MINI-REVIEW

Insights into the Diverse Roles of miR-205 in Human Cancers

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Abstract

The recent discovery of tiny microRNAs (miRNAs) has brought about awareness of a new class of regulators of diverse pathways in many physiological and pathological processes, such as tumorigenesis. They modulate gene expression by targeting plethora of mRNAs, mostly reducing the protein yield of a targeted mRNA. With accumulation of information on characteristics of miR-205, complex and in some cases converse roles of miR-205 in tumor initiation, progression and metastasis are emerging. miR-205 acts either as an oncogene via facilitating tumor initiation and proliferation, or in some cases as a tumor suppressor through inhibiting proliferation and invasion. The aim of this review is to discuss miR-205 roles in different types of cancers. Given the critical effects of deregulated miR-205 on processes involved in tumorigenesis, they hold potential as novel therapeutic targets and biomarkers.

Keywords: miRNA - miR-205 - biomarker - oncogene - tumor suppressor - EMT

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Introduction

MicroRNAs (miRNAs), as a subset of small non-coding RNAs, have been subject of extensive research work due to their pervasive effect on gene expression modulation mostly in post-transcriptional stages (Sevignani et al., 2006; Chekulaeva and Filipowicz, 2009; Fabian et al., 2010). They function in the form of ribonucleoproteins (RNPs) in conjunction with specific proteins (e.g. Argonaute family and GW182) (Wang et al., 2010; Pfaff and Meister, 2013). miRNAs are mostly known as negative regulators of their target mRNA expression via translation inhibition and/or mRNA decay (Nilsen, 2007; Cai et al., 2009). Aberration or perturbation in their expression levels has significant correlation with serious clinical consequences, including disease of divergent origin and malignancy (Darnell et al., 2006; Croce, 2012; Jansson and Lund, 2012; Suzuki et al., 2012).

A growing number of evidence indicates the involvement of miRNAs in the biology of human cancer. Studying the field of miRNAs in cancer has gradually switched from profiling studies to biological demonstrations of the causal role of these small molecules in the tumorigenic process, modulating oncogenic or tumor suppressive pathways, and the possible implications as biomarkers or therapeutic tools.

Several functional experiments in various cancers such as epithelial-originated showed the importance of miRNAs in different stages of cancer including initiation, progression and metastasis (Calin et al., 2004; Lu et al., 2005). miR-205 resides in 1q32.2 chromosome and its expression pattern is in conjunction with miR-200 family (Lim et al., 2003; Gregory et al., 2008; Wiklund et al., 2011). Human miR-205 was first predicted by computational approaches, based on its high conservation with mouse and Fugu rubripes (Lim et al., 2003); and subsequently, its expression was validated in zebrafish and human (Wienholds et al., 2005; Landgraf et al., 2007). Its homologs have been discovered among several species (data was shown in miRBase database).

As many experimental studies revealed the characteristics of miR-205, it appears to have controversial roles in malignancy (Babak et al., 2004; Zhang et al., 2007; Wang et al., 2010). While in some specific cell factors and target genes, miR-205 acts as an oncogene via facilitating tumor initiation and proliferation, in some others it serves as a tumor suppressor through inhibiting proliferation and invasion (Volinia et al., 2006; Yanaihara et al., 2006; Wu et al., 2009). In this review, therefore, we will investigate the conflicting role of miR-205 in reported cancers to better understand its mechanism with the aim to use it in practical implications as a biomarker and drug target in cancer managements.

miR-205 Roles in Epithelial Differentiation

It was validated that miR-205 has a deep role in epithelium morphogenesis during embryogenesis (Shingara et al., 2005). It has been also reported that miR-205 is highly expressed in two early embryonic germ cell layers, including endoderm and ectoderm, but not in mesoderm, which shows its specific expression in epithelium differentiation (Darnell et al., 2006). Sempere et al. (2007) verified the role of miR-205 in epithelial

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development. They implied that miR-205 acts not only in epithelium biogenesis, but also in its maintenance.

The epithelial-mesenchymal transition or transformation (EMT) is a vital process in numerous developmental processes such as the implantation of the embryo and the initial of placenta formation (Zhu et al., 2013). Through EMT, epithelial cells lose their cell polarity and cell-to-cell adhesion and gain an ability to migrate and invade leading to constriction and extrusion of newly mesenchymal cells (Kalluri and Weinberg, 2009). On the other hand, initiation of metastasis requires invasion. It has been recently shown that EMT has a significant role in the promotion of tumor invasion and metastasis (Chaffer and Weinberg, 2011; Matsushima et al., 2011; Fassina et al., 2012; Said et al., 2013).

miR-205 expression is observed to reduce in cells undergoing EMT that is accompanied by a significant decrease in E-cadherin and an increase in N-cadherin and fibronectin (Gregory et al., 2008). Furthermore, miR-205 is reported to counteract EMT which is essential in the progression of malignant mesothelioma (Fassina et al., 2012). Reported target mRNAs for miR-205 include regulators of proliferation, apoptosis and the EMT confirmed the role of miR-205 in epidermal development and homeostasis and enhance the note that miR-205 expression is epithelial specific (Adachi et al., 2011; Cufí et al., 2012).

miR-205 in Breast Cancer

An increasing body of evidence highlights an intriguing interaction between miR-205 expression levels and breast cancer. In 2005, Iorio et al. (Iorio et al., 2005) described that miRNA signature is unique for breast cancer and their expression is associated with specific pathological features.

miR-205 was found to be up- or down-regulated in breast cancer and it may function as either a tumor suppressor or an oncogene. As mentioned above, mir-205 can function through both in normal development and cancer initiation, progression and metastasis (Savad et al., 2012). Its expression was found to be restricted to the myoepithelial/basal cell section of normal mammary ducts and lobules (Sempere et al., 2007). Moreover, a high level of miR-205 expression has been observed in normal lobular and ductal mammary epithelial cells showing a putative role in normal processes (Greene et al., 2010); whereas, their accumulation was mostly reduced in matching tumor specimens (Radojicic et al., 2011).

A comparative genomic analysis revealed an amplified genomic region on chromosome 1 related to miR-205 locus in some clinical samples of human breast cancer (Blenkiron et al., 2007). In mouse mammary epithelial cell (MEC) line, miR-205 expression is critically increased in the subpopulation of progenitors where miR-205 targets PTEN, a tumor suppressor gene, resulting in expansion of the progenitor-cell population along with escaping from contact-mediated growth inhibition and promoting the colony-forming potential of these cells, supporting a tumor initiation property of miR-205 (Greene et al., 2010a; 2010b). However, increasing body of reports show down-expression of miR-205 in ER−PR−Her2− tumors, known as triple negative breast cancer (TNBC), (Iorio and Croce, 2009; Wu et al., 2009), metastatic breast cancer cell lines and clinical samples of metastatic breast (Iorio et al., 2005; Sempere et al., 2007), suggesting the role of miR-205 as an onco-suppressor by reducing cellular proliferation (Radojicic et al., 2011; Piovan et al., 2012).

To date, several target mRNAs ascribed to miR-205 including PTEN (Greene et al., 2010) and SHIP2 (Yu et al., 2008), as tumor suppressors, HER3 (Iorio et al., 2009), E2F1, E2F5, and PKCε (Gandellini et al., 2009), as oncogenes, Zeb1 and Zeb2 (Gregory et al., 2008), as pro-metastatic genes, and VEGFA (Wu et al., 2009), as an angiogenic factor. What strikes in the mind, however, is the functions that miR-205 exerts in breast cancer, both in formation of cancer and its metastasis, depending on cellular context, and is likely specific to the subtype of tumor, as well as its cells origin and stage of tumor progression.

miR-205 in Prostate Cancer

Prostate cancer (PCa) is the most frequent cancer among men and second cancer that cause death in occidental male population (Mimeault and Batra, 2006). Many studies conducted thus far, have shown correlation between miR-205 deregulation and PCa susceptibility (Boll et al., 2013; Hagman et al., 2013; Verdoodt et al., 2013). miR-205 expression has been verified to be localised in the basal cells of benign prostate tissues, and its expression is inversely correlated to the occurrence of metastasis and shortened overall survival, which is lower in PCa patients (Hagman et al., 2013). Experimental research work revealed the tumor-suppressive function of miR-205 in PCa, where miR-205 sustains epithelial cell phenotype by repressing genes involved mostly in the acquisition of invasive behaviour and increasing cell-to-cell adhesion. Therefore, down-regulation of miR-205 in PCa patients leads to oncogenic phenomena and inducing cell invasion by reducing E-cadherin expression (Gandellini et al., 2009). In two recent studies conducted on PCa clinical samples, miR-205 was considered as a guarantee to act against tumor initiation and progression by basement membrane (BM) maintenance or repressing the mitogen-activated protein kinase (MAPK) and androgen receptor (AR) signalling pathway (Gandellini et al., 2012).

Although the accepted notion is that miRNAs mediate gene regulation through gene silencing, Majid et al. (Majid et al., 2010) have provided a proof of principle that miR-205 may elicit its tumor suppressive function by up-regulating the tumor suppressor genes IL24 and IL32 through targeting specific sites in their promoters.

Taken together, these findings imply that miR-205 might have therapeutic potential and suggest miR-205 as a possible tool to reprogram the phenotype of PCa cells toward a less malignant state.

miR-205 in Lung Cancer

Lung cancer, the second most common cancer in both males and females, can be classified as either small cell(SCLC) or non-small cell lung cancer (NSCLC) depending on the type of cells affected (Stang et al., 2006; Jemal et al., 2011). NLSCLC includes adenocarcinoma (AD), squamous cell lung cancer (SqCC), and large cell carcinoma (Campobasso et al., 1993).

mir-205 is of important miRNAs that shows tissue specificity and is believed to be a putative marker of stratified squamous epithelium and has a maintained expression in SqCC of upper and lower respiratory tracts (Jiang et al., 2005; Yanaihara et al., 2006). Expression level of miR-205 is proved to be a highly reliable method of distinguishing SqCC from AD (Solomides et al., 2012), where miR-205 is the only critically over-expressed in SqCC when compared with AD (Hamamoto et al., 2013). It is reported that the differential expression of miR-205 is a novel approach of classifying NSCLC (Bishop et al., 2010; Xing et al., 2010; Yu et al., 2010). Furthermore, the diagnostic and prognostic value of miR-205 expression aberration in lung cancer has been studied in recent years revealing that miR-205 may serve as a potential inhibitor of tumor metastasis, where it modulates a tumor cell migration factor (LPR1) expression (Song and Bu, 2009; Võsa et al., 2013). In addition to its classifier capability, the therapeutic value of miR-205 has been established, once FDA-approved target therapies have been applied to patients with lung cancer (Cohen et al., 2007).

miR-205 in Esophageal Cancer

Esophageal cancer(EC), an upper gastrointestinal cancer, has two common forms including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAD) (Shah and Kurtz, 2010). Although recent progresses in surgery and radiotherapy lead to a gradual decrease in the incidence of ESCC mortality, the number of observed EAD increases sharply (Hesketh et al., 1989; Blot et al., 1993; Benjamini and Hochberg, 1995).

miRNA profiling and microarray analysis have been engaged in many EC patients, and miR-205 deregulation has been reported in most cases (Feber et al., 2008; Feber et al., 2011; Gu et al., 2013), where an exclusively high expression of miR-205 has been reported in both malignant and benign ESCCs (Kimura et al., 2010; Matsushima et al., 2010; Saad et al., 2013). Therewith, in a study carried out by Matsushima et al. (Matsushima et al., 2011) the function of miR-205 in ESCCs pronounced to be tumor suppressor by targeting ZEB2 and thereby, inhibiting EMT. It is also able to restrain proliferation and invasion along with activation (Kimura et al., 2010).

Therefore, similar to lung cancer, miR-205 expression level might become a specific biomarker to distinguish ESCC from EAD; and consequently, useful to determine the cell origin carcinomas as well as to locate the primary site of metastatic carcinomas, underlying a potential etiological role of miR-205.

mir-205 in Renal Cell and Renal Pelvis Cancer

Renal cell carcinoma (RCC) is one of the most common cancers and was estimated to cause 13,000 deaths in 2009 (Jemal et al., 2009). miR-205 expression was found to be significantly down-regulated in renal cancer tissue samples and cell lines in a number of previous reports (Gottardo et al., 2007). However, no attributed direct target mRNA was found for miR-205 in renal cancer by mid-2011. Previously, It was reported that miR-205 targets VEGF-A in Src-mediated pathways (Wu et al., 2009), and finally, in consistent with this, Majid et al.(Majid et al., 2011) demonstrated a direct mRNA target for miR-205 for the first time. They reported that miR-205 leads to increased apoptotic, migratory and invasive properties by targeting, and consequently suppressing Src family members and down-regulating the Ras/Raf/ERK1/2 pathway in renal carcinoma.

Then an experimental study, carried out in 2012, uncovered another role for miR-205 in renal tubular cells. It is now clear that miR-205 may serve as a protector against both oxidative and ER stresses by inhibiting EGLN2 which leads to a significant decrease in intracellular reactive oxygen species(ROS) level (Muratsu-Ikeda et al., 2012).

In conclusion, miR-205 reconstitution in renal cancer and its subtraction in non-malignant cells increase proliferation and cell-cycle arrest; impair cell viability and invasion; and may represent a novel therapeutic target in AKI and CKD associated with oxidative or ER stress in renal cell carcinoma.

miR-205 in Head and Neck Cancer

Head and neck cancer is the sixth most common malignancy in the world. The most common type is squamous cell carcinoma (HNSCC), and despite advances in surgical and other treatments, its survival rates have remained unchanged throughout the last 3 decades (American Cancer Society 2007).

Numerous studies have highlighted the expression level of miR-205 in HNSCC clinical samples and cell lines compared with normal tissue or other cancer types (Jiang et al., 2005; Childs et al., 2009). Accumulating evidence demonstrates that miR-205 is a relatively enriched species in head and neck, and have higher expression in the HNSCC lines than any of the other cell lines derived from different cancers (Tran et al., 2007; Zidar et al., 2011). Notably, overexpression of miR-205 could effectively reverse the EMT phenotype, block migratory/invasive abilities, and further increase the chemosensitivity (Chang et al., 2011).

Acting as an angel by inhibiting proliferation and migration; therefore, miR-205 brings the potency of positive prognostic marker of head and neck cancer survival and recurrence (Ginos et al., 2004; Fletcher et al., 2008; Kimura et al., 2010). With mRNA expression,

further dissection of involved pathways and determination of miR-205 target genes can be used to shed new light on alterations associated with HNSCC carcinogenesis.

miR-205 in Endometrial Cancer

Endometrial cancer is one of the most common malignancies of the female genital tract (Siegel et al., 2012). A number of recent studies have investigated the expression profiles of miRNAs in endometrial cancer (Wu et al., 2009; Cohn et al., 2010; Ratner et al., 2010; Snowdon et al., 2011). Several studies reported elevated expression level of miR-205 in different types of endometrial cancer compared to normal endometrial tissues and plasmas (Boren et al., 2008; Hiroki et al., 2010; Karaayvaz et al., 2012). Its aberrant expression is proved to be associated with advanced stage in endometrial cancer (Chung et al., 2009), and with overall ratio of survival such that patients with higher levels of miR-205 tend to have a worse survival phenotype (Karaayvaz et al., 2012). miR-205 is further confirmed to negatively regulate cellular proliferation, migration and invasion properties (Su et al., 2013), with this regard, a number of target mRNAs are investigated to be associated with miR-205 in endometrial cancer. Previous studies have identified PTEN to be mutated in 34-55% of endometrial cancers (Kong et al., 1997; Risinger et al., 1997; Tashiro et al., 1997), and acts as an important tumor suppressor in endometrial cell lines (Greene et al., 2010). Some cohort studies revealed that high levels of miR-205 are significantly inversely correlated with the PTEN expression levels, and associated with poor survival of patients, implying the notion that expression levels of miR-205 may consider as a putative negative prognostic biomarker in endometrial cancer (Karaayvaz et al., 2012; Qu et al., 2012). Su et al. (Su et al., 2013) identified estrogen-related receptor γ (ESRRG) as a direct target of miR 205 in human endometrial endometrioid carcinoma (EEC).

Conclusively, by combination of microRNA target prediction algorithms and experimental work, other involved targets of miR-205would be identified, which could be helpful to elucidate mechanisms underlying the tumorigenesis of endometrial cancer.

miR-205 in Other Cancers

Numerous studies investigated miRNA profiling signature of bladder carcinomas distinguishing different classes, stages of progression and outcomes (Wiklund et al., 2011; Dip et al., 2012; Wang et al., 2012; Tran et al., 2013). For instance, Neely et al. (2010) noted that a miR-21:miR-205 expression ratio can be used to distinguish invasive and non-invasive bladder tumors. In human cervical cancer cells, miR-205 was observed to be up-regulated which leads to induced cell proliferation and migration by targeting two confirmed targets:CYR61 and CTGF (Witten et al., 2010; Xie et al., 2012).

miR-205 was shown to be over-expressed in nasopharyngeal carcinoma (NPC) and to be an initiation factor of NPCs (Iorio et al., 2007). Furthermore, elevated expression of miR-205 causes PTEN inhibition followed by increased radio resistance in NPC patients with higher clinical stages (Qu et al., 2012).

In melanoma specimens, miR-205 functions as a tumor suppressor by targeting E2F1 which leads up a mediation of E2F1-regulated Akt phosphorylation and proliferation inhibition (Dar et al., 2011; Xu et al., 2012). Also, miR-205 has the capability to distinguish cutaneous t-cell lymphoma CTCL from high specific and sensitive benign disorders (Ralfkiaer et al., 2011).

Conclusions

MicroRNAs are a subset of endogenously small noncoding RNAs which have the capability of modulating gene expression at post-transcriptional level. miRNAs have gained significant attention because of their ability to be involved in regulation of multiple oncogenic and tumor suppressor signaling pathways, placing them in the center of the cancer managements that has gradually switched from prognostic profiling studies to biological demonstrations of the causal role of these small molecules in the tumorigenic process and the possible implications as biomarkers or therapeutic tools. miR-205 is of the most important microRNAs investigated in various tumor types. The expression level of miR-205 is controversial as it can be down-regulated or up-regulated depending on the cell type. It is predicted that miR-205 can target over 2000 genes if all computational approaches are taken into account, and a micro-environment between miR-205 and its multiple target mRNAs could be established. miR-205 exerts dual function, as tumor suppressor or oncogene, depending on tumor context and target mRNA, by inducing or inhibiting hallmarks of tumorigenesis such as proliferative signalling maintenance, growth suppressors evading, cell death resistance, replicative immortality, angiogenesis induction, and invasion and metastasis activation. Given the complexity of its functionality, it would be of interest to investigate the expression levels of miR-205 and modulate its tumor microenvironment in order to utilize it as a promising biomarker and therapeutic target to discriminate the site of origin in those patients presenting with metastatic spread, and finally, to throw light on reducing death estimation caused by cancer diseases.

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