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Let-7d A Novel Regulator in Oral Squamous Cell Carcinoma

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Abstract

Oral squamous cell carcinoma (OSCC), is the sixth most prevalent cancer worldwide and accounts for approximately 8-10% of all cancers in Southeast Asia. Malignant transformation of mucosal lesions predispose to oral cancer. The World Health Organization (WHO) defined these lesions as "potentially malignant disorders (PMD)". Betel quid chewing, alcohol consumption and smoking habits have been indicated to increase the risk of malignant transformation. The number of new OSCC cases is increasing day by day worldwide, especially in the developing countries, and the prognosis remains poor in spite of recent advances in the diagnostic and therapeutic modalities due to expensive diagnosis. 50% of the OSCC patients die or complications within 5 years under current therapies. To increase patient survival rate, investigations elucidating the mechanisms of tumorigenesis in OSCC are in need. Some studies have suggested that tumor initiating cells (TICs) are responsible for tumor progression as well as recurrence after the chemotherapy.

Introduction

In present time the most common type (84–97%) of oral cancer is Oral squamous cell carcinoma (OSCC)[1]. In Asia the major risk factor for OSCC is the betel quid, tobacco, smoking. Malignant transformation of mucosal lesions predispose to oral cancer. The World Health Organization (WHO) defined these lesions as "potentially malignant disorders (PMD)". Betel quid chewing, alcohol consumption and smoking habits have been indicated to increase the risk of malignant transformation[2,3]. The number of new OSCC cases is increasing day by day worldwide, especially in the developing countries, and the prognosis remains poor in spite of recent advances in the diagnostic and therapeutic modalities due to expensive diagnosis. Usually, OSCC detection depends on the clinical examination of oral cavity, followed by a biopsy for histological analysis. However, despite the easy access for visual examination, OSCC is often detected at advanced stages which reduces patient survival rate. In spite of the recent advances in diagnosis and treatment modalities, less than 50% of OSCC patients survive for 5 years[4]. Late

diagnosis, regional lymph node metastasis, and recurrences are responsible for the poor prognosis and reduced survival for OSCC patients[5,6]. Some protein coding tumor suppressor genes and/or oncogenes found to be responsible for tumor development[7,8]. While in recent research thousands of genes that transcribe noncoding RNAs (including miRNAs) makes it obvious that cancer biology is even more complex than initially expected. Oral squamous cell carcinoma (OSCC), is the sixth most preva-lent cancer worldwide and accounts for approximately 8-

10% of all cancers in Southeast Asia[9,10]. There are three major etiologic factors that contribute to OSCC risk and prognosis: tobacco use, alcohol consumption and human papillomavirus (HPV) infection[10,11]. In addition, genetic variation has been shown to modify the risk of disease and in certain instances has been associated with patient survival[12,13,14]. 50% of the OSCC patients die or complications within 5 years under current therapies[10]. To increase patient survival rate, investigations elucidating the mechanisms of tumorigenesis in OSCC are in need[10]. Some studies have suggested that tumor initiating cells (TICs) are responsible for tumor progression as well as recurrence after the chemotherapy[11]. However, there is lack of suitable markers for isolating the crucial subset of tumor cells that is capable of reforming new tumors *in vivo* and accounts for tumor relapse in OSCC, according to CSC hypothesis of tumorigenesis. The latter strategy now includes microRNA (miRNA)-related single nucleotide polymorphisms (SNPs) which can occur in miRNA genes themselves, or in their target sequences[15,16].

Diagnostic and Prognostic Value of miRNAs in OSCC

MiRNAs are short non-coding RNAs which prevent translation of their target genes by binding the highly evolutionarily conserved 3# untranslated regions (UTRs) of mRNAs[17]. The highly critical role miRNAs play in gene regulation is widely accepted, and altered expression of miRNAs in human cancers has been well documented[18]. Recently, critical examinations of miRNA expression profiles in OSCC have underlined the importance of miRNA expression alterations in OSCC tumorigenesis[19,20].

Let-7b

Let-7b is the firstly discovered miRNA which plays a key role of regulator for cell proliferation and differentiation[21,22]. This miRNA is found as a regulator in many types of cancers like colon, pancreatic endocrine and pancreatic adenocarcinoma[23]. It was found that let-7b, but not let-7a, was significantly reduced in oral cancer cell lines compared with control cells[24]. Over-expressed let-7b reduces the expression of its target gene Dicer. Dicer is the RNase III endonuclease required for miRNA maturation and aberrantly expressed in different types of cancer[24]. Another study found that let-7b also targets insulin-like growth factor 1 receptor (IGF1R), which is activated by IGF1 or IGF2 through autocrine and paracrine signaling. Let-7b inhibits cell proliferation and colony formation and triggers S/G2 cell cycle arrest by targeting IGF1R and IRS-2 through the Akt pathway. Hence, let-7b down-regulation contributes to oral cancer progression. Over-expressing let-7b could be a potential therapy target for inhibition of cancer cell proliferation.

Tumor Supresssors

MicroRNAs (miRNAs) are highly conserved small RNA molecules which regulate the expression of gene and can act as a tumor suppressor agent. SNPs in miRNA-binding site is influencing the risk of cancer has among which let-7 complementary site SNP in the 3# UTR of KRAS is one of them[25]. Let-7 gene family was one of the first mammalian miRNAs to be discovered[26]. As the cancer cell progresses Let-7 family members starts showing the down-regulation property[25].

Let-7d acts as a tumor suppressor, by targeting the RAS[27]. miRNAs let-7 family regulates the KRAS[27]. A member of the family of RAS oncogenes that are well-characterized GTPases, KRAS is activated by somatic mutation in many human cancer types[28]. Activation of the KRAS proto-oncogene via mutation in adenocarcinomas of the lung, colon and pancreas is well documented while mutations of KRAS in OSCC are relatively rare[28,29]. although the growth-promoting character of KRAS activation (associated with companion modes of activation of this and related pathways0p) is almost certainly a feature of

most solid tumors and, in fact, amplification of KRAS has been reported to promote growth of OSCC[30]. Further, these authors characterized the function of the KRAS-LCS6 SNP, determining that the variant allele was associated with both increased KRAS expression and decreased let-7 levels[25]. Activation of the KRAS pathway might be accomplished in squamous cell carcinomas via action of this normal variant and thereby associated with susceptibility to this disease and with patient outcome.

The region upstream of let-7d promoter is modulated by transforming growth factor (TGF)-β transcription factor SMAD3[28]. The expression of let-7d was found to be significantly down-regulated in chemo-resistant cancer also[30]. Dysregulation of let-7d also indicate its possibility in involvement of cancer progression[26,28,31,32,33]. Combined underexpression of miR-205 and let-7d is also associated with poor survival of OSCC patients[34].

Conclusion

The finding of abnormalities in miRNAs gives new insights into the pathogenesis and progression of OSCC. Lots of aberrantly expressed miRNAs have been verified either as oncogenes or tumor suppressors, participating in various biological processes of OSCC, including proliferation, apoptosis, metastasis and chemoresistance. miRNAs have been found to have a potential as diagnostic and prognostic tools. Also, the role of miRNAs in cancers makes it possible to design miRNA-based therapy for OSCC. Although still largely unknown in this area, compelling evidence gives exciting promise that miRNAs will advance the management of OSCC in the near future. It is important to further elucidate the mechanisms by which downstream factors are regulated by let-7d in OSCC. Let-7d in the malignant OSCC or recurrent OSCC after chemotherapy may be useful in the future as a potential anti-cancer therapeutic strategy. Overall, restoration of let-7d in malignant oral cancer may initiate a new approach for therapeutic treatment in the future.

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