PROSPECTS
Journal of Cellular Biochemistry 115:605–610 (2014)

Journal of Cellular Biochemistry

Emerging Role of MicroRNAs in Cancer and Cancer Stem Cells

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ABSTRACT

Cancer stem cells (CSCs), or cancer cells with stem cell properties, represent a small fraction of tumor bulk and are thought to be responsible for tumor formation and metastasis. However, the mechanisms of how CSCs are generated and regulated at the molecular level are poorly understood. Recent progress has highlighted the significance of microRNAs (miRNAs) in cancer progression and CSC function. The function and dysfunction of miRNAs in the development of cancer and CSCs have become a burgeoning area of intense research. A new finding has elucidated a mechanism of antagonistic miRNA crosstalk whereby one miRNA can inhibit another miRNA in regulating CSCs. Herein we make this short review to summarize the current understanding of the regulatory mechanisms of miRNAs in cancer and CSCs and discuss the implications of targeting CSCs for cancer therapeutics. J. Cell. Biochem. 115: 605–610, 2014.

KEY WORDS: MicroRNA; CANCER; CANCER STEM CELLS; MicroRNA-ANTAGONISM; CANCER THERAPY

Despite the continuous progress in the development of treatment strategies, cancer still remains one of the most lethal diseases plaguing our society today [Jemal et al., 2011]. The 5-year survival rate was about 68% in cancer patients, underlining that more progress is needed to understand such a disease [Baccelli and Trumpp, 2012]. The hallmarks of cancer include unlimited replication, insensitivity to anti-growth signals, avoidance of apoptosis and metastasis [Vira et al., 2012]. Of all the features, metastasis remains as the most challenging problem of cancer therapeutics. Recent studies have indicated that during cancer progression, genetic and epigenetic mechanisms may lead to the emergence of a metastatic cancer cell with stem cell properties, which is named as cancer stem cell (CSC) or cancer-initiating cell (CIC) [Visvader and Lindeman, 2008; Ito et al., 2009]. These metastatic CSCs can detach from the primary site, eventually enter the blood and seed secondary tumors in distinct organs, and are recognized as the main cause of death in cancer patients. Therefore, further understanding of the regulatory mechanisms of CSCs at molecular level is highly necessary for better cancer therapeutics.

MicroRNAs (miRNAs) are small noncoding RNAs with 21–25 nucleotides (nt) in length. They can silence their cognate target genes by inhibiting mRNA translation or degrading the mRNA molecules by binding to their 3′-untranslated region [Bartel, 2004]. MiRNAs have also been recognized as the key regulator for stemness and metastasis of cancer cells, indicating that they may play pivotal roles in cancer diseases [Calin et al., 2005; Ma et al., 2007]. Recently, several miRNAs have been elucidated to regulate CSC functions and the differential expression profiles of miRNAs from normal tissues across cancers confirm their close relation to tumorigenesis [Lu et al., 2005]. Such regulatory functions of miRNAs in CSCs have emerged as potential therapeutic candidates for cancer disease by virtue of their ability to regulate cancer progression and metastasis. Herein we review the current understanding and recent advance of miRNAs involved in the control of CSC functions, which will broaden our understanding of the regulatory mechanisms of CSCs and may contribute significantly to the cancer therapy.

CANCER STEM CELLS AND CANCER

Over the past 10 years, the concept of CSC has emerged after the identification of CSC-enriched populations in several distinct cancer entities [Reya et al., 2001]. However, the existence of such cell

Jin Hao and Sen Zhao contributed equally to this work.
The authors declare no conflict of interest.

Grant sponsor: National Natural Science Foundation of China; Grant numbers: 30900286, 31370992, 81030034; Grant sponsor: Science and Technology Fund of Sichuan Province; Grant number: 2011SZ0096.

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Manuscript Received: 26 September 2013; Manuscript Accepted: 21 October 2013
Accepted manuscript online in Wiley Online Library (wileyonlinelibrary.com): 26 October 2013
DOI 10.1002/jcb.24702 • © 2013 Wiley Periodicals, Inc.

populations has remained a topic of intense debate due to questions about the robustness of CSC markers [Magee et al., 2012], till new findings identified and tracked CSCs in mouse models of brain [Chen et al., 2012], skin [Driessens et al., 2012], and intestinal tumors [Schepers et al., 2012]. These findings resolved the CSC debate and provided further supports that cancer progression is mostly driven by CSCs. In relation to the origin of CSCs, it is believed that CSCs may come from two different sources. One theory suggests that CSCs originate from transformation of normal stem cells. One alternative theory points put that CSCs were generated from normal tissue cells which acquire stem cell-like properties. For instance, non-CSC cancer cells gain CSC-like properties through EMT process [Mani et al., 2008]. A great number of CSCs have been isolated using cell surface markers like CD24, CD29, CD44, CD90, CD133, aldehyde dehydrogenase1 (ALDH1) and epithelial-specific antigen (ESA) [Al-Hajj et al., 2003; Singh et al., 2003; Ginestier et al., 2007] (Table I). And it is notable that the expression of surface markers in CSCs is cancer type-specific or subtype-specific. So far, CSCs have been identified in breast, pancreatic, prostate, colon, head and neck, ovarian and liver cancers, melanoma and brain tumors [Leal and Lleonart, 2012].

Classically, CSCs are defined by the following properties: (1) high tumorigenicity, (2) the ability to differentiate into non-CSC daughter cells, (3) unlimited self-renewal abilities, and (4) remarkably resistant to conventional therapies. These findings imply that CSCs may account for cancer formation, treatment resistance, metastases, and cancer progression. Hence, complete cure of cancer cannot be achieved until and unless all CSCs are totally ablated [Li et al., 2012]. Recently, miRNAs have been reported to be frequently deregulated in distinct cancer types. They function either as oncogenes or as tumor suppressors and initiate tumor formation, metastasis, epithelial–mesenchymal transition (EMT) process and the overall "stemness" of cancer cells [Ali et al., 2012, 2013]. Therefore, targeting these miRNAs appears to be very promising therapeutic strategies.

MICRORNA REGULATION OF CANCER AND CANCER STEM CELLS

Enormous evidence has proven that developmental genes in somatic stem cells are regulated by miRNAs and vice versa. MiRNAs can regulate mRNA at post-translational level by binding to an 8-base seed sequence at the 3′-UTR of mRNAs. Thus, miRNAs are recognized to play critical roles during development. Downregulated miRNA expression is linked to various human diseases including cancer [Mendell and Olson, 2012]. Several profiling studies have also determined potential implications of high percentage miRNAs in cancer due to their close proximity to cancer associated genomic regions and fragile sites, chromosomal breakpoints, and dysregulated expression levels in many malignancies [Garg, 2012]. Moreover, CSCs have been proposed to be originated from normal stem cells or EMT, and such dysregulation of CSCs by acquired epigenetic abnormalities may include the aberrant expression of miRNAs. Here we discuss the major findings of very recent studies highlighting the CSC-specific miRNAs in certain cancer types.

Over the past few years, research in the area of cancer biology has shown that miRNAs may have both suppressive and promoting roles in cancer progression [Hammond, 2006]. For example, studies have shown that upregulated miR-200c expression disrupts breast CSCs-mediated colony formation in vitro and inhibits tumorigenesis in vivo. In addition, miR-34 family members can be activated by p53 and mediate cell apoptosis and cell cycle arrest [He et al., 2007], and let-7 miRNAs target oncogenes like HMGA2 and RAS [Johnson et al., 2005; Mayr et al., 2007]. Both miRNAs are suppressed in various tumor types and their reintroduction can reduce tumor growth. In contrast, miR-155 and miR-181 family members (miR-181a and miR-181b) have been evidenced as oncomiRs, which could intensely promote the self-renewal, colony formation of breast cancer cells and tumor development in breast cancer [Jiang et al., 2010]. The miR-19 was identified as the major oncogenic miRNA of the miR-17–19 cluster [Mavrakis et al., 2010]. Moreover, some pathways controlled by miRNAs have been shown to play critical roles in regulating CSCs. For example, in prostate cancer cell lines, let-7b, miR-34a, miR-141, and miR-106a were reported to be inhibited in CSCs, while miR-452 and miR-301 were observed to be highly expressed [Liu et al., 2012]. In breast CSCs, miRNA profiling observed that miR-200c, miR-203, and miR-375 expressions were significantly downregulated, while the expression of miR-125b, miR-100, miR-221, and miR-222 was notably upregulated [Wang et al., 2012]. Other miRNAs that have been shown to be involved in various cancer types are roughly summarized in Table II.

Recently, a very interesting research conducted by Song et al. have observed that during the regulation of CSCs, one miRNA can function

TABLE I. CSC Markers for Different Solid Cancer Types

Cancer	CSC markers
Breast	ALDH1, CD24, CD44, CD90, CD133, α6-integrin, Hedgehog-Gli activity
Liver	CD13, CD24, CD44, CD90, CD133
Lung	ABCG2, ALDH1, CD90, CD117, CD133
Colon	ABCB5, ALDH1, CD24, CD26, CD29, CD44, CD133, CD166, β-catenin activity, LGR5
Glioma	CD15, CD90, CD133, α_6-integrin, Nestin
Melanoma	ABCB5, ALDH1, CD20, CD133, CD271
Pancreatic	ABCG2, ALDH1, CD24, CD44, CD133, c-Met, CXCR4, Nestin, Nodal-Activin
Prostate	ALDH1, CD44, CD133, CD166, $\alpha_2\beta_1$-integrin, α_6-integrin, Trop2
Ovarian	CD24, CD44, CD117, CD133

Markers are not ordered according to their importance, and this is not an exhaustive list of all identified markers.

TABLE II. CSC-Specific miRNAs and Their Targets in Cancers

MiRNAs	Cancer types	Targets	References
miR-7	Breast	KLF4	Okuda et al. [2013]
miR-17–92	Leukemia	p21	Wong et al. [2010]
miR-145	Liver, brain	OCT4, SOX2	Jia et al. [2012], Yang et al. [2012]
miR-93	Colon	HDAC8, TLE4	Yu et al. [2011]
miR-21	Colon, ovarian	T GFβR2	Chung et al. [2013], Yu et al. [2012]
miR-22	Breast	miR-200, TET	Song et al. [2013a]
miR-30	Breast	UBC9, ITGB3	Yu et al. [2010]
miR-150	Liver	c-MYB	Zhang et al. [2012]
miR-128	Glioma, breast	BMI1, ABCC5	Godlewski et al. [2008], Zhu et al. [2011]
miR-143	Prostate	FNDC3B	Fan et al., 2013
miR-451	Colon, brain	COX-2, ABCB1, MYC	Bitarte et al. [2011], Gal et al. [2008]
miR-125	Brain	CDK6, CDC25A	Shi et al. [2010], Shi et al. [2012]
miR-126	Gastric	SOX2, PLAC1	Otsubo et al. [2011]
miR-128	Brain	PRC, BMI1	Nanta et al. [2013], Peruzzi et al. [2013]
miR-200 family	Breast, ovary, lung, nasopharyngeal carcinoma, pancreatic, colorectal	ZEB2, CTNNB1, BMI1, SUZ12	Iliopoulos et al. [2010], Lo et al. [2011], Shimono et al. [2009], Tellez et al. [2011], Wellner et al. [2009], Xia et al. [2010]
miR-181	Liver, breast	RASSF1A, CTNNB1, ATM	Ji et al. [2009], Meng et al. [2012], Wang et al. [2011]
let-7	Breast, liver	SOCS-1	Yang et al. [2010], Yu et al. [2007]
miR-495	Breast	CDH1, REDD1	Hwang-Verslues et al. [2011]
miR-130b	Liver	TP53INP1	Ma et al. [2010]
miR-326	Leukemia	Hedgehog	Babashah et al. [2013]
miR-328	Brain	ABCG2	Li et al. [2010]
miR-124, miR-137	Brain	CDK6, SLUG	Silber et al. [2008], Xia et al. [2012]

BMI1, B lymphoma Mo-MLV insertion region 1 homolog; FNDC3B, fibronectin type III domain containing 3B; HDAC8, histone deacetylase 8; KLF4, Krüppel-like factor 4; NPC, nasopharyngeal carcinoma; PRC, polycomb repressor complex; Sox2, SRY (sex determining region Y)-box 2; TET, ten eleven translocation; TLE4, transducin-like enhancer protein 4.

at another miRNA. They have demonstrated that miR-22 acts as a crucial epigenetic modifier and promoter of EMT and breast cancer stemness toward metastasis by silencing anti-metastatic miR-200 through direct targeting of the ten eleven translocation (TET) family of methylcytosine dioxygenases [Song et al., 2013a] (Fig. 1). Almost by the same mechanism of TET protein, Song et al. has also identified miR-22 as a potent proto-oncogene in hematopoietic malignancies [Song et al., 2013b]. These miRNAs might provide novel targets for efficient and specific therapies for cancer and CSCs.

In short, miRNAs have been recognized as critical regulators of cancer and CSCs. Understanding the functional role of miRNAs in a specific type of cancer, miRNA-based therapies can be targeted to these CSCs in order to correct their expression levels and restoring the tumor suppressor functions via the RNAi methods.

THERAPEUTIC IMPLICATIONS AND FUTURE PERSPECTIVES

As discussed above, dysregulation of miRNAs has been evidenced to be implicated in cancer progression, and miRNAs may modulate tumor formation and metastasis by regulating CSC functions. For example, let-7 control cell-cycle and differentiation of breast CSCs; miR-34a can restrict the migration and invasiveness of prostate CSCs by directly targeting CD44; and miR-200c may regulate the self-renewal of breast CSCs by modulating BMI1 (Fig. 1). Moreover, recent findings also suggest that miR-22 may exert its metastatic potential by targeting miR-200, thereby inhibiting demethylation of miR-200 promoter. These new findings better our knowledge and understanding of CSC function and provide novel insight into more effective therapeutic strategies to target cancer and CSCs. Given that miRNAs exert broad regulatory functions on cancer progression and development, miRNA-based therapeutics may open up new areas in the anti-cancer arena.

However, in spite of tremendous progress in this field, we still have a long way to go before a fully understanding of such regulatory mechanism is achieved. The phenotypic consequences of manipulating miRNAs in vivo are hard to predict, and most miRNAs mentioned above were discovered and studied in *C. elegans* with little knowledge about their regulation in human development and physiology. Hopefully, these problems mentioned above could be solved as we get better insights into the miRNA regulation of cancer and CSCs. Moreover, different miRNAs seem to concertedly and distinctively modulate functional properties of CSCs, complete eradication of CSCs may entail targeting of multiple miRNAs. Therefore, miRNA expression profiling in CSCs or certain types of cancer at various clinical stages might have great diagnostic and prognostic values.

Overall, research into CSC will provide innovative approaches to the therapeutics of cancer diseases, and miRNA-based therapeutic strategies hold great promise in this area. Combining the potential of CSCs and the advantages provided by miRNAs, a novel therapeutic approach could fill the gap in the treatment of cancer patients.

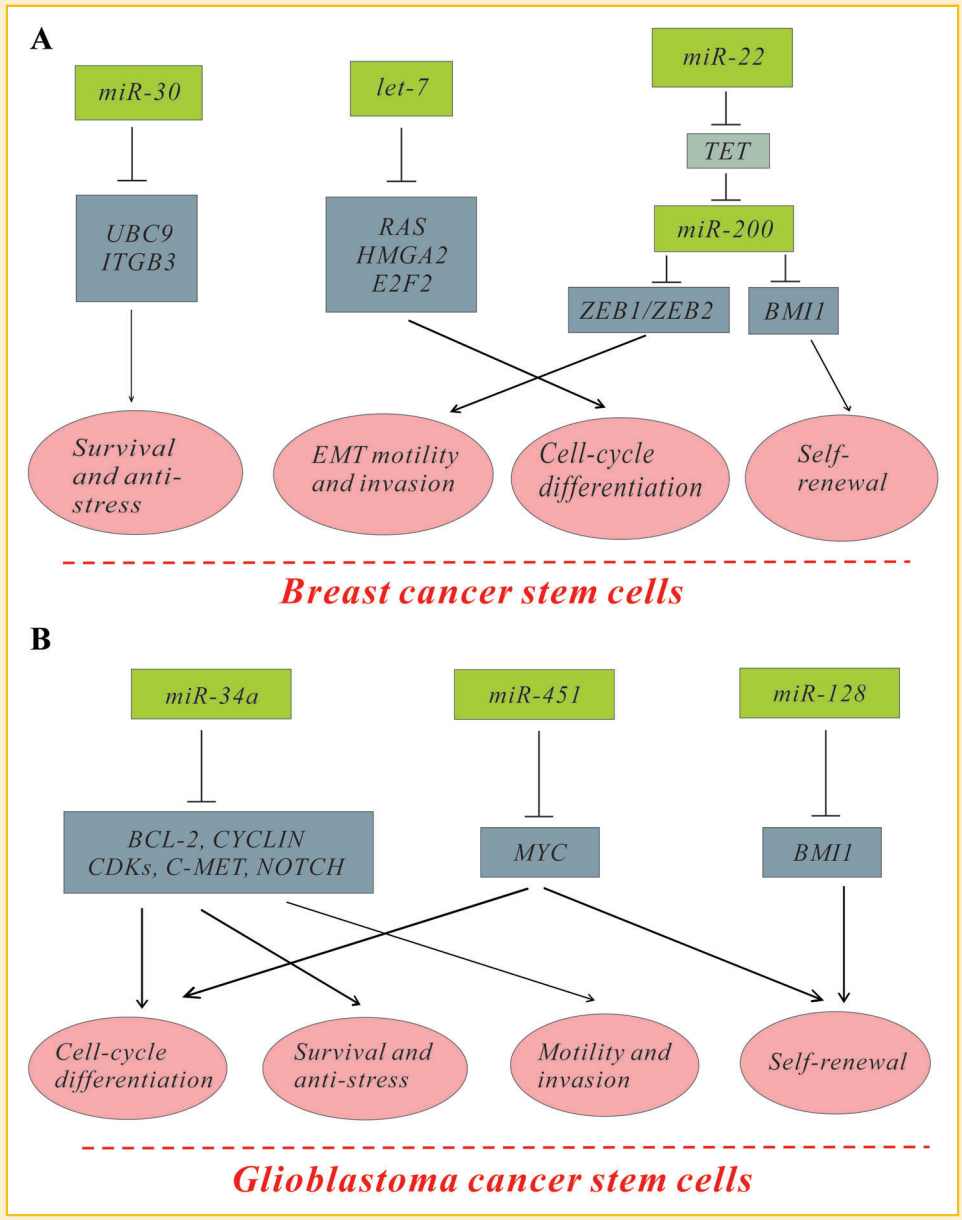

Fig. 1. Representative miRNAs that regulate key properties of CSCs. A: miR-30, let-7, miR-22, and miR-200 can regulate breast CSC functions by targeting critical downstream signals. B: miR-34a, miR-451, and miR-128 concertedly and distinctively modulate key properties of CSCs in glioblastoma (GBM).

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