downregulation of miR-6510 was reported in psoriatic skin (Gudjonsson et al. 2010) while miR-4632 is implicated in psoriatic arthritis(Reese et al. 2010; Ye & Cao 2014). miR- 146a and miR-155 are involved in the pathogenesis of rheumatoid arthritis (Watanabe-Tanaka & Asahara 2015).In chronic obstructive pulmonary disease (COPD), miR-146a and miR-155 play a regulatory role in inflammation. miR- 146a expression and cytokine-stimulated prostaglandin E2 production in cultured fibroblasts correlated with clinical severity of chronic obstructive pulmonary disease (COPD) suggesting a pathogenic role of miR-146a (Sato et al. 2010; Kishore et al. 2014). The most frequently altered miRNAs found in Alzheimer's Disease is miR-9 it targets the fibroblast growth factor receptor 1 (FGFR1), NFkB and sirtuin 1 (SIRT1), a deacetylase interacting with tau which probably results in hyperphosphorylation of tau (Femminella et al. 2015). The mir-107 expression has a negative correlation with BACE1 and with neuritic plaque density, as well as neurofibrillary tangles and it has been proven that it targets BACE1, thus regulating amyloid production (Goodall et al. 2013). *In vitro* studies on miR-29 have revealed its role in increasing amyloid production and its expression is inversely correlated with BACE1 (Hebert et al. 2008).Expression of p53 associated with tau phosphorylation in Alzheimer's Disease is regulated by miR-34 (Hooper et al. 2007). miR-106a and miR-106b are known to regulate the expression of the transporter ABCA1, which is involved in ApoE production, suggesting their multiple roles in AD pathophysiological processes (Kim et al. 2012).

1.1. MicroRNAs in cancer

Cancer progression is mediated by overexpression of oncogenes and downregulation or loss of tumor suppressors. The initial evidence for the involvement of miRNAs in cancers came from a molecular study characterizing the 13q14 deletion in human chronic lymphocytic leukemia (CLL) (Calin et al. 2002), Calin et al. discovered that both genes were deleted or downregulated in greater than 60% of B-cell human CLL, indicating that these genes behave as tumor suppressors in CLL (Calin et al. 2002) .Consequently, the same group found that a significant percentage of miRNAs is located at fragile sites and in regions altered in cancers, including regions of amplification or loss of heterozygosity or breakpoints, suggesting miRNAs as a new class of genes having a relevant role in human cancer pathogenesis (Calin et al. 2004).The dynamic nature of MicroRNAs expression within the same cells is responsible for their unique ability to act as both tumor suppressors or oncogenes in different circumstances, for example,miRs-34a/b/c are directly regulated by p53 within a positive feedback loop to affect numerous proapoptotic proteins (Yamakuchi et al. 2008).However, the loss of p53 prevents the production of miRs-34a/b/c resulting in cancer progression by enabling cells to avoid apoptosis at numerous levels and also affecting other miRNA targets (Catto et al. 2011). Recent advances in research have confirmed the involvement of miRNA in multiple cancers miRNA such as miR- 155 is overexpressed in chronic lymphocytic leukemia (CLL), B-cell lymphomas, Hodgkin's lymphomas, Burkitt lymphomas and in human breast cancer cells suggesting its involvement as an oncogene (Balatti et al. 2015; Costinean et al. 2006

1.1.1.miR-155 in cancer

The oncogenic role of microRNA-155 (miR-155) has been well established in a wide range of cancer such as hepatocellular carcinoma(HCC) (Tang et al. 2016), colorectal carcinoma (CRC) (Chi & Zhou 2016), esophageal squamous cell carcinoma (Zhang et al.2014), lung cancer (Liu et al. 2015), pancreatic cancer (Wang et al. 2015), Thyroid Carcinoma (Zhang et al. 2013), cervical cancer (Fang et al. 2016), breast cancer

(Kong et al. 2013). The invasion and proliferation in HCC are mediated by miR-155 by inhibiting multiple tumor suppressor genes such as sex- determining region Y-gene related high-mobility-group box gene and suppressing in cytokine signaling 1 (Guan et al. 2015; Yan et al. 2013; Xie et al. 2011). Another study revealed the possible role of miR-155 in promoting tumorigenesis in hepatocellular carcinoma by targeting ARID2-mediated Akt phosphorylation pathway(Zhang et al. 2016). *In vitro* studies on HCC cells have demonstrated that miR-155 activates PI3K/SGK3/β-catenin signaling pathways enhancing epithelial-mesenchymal transition (EMT) and metastasis (Kong et al. 2016). *In vitro* studies on HT-29 cell lines revealed that overexpression miR-155-5p enhance CRC cells proliferation invasion-metastasis effect of colorectal carcinoma cells (Qu et al.2015).The ability of miR-155 to target multiple components of the mismatch DNA repair system leads to an elevated rate of DNA mutations and microsatellite instability in colorectal cancer (Valeri et al. 2010). Intracellular cytokine signaling and T cell antitumor immunity is enhanced by miR-155 via suppression of cytokine signaling (SOCS) proteins as well as phosphoinositide and tyrosine-specific phosphatases (Ji & Gattinoni 2015). miR-155 acts as an oncogene by targeting tumor protein p53-induced nuclear protein 1 (TP53INP1) a tumor suppressor gene in esophageal squamous cell carcinoma (Zhang et al.2014). *In vivo* study of tumorigenesis of non-small cell lung cancer (NSCLC) in nude mouse model revealed that overexpression of miR-155-5p significantly promoted the tumorigenesis of non-small cell lung cancer (NSCLC) cells as compared with the vector control (Xie et al.2015). Zhang et al. reported that miR-155 targets adenomatous polyposis coli (APC) expression and activates Wnt/ β- catenin signaling promoting Papillary Thyroid Carcinoma(PTC) cell growth (Zhang et al. 2013). The proliferation of cervical cancer cells is promoted by miRNA-155 regulation of human tumor suppressor LKB1 expression (Lao et al. 2014).

1.1.2.miR-17-92 in cancer

The most prominent oncogenic cluster is the miR-17-92 polycistron also known as OncomiR-1 because it was the first detected miRNA that was acting as a mammalian oncogene (Hammond 2006). The precursor transcript derived from the mir-17-92 gene contains six tandem stem-loop hairpin structures that ultimately yield six mature miRNAs: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1 (Tanzer & Stadler 2004).MiR-18a levels in diffuse large B-cell lymphoma was found to be negatively correlated with survival (Alencar et al. 2011).In a tumor engraftment model study upregulation of the cluster by Myc in colonocytes increased tumorigenesis by promoting angiogenesis through direct repression of TSP-1 and CTGF by miR-18a and miR-19, respectively (Dews et al. 2006). miR-92a directly targets the anti-apoptotic molecule BCL-2-interacting mediator of cell death (BIM) in colon cancer tissues (Tsuchida et al. 2011). *In vitro* studies on colorectal cancer revealed that enforced expression of miR-19a overrides adenomatous polyposis coli (APC) tumor suppressor activity (Li et al. 2016). *In vitro* and *in vivo* studies on hepatocellular carcinoma demonstrated that overexpression of miR-17-92 cluster was cancer cell proliferation, colony formation and invasiveness (Zhu et al. 2015). Overexpression of the mir-17-92 cluster significantly improved the migration and invasion of the DU145 prostate cancer cells by induction of integrin β-1 (Zhou et al. 2016). Overexpression of miR-19a and miR-19b associated with translational suppression of PTEN and induces cell growth in anaplastic thyroid cancer (Takakura et al. 2008). miR-17-92 overexpression in T-cell acute lymphoblastic leukemia suppresses apoptosis by decreasing the E2F1 level (Nagel et al. 2009). miR-17-5p and miR-20a overexpression are responsible for enhancing cell proliferation in renal cell carcinoma (Chow et al. 2010).

1.1.3.miR-221 in cancer

The miR-221 is one of the most widely studied oncogenic miRNAs.It is encoded in tandem from a gene cluster on the X chromosome and has been shown to target critical cancer-related pathways in various cellular contexts. MiR-221 is overexpressed in papillary thyroid carcinoma (Yoruker et al. 2016), glioblastoma (Zhang et al. 2010), colorectal cancer (Qin & Luo 2013) pancreatic cancer (Xu et al. 2015), prostate cancer (Hassan et al. 2012) hepatocellular carcinoma (Rong et al. 2013),gastric cancer (Liu et al. 2012), renal carcinoma (Lu et al. 2015) and breast cancer (Nassirpour et al. 2013). miR-221 inhibits cell apoptosis by targeting pro-apoptotic gene PUMA in human glioma cells(Zhang et al. 2010). In a xenograft model knockdown of miR-221 induces PUMA expression and cell apoptosis considerably decreases tumor growth in glioblastoma (Zhang et al. 2010). Cell proliferation is promoted in colorectal cancer cells due to inhibition of cell cycle inhibitor CDKN1C/p57 by overexpressed miR-221 (Sun et al. 2011). *In vitro & in vivo* studies have despite the recent advances in the field of miRNAs and cancer research we are still in the initial stages of deciphering the complex association of miRNAs in cancer progression. miRNAs may act as oncogenes or tumor revealed that miR-221 promoted metastasis in colorectal cancer by targeting Reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) (Qin & Luo 2013). miR-221 directly binds

to tissue inhibitors of metalloproteinase-2 (TIMP-2), upregulates matrix metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) expression promoting cell invasion in pancreatic cancer (Xu et al. 2015). miR-221 suppresses p27kip1 which results in the development and metastasis of prostate cancer (Galardi et al. 2007). miR-221 targets PTEN and TIMP3 tumor suppressors and enhances cellular migration through the activation of the AKT pathway and metallopeptidases in hepatocellular carcinoma (Garofalo et al. 2009).miR-221 regulates two key mechanisms to promote the aggressive tumorigenic characteristics observed in triple-negative breast cancer cells (TNBCs): it promotes cell cycle progression by inhibiting p27kip1 and secondly it promotes EMT transition by inhibiting the expression of E-cadherin. Both of these mechanisms account for the aggressive cellular proliferation, suppression of apoptosis, as well as higher cell migration and invasion characteristics associated with TNBCs (Nassirpour et al. 2013).

2. Conclusion

Despite the recent advances in the field of miRNAs and cancer research, we are still in the initial stages of deciphering and modulating the miRNA expression of cancer cells could be a promising therapy in cancer treatment.Several successful attempts have been made in this direction, for example, anti-miR21 is an effective therapeutic strategy for colon cancer by regulating miR21 pathway in the nucleus and inhibiting angiogenesis regulated anti-miR21 as perturbing miR30 (Song & Rossi 2014).Studies on miR-10b antagomir revealed that it acts as a promising anti- metastasis agent by blocking the ability of tumor cells to launch metastases in mouse mammary tumor model (Ma et al. 2010). This promising therapeutic potential of miRNAs in cancer therapy needs to be further evaluated for long term efficacy and safety concerns for human use.

3. Acknowledgements

The author is thankful to the Department of Biotechnology, MIET, Meerut for providing infrastructure and financial support for the project.

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How to cite this paper: A.Ahuja.2016.An insight into oncogenic role of miRNA. *Biological Insights 1(2016)47-53*