

REVIEW

microRNAs, an active and versatile group in cancers

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microRNAs (miRNAs) are a class of non-coding RNAs that function as endogenous triggers of the RNA interference pathway. Studies have shown that thousands of human protein-coding genes are regulated by miRNAs, indicating that miRNAs are master regulators of many important biological processes, such as cancer development. miRNAs frequently have deregulated expression in many types of human cancers, and play critical roles in tumorigenesis, which functions either as tumor suppressors or as oncogenes. Recent studies have shown that miRNAs are highly related with cancer progression, including initiating, growth, apoptosis, invasion, and metastasis. Furthermore, miRNAs are shown to be responsible for the cancer-related inflammation, anti-cancer drug resistance, and regulation of cancer stem cells. Therefore, miRNAs have generated great interest as a novel strategy in cancer diagnosis and therapy. Here we review the versatile roles of miRNAs in cancers and their potential applications for diagnosis, prognosis, and treatment as biomarkers.

Keywords: microRNAs; cancer; epithelial-mesenchymal transition; inflammation; cancer stem cells; drug resistance

International Journal of Oral Science (2011) 3: 165-175. doi: 10.4248/IJOS11063

Introduction

microRNAs (miRNAs), which negatively regulate gene expression at the post-transcriptional and/or translational level, are short non-coding RNAs 19–25 nucleotides in length, first discovered in *Caenorhabditis elegans* to control developmental timing [1-3]. Mature miRNAs are formed from longer primary transcripts by two sequential processing steps mediated by a nuclear (Drosha) and a cytoplasmic (Dicer) RNase III endonuclease [4-5]. In most animals, miRNAs direct gene regulation at the level of translation. They can down-regulate gene expression either by degradation of messenger RNA (mRNA)

through the RNA interference (RNAi) pathway or by inhibiting protein translation [6]. To date, over 1 000 miRNAs have been identified in animal genomes through cloning and bioinformatics approaches. Although the biological roles of only a small fraction of identified miRNAs have been elucidated, in mammals, these miRNAs regulate processes essential to cell growth, embryogenesis, stem cell maintenance, hematopoietic cell differentiation, and brain development [7-11]. Since Croce's research group first reported the link between the abnormal expression of miRNAs and cancer in 2002 [12], more and more studies have shown that many miRNAs take part in the progressions of various cancers, including tumor growth, differentiation, adhesion, apoptosis, invasion, and metastasis [13-15]. Cancer is ultimately a consequence of disordered gene expression. miRNA profiling experiments have revealed that many miRNAs are abnormally expressed in clinical cancer samples. In addition, in *in vitro* and *in vivo* models, these abnormal expressions have been pointed out to be closely related to various

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Received 15 June 2011; Accepted 8 July 2011

biological behaviors of cancers [16-17]. Thus, alterations of miRNAs expression may promote tumor formation by modulating the functional expression of critical genes involved in tumor development and progression [18]. Here we present the progress of miRNAs in cancers and prospect the great potential of miRNAs in cancer diagnosis and therapy in the future.

Tumorigenesis

miRNAs were reported to be involved in tumorigenesis by targeting tumor suppressor genes or oncogenes directly or indirectly. Because miRNAs are negative regulators of gene expression, the changes of the expression level of these miRNAs can be tumorigenic if they target mRNAs from a tumor suppressor gene, as well as an oncogene. For example, miR-373 was identified as an oncogene that cooperates with Ras in oncogenic transformation by a suppressing signaling through the p53 pathways [19]; miR-31 was found to directly target tumor suppressor genes, large tumor suppressor 2 (LATS2) and protein phosphatase 2A (PP2A) regulatory subunit B alpha isoform, and repress lung cancer cell growth and tumorigenicity independently and substantially [20]; miR-183, as an oncogene by targeting early growth response 1 (EGR1) and phosphatase and tensin homolog (PTEN), was significantly overexpressed in synovial sarcoma, rhabdomyosarcoma, and colon cancer cell lines, and promoting the tumor cell migration [21]; miR-93, one of the miRNAs within the miR-106b-25 cluster, was able to promote tumor growth and angiogenesis by targeting integrin- β 8 which was associated with cell death in tumor mass *in vivo* [22]; Another well-characterized example is the miR-17-92 cluster which is transcriptionally activated by the oncogene c-Myc. They are susceptibility gene at the chr13q13 amplicon and reported to have the causal role in cancer. In a mouse model for lymphoma, co-expression of miR-17-19b, a truncated portion of miR-17-92, strongly accelerated lymphomagenesis [23]; miR-17-5p and miR-20a, two of the miRNAs in the miR-17-92 cluster, could repress the translation of E2F1, a protein that is increased by c-Myc and enhance both cell cycle progression and apoptosis [24-25]. Medina *et al.* [26] showed that overexpression of miR-21 led to a pre-B malignant lymphoid-like phenotype *in vivo*. When miR-21 was inactivated, the tumors regressed completely in a few days, partly as a result of apoptosis. Their results supported efforts to treat human cancers through pharmacological inactivation of miRNAs such as miR-21. This conclusion was also confirmed in breast cancer, colon cancer, pancreas cancer, lung cancer, prostate cancer, liver cancer, stomach

cancer, and oral squamous cell carcinoma (OSCC) [27-32]. Evidence above showed that these tiny non-coding RNAs were playing important roles in the malignant progression of tumors.

Tumor suppressor

miRNAs have been implicated as tumor suppressor genes. Typical examples are miR-15a and miR-16, which are down-regulated in 68% of chronic lymphocytic leukemia (CLL). Since these two miRNAs can negatively regulate the expression of the anti-apoptotic factor BCL2, their down-regulation could result in higher BCL2 protein level and anti-apoptotic activity [33-34]. Let-7/miR-98 family is another example for down-regulation of miRNAs that target a number of well-known oncogenes. The roles of let-7 and miR-98 as suppressors in lung cancer were supported by experiments showing that they negatively regulate the expression of the Ras and Myc oncogenes [35-36]. miR-330 was reported to have the suppression roles by negatively regulating E2F1 and inducing apoptosis through E2F1-mediated suppression of Akt phosphorylation in human prostate cancer cell lines PC-3 [37]. A similar situation was also applied to miR-34a, which was reported to directly target E2F3 and significantly reduced the level of E2F3 protein (a protein transcriptional inducer of cell-cycle progression), acting as a potential tumor suppressor by inducing apoptosis. miR-34a also participated in the regulation of tumor cell scattering, migration, and invasion *via* down-regulation of c-Met and its downstream signaling cascades [38]. In general, the genomic alterations, particularly tumor suppressor genes amplification or oncogene deletion, can be a major mechanism of inactivation of the tumor suppression function of miRNAs.

Interestingly, recent estimates suggested that as many as 50% of all nucleotides were transcribed and only 2% of nucleotides reside in known exons. Moreover, more than half of such transcripts are non-polyadenylated. These RNAs would be invisible to many analyses because the first step is often reverse transcription from the "canonical" polyA tail. And miRNAs are one major group of these hidden RNAs. It is remarkable, because these findings raise the possibility that many miRNAs as oncogenes or suppressors remain to be discovered [39-40].

Invasion and metastasis

Invasion and metastasis are responsible for >90% of cancer-related mortality. As tumors progress with increased malignancy, cells within them develop the ability to invade into surrounding normal tissues and through

tissue boundaries to form new growths (metastases) at sites distinct from the primary tumor. The molecular mechanisms involved in this process are associated with cell-cell and cell-matrix adhesion, with the degradation of extracellular matrix, and with the initiation and maintenance of early growth at the new site [41-42].

Epithelial-mesenchymal transition (EMT), mainly characterized by E-cadherin degradation, is an important event in invasion and metastasis. E-cadherin, which is encoded by E-cadherin gene (CDH1) and regulated by Snail, Slug, Zeb1, Zeb2, Klf8, Twist1 and Twist2, is a well-known molecule which maintains the cell-to-cell junctions in epithelial cells [43-44]. Its aberrant expression has been implicated in cancer progression and metastasis [45-46]. miR-373 was considered to have an effective role in E-cadherin targeting. It has been confirmed that the transfection of miR-373 and its precursor hairpin RNA into PC-3 cells readily induced E-cadherin expression. Together with miR-520c, they are considered to be metastasis-promoting miRNAs by direct suppression of CD44 which is consistently reduced in metastatic breast, colon and prostate cancers [47-50].

In breast cancer cells, both miR-10b and -9 are important participants of invasion and metastasis. Homeobox D10 (HOXD10) is a validated target of miR-10b. Ectopic expression of miR-10b has consistently led to the down-regulation of HOXD10 expression, and in turn, the induction of RhoC expression. Importantly, either over-expression of HOXD10 or knockdown of RhoC almost completely reversed miR-10b-induced migration and invasion *in vitro* [51]. It has been shown that miR-9 could directly target CDH1, the E-cadherin encoding mRNA, leading to increased cell motility and invasiveness [52]. miR-21 was found up-regulated in many solid tumors. When anti-sense oligo against miR-21 was introduced into metastatic cancer cells, their metastatic ability was inhibited, as gauged by a tail-vein metastasis assay and a chick-embryo chorioallantoic-membrane metastasis assay. With further study, it was found that miR-21 could target phosphatase and tensin homolog (PTEN), tumor suppressor gene tropomyosin 1 (TPM1), and programmed cell death 4 (PDCD4), to promote the metastasis of cancers [53-57]. Meanwhile, some miRNAs play a role in inhibiting tumor invasion and metastasis. The let-7 miRNA family of tumor suppressors is down-regulated in a variety of tumors. This family of miRNAs has been identified as the silencer of the Ras and HMGA2 oncogenes which promote tumor metastasis [36, 58-60]. The miR-200 family, organized as two clusters in the genome, were expressed during EMT and able to hinder EMT by enhancing E-cadherin transcriptional expression through directly targeting Zeb1 and

Zeb2 [61-63]. Martello have shown that high levels of miR-103/-107 were associated with metastasis and poor outcome in human breast cancer. At the cellular level, a key event fostered by miR-103/-107 was the induction of EMT, attained by down-regulating miR-200 levels [64]. Hedgehog signaling cascade cross-talks with Wnt, epidermal growth factor (EGF)/fibroblast growth factor (FGF), and tumor growth factor- β (TGF- β /Activin/Nodal/bone morphogenetic protein (BMP) signaling cascades, which are implicated in epithelial-mesenchymal transition (EMT) through E-cadherin repression [65-67]. It was reported that TGF- β could down-regulate the expression of human miR-141, -200a/b/c, -205, and -429, which in turn down-regulate Zeb1 and Zeb2. It is noteworthy that these miRNAs may play important roles in EMT as participants in the Hedgehog signaling cascade [68].

Angiogenesis is another important mechanism in cancer invasion and metastasis. It frequently happens in various tumors and is highly related with invasion, metastasis and poor outcome [69]. Early studies have indicated the contribution of specific miRNAs (*e.g.* miR-21, -155, and 126) to vascular diseases [70]. At present, miR-126 is widely accepted as an important factor for angiogenesis. Two groups published their investigations back-to-back that miR-126 could regulate the response of endothelial cells to vascular endothelial growth factor (VEGF), and regulate vascular integrity and angiogenesis *in vivo* [71-72]. Nicoli *et al.* [73] reported that zinc finger transcription factor Klf2a induced the expression of miR-126 leading to the activation of the VEGF signaling pathway. Their work described a novel genetic mechanism in which a miRNA facilitated the integration of a physiological stimulus with growth factor signaling in endothelial cells to guide angiogenesis. Epidermal growth factor-like domain 7 (EGFL7) was described as a novel endothelial cell-derived factor involved in the blood vessel formation. Fish and colleagues described the transcriptional regulation of EGFL7 in human endothelial cells by miR-126 [71]. Sun *et al.* [74] reported that EGFL7 was a direct target of miR-126 in lung cancer cells and hinted that this could be at least partly explain the observed effect of miR-126 on tumorigenesis. Taken together, these results demonstrated that miR-126 and EGFL7 may share a tightly regulated function in tumor vessel formation. Except the miRNAs mentioned above, miR-17/-20, -31, and -335 have all been shown to have inhibitory roles in tumor invasion and metastasis as demonstrated in recent studies [75-76].

miRNAs and cancer-related inflammation

Chronic inflammation is a major cause of cancer.

Epidemiologic and clinical studies show that approximately 25% of all human cancers in adults result from chronic inflammation. The oncogenic mechanisms in chronic inflammation are complicated and not fully revealed. Some studies have suggested that induced epigenetic changes and genomic instability were involved in inflammation-induced carcinogenesis. Several transcription factors and key inflammation mediators, such as tumor necrosis factor- α (TNF- α), cyclooxygenase-2 (COX-2), cytokines, hypoxia inducible factor-1 α (HIF-1 α), and nuclear factor- κ B (NF- κ B), have been identified as playing important roles in inflammation-induced cancers [77-79]. miRNAs have emerged as a critical regulatory factor in the mammalian immune system. Genetic ablation of the miRNA machinery, as well as loss or deregulation of certain individual miRNAs, severely compromises immune response leading to immune disorders like autoimmunity and cancer [80].

miR-146a is one of the first miRNAs identified to be involved in the regulation of immune function. Lipopolysaccharide (LPS)-induced induction of miR-146a was observed in several other cell lines of myeloid origin, but not in B cell lines, suggesting the LPS-induced regulation of miR-146a is cell-type specific. In addition to the effect on Toll-like receptor (TLR) ligands, miR-146a was induced by TNF- α and interleukin (IL)-1 β in an NF- κ B dependent manner [81-82]. miR-21 is one of the most abundant miRNAs in T cells in the immune system, indicating that it is critical for T cell homeostasis [83]. In the expression profiling studies during the innate immune response to aerosolized LPS in the mouse lung, miR-21 was found to be involved in the inflammatory responses [84]. Recent research has shown that miR-21, expressed by inflammatory leukocytes, was the most highly induced miRNA in an IL-13-induced asthma mode. One potential target for miR-21 is IL-12p35, a subunit of IL-12, a key cytokine from macrophages and dendritic cells involved in adaptive immune responses [85]. Schetter *et al.* [86] examined the expression of 23 inflammatory genes in colon adenocarcinomas and adjacent noncancerous tissues from 196 patients. The results showed that miR-21 was functionally associated with IL-6, -8, -10, -12a and nitric oxide synthase 2a (NOS2a), suggesting that miR-21 expression was associated with cancer-specific mortality and cancer-related inflammation. These results imply that miR-21 might contribute to the inflammation-induced cancers, at least part, by modulating cytokine responses. miR-155 is regarded as a multifunctional miRNA. Besides acting as an important oncogene, it plays essential roles in both B and T cell response identified by two independent groups [87-89]. Similar to

miR-146, miR-155 is regulated by LPS in mouse macrophages. It is also regulated by virally relevant stimuli, such as the synthetic TLR3 ligand poly and by antiviral response cytokines (interferin (IFN)- β , - γ), suggesting that miR-155 is a component of the innate immune response [81, 90-91]. Overexpression of miR-155 also caused the repression of tumor through targeting p53-induced nuclear protein 1, a pro-apoptotic gene downstream of p53 signaling, suggesting that miR-155 has a pro-tumorigenic function *via* regulation of inflammation-induced carcinogenesis [92].

miR-17-92 cluster encodes six miRNAs (miR-17, -18a, -19a, -19b-1, -20a, and -92-1) in the human genome. Studies on mouse models have implicated the importance of miR-17-92 cluster in B cell development and T cell function. In addition, *in vivo* studies indicate a role for these miRNAs in monocytic development [93-95]. These findings suggest that there might be a potential link between the expression of miR-17-92 cluster and immune system. However, the exact roles of miR-17-92 in inflammation need further investigations. Iliopoulos *et al.* [96] found that let-7 directly inhibited IL6 expression, resulting in higher levels of IL6 than achieved by NF- κ B activation in several cancer cell lines. This result suggests that let-7 might be important to the cancer-related inflammation. Except the miRNAs described above, many other miRNAs, such as miR-9, miR-101, -192, and -203, have been also associated with inflammatory diseases or immune responses [97-102].

miRNAs and cancer stem cells

Cancer stem cell (CSC) model in tumorigenesis proposes that a small fraction of cells in a tumor has properties of stem cells, being responsible for initiating and maintaining the tumor. miRNAs have been found specially expressing in CSCs and controlling their self-renewal and differentiation through regulating the expression of certain key genes [103-106]. Yu *et al.* [107] found that let-7 regulated multiple stem cell-like properties of breast tumor-initiating cells (BT-ICs) by silencing Harvey rat sarcoma virus oncogene or high mobility group AT-hook 2 (HMGA2). Another study showed that enforced let-7 expression depleted the self-renewing compartment through identification of miRNA signature in a population of purified self-renewing progenitor cells [108]. miR-205 and -22 were found to highly express in mammary progenitor cells, while let-7 and miR-93 were depleted. Further studies demonstrated that let-7 sensors could be used to prospectively enrich self-renewing populations, and that enforced let-7 expression induced loss of self-renewing cells from mixed cultures. These

results revealed a role for let-7 in regulating stemness, suggesting that miRNAs might play important roles in CSC proliferation, differentiation and tumor formation. Some miRNAs themselves are considered to be stem cell-like miRNAs recently. Cairo *et al.* [109] reported that undifferentiated aggressive hepatoblastoma (HBs) overexpressed the miR-371-3 cluster with concomitant down-regulation of the miR-100/let-7a-2/miR-125b-1 cluster. Their combined deregulation cooperated in modulating the hepatic tumor phenotype, implicating stem cell-like regulation of Myc-dependent miRNAs in poorly differentiated HBs. This important finding adds miRNAs as new role in tumor regulation.

miRNAs and anticancer drug resistance

Drug resistance remains a major clinical obstacle to successful treatment. The understanding of the drug resistance mechanism is important for the cancer therapy. Increasing evidence has indicated that aberrant miRNA expression is strongly implicated in anticancer drug resistance [110-112]. Significant overexpression of 8 miRNAs and down-regulation of 7 miRNAs were detected in a tamoxifen-resistant breast cancer cell line compared with the tamoxifen-sensitive cell line [113]. Kovalchuk *et al.* [114] reported that miR-451 regulated the expression of multidrug resistance 1 (MDR-1) gene in the doxorubicin-resistant human breast adenocarcinoma cell line MCF-7. In ovarian cancer, Yang *et al.* [115] demonstrated that the up-regulation of miR-214 promoted the survival of ovarian cancer cells and induced resistance of cisplatin. Sorrentino *et al.* [116] showed that a panel of miRNAs (let-7e, miR-30c, -125b, -130a and -335) were diversely expressed in all the resistant cell lines of ovarian cancer. In non-small cell lung cancer, 5 miRNAs (miR-15b, -100, -125b, -221, and -222) were found to up-regulate in the resistant cell lines [117]. Forced overexpression of the miR-222, -100, and -221 in the sensitive H460 cells increased resistance to TNF-related apoptosis inducing ligand (TRAIL), indicating that inhibition of their target proteins results in TRAIL resistance. Bertino *et al.* [118] put forward the concept of miRNA pharmacogenomics, a novel and promising field of research that holds new possibilities for medical therapy. This model can be defined as the study miRNAs and the miRSNPs/polymorphisms in their target genes may determine drug behavior in order to improve efficiency of drugs. Upon reaching a deeper understanding of the mechanism of miRNA in anticancer drug resistance, miRNAs might well fulfill their promise as valuable therapeutics in overcoming anticancer drug resistance.

miRNAs related cancer diagnosis and therapy

As the important roles of miRNAs in cancer are gradually revealed, their potential applications as useful and effective targets have generated great interest in cancer gene therapy strategies, as well as diagnosis, classification, prognosis and risk factor evaluations. Based on microarrays for miRNA expression profiling studies, differences in miRNA expression could be detected between normal and cancer tissues, which can classify different tumor types and tumor grades [119-121]. Certain miRNA signatures are correlated with prognosis and can potentially be used to determine the specific course of treatment. Michael *et al.* [122] found aberrant miRNA expression in solid tumors as they identified 28 different miRNAs in colonic adenocarcinoma compared with normal mucosa. miR-143 and -145 were significantly down-regulated in the cancer. Similar situation was detected in other cancers, as miR-221, -222, and -146 in papillary thyroid carcinoma [123], miR-21 and -155 in pancreatic cancer [124], and miR-141 in prostate cancer [125]. Through analyzing the expression of 217 miRNAs in 334 samples that included primary tumors, tumor-derived cell lines and normal tissues, Lu *et al.* [16] found that miRNA profiles can distinguish between normal and cancer tissues, separate different cancer types, stratify the cancer differentiation state and cluster sample groups according to their embryonic lineage. Single nucleotide polymorphisms (SNPs) within the miRNA coding genes or within miRNA target genes are likely to be deleterious and can affect an individual's risk to develop diseases such as cancers. Yu *et al.* [126] found that 12 miRNA-related SNPs showed an aberrant allele frequency in human cancers. Chin *et al.* [127] identified an SNP in let-7 complementary site 6 (LCS6) in the KRAS 3' UTR that is associated with smoking-induced lung cancer risk. This variant allele is found in 20% of the 74 non-small cell lung carcinoma patients in the study. These unique miRNA expression signatures might be the hallmarks of tumor progressions and prognosis evaluations.

Many miRNAs, as discussed above, have great potential in tumorigenesis, tumor invasion, metastasis, malignant progression, and poor prognosis. In *in vitro* and *in vivo* experiments, it has been confirmed that knockdown of certain miRNAs could change the tumor progression and biological characteristics as potential therapeutic targets [128-129]. In cell culture and xenograft mice models, synthetic anti-miRNA oligonucleotide (AMO) with 2'-O-methyl modification have been shown to effectively inhibit endogenous miRNAs. Krützfeldt *et al.* [130] studied the utility of AMOs *in vivo* through

intravenous injection of modified AMOs to target the liver-specific miR-122. Impressively, a single injection of 240 mg kg⁻¹ body weight conferred specific miR-122 silencing for up to 23 days. As an alternative to 2'-hydroxyl-modified AMOs, lock nucleic acid based oligonucleotides (LNA-antimiR) have been shown to be more stable and less toxic in inhibiting endogenous miRNAs *in vivo*. Kota *et al.* [131] showed that the systemic delivery of a single miRNA could cause tumor regression in a mice model of liver cancer. They delivered adeno-associated virus 8 (AAV8)-expressing miR-26a intravenously in Myc-induced mice harboring preformed liver tumors. After 3 weeks, they observed a significant regression of tumors in mice with the miR-26a treatment. These findings indicate a possibility of specific miRNAs-target therapy.

Conclusion and perspective

The importance of miRNAs in cancer has been well established and some special miRNAs have been regarded as hallmarks in tumor progressions and hot targets in cancer therapy. However, there is still a long and arduous way to go for substantial applications of miRNAs in cancer treatments. To date, the exact mechanisms and entire networks of miRNAs in cancer progressions are still unclear, and there is even some controversy about their roles in tumor regulation. For example, Ma *et al.* [52] reported that miR-9 acted as an oncogene and regulates the metastasis of lung cancer cell, while Wan *et al.* [132] suggested miR-9 as a tumor suppressive gene by targeting NF- κ B in gastric cancer; Similarly to miR-9, -107 and -125b function as oncogenes in some tumors and as a tumor-suppressor in others [133-138]. In OSCC, expression of miR-31 was reported to be up-regulated [139-140]. However, it appeared to down-regulation in gastric carcinoma and prostate carcinoma [141-142]. These results need to be further confirmed. It is also possible that the contradictory results implied regulation mechanisms uncovered in the relationships between miRNAs and cancers. One hypothesis is that certain miRNAs might have different roles in different tissues or different cancer types, or even there are some unknown molecules or genes regulating the same miRNAs to perform various roles in different situations. As a "star molecule" since 2002, miRNAs have become the focus in recent years and the studies of their roles in cancers have continued. In 2010, Guo *et al.* [143] found that changes in mRNA levels closely reflected the impact of miRNAs on gene expression, indicating that destabilization of target mRNAs was the predominant reason for reduced protein output. This means that miRNAs play

their roles mainly by degrading the target mRNA ($\geq 84\%$ lowered mRNA levels account for of the decreased protein production) rather than by inhibiting their translation. Meanwhile, Zhang *et al.* [144] reported that cells can secrete miRNAs and deliver them into recipient cells where the exogenous miRNAs can regulate target gene expression and recipient cell function as signaling molecules mediating intercellular communication. These results provide the potential mechanism of miRNAs in cancers, and indicate a novel approach for future research. Although our knowledge about the exact roles of miRNAs as well as their regulating genes in cancers is limited, we believe that the prospects of cancer research on miRNA field are broad.

Acknowledgement

We thank Xiao-wei Wang at Washington University in St. Louis for the proofreading. This work was supported by National Natural Science Foundation of China grants (No. 30872889, 81072215, 81001210, 81172580), by Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (No. 20098-8-2) and by State Key Laboratory of Oral Diseases Open Funding (SKLODOF2010-05) and the Fundamental Research Funds of the Central Universities of China (2011).

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