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Review

Cell cycle-regulatory cyclins and their deregulation in oral cancer

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SUMMARY

Oral cancer is a growth-related disorder, and cyclins are the prime regulators of cell division. Cyclins are associated with the pathogenesis of oral cancer and are considered valuable biomarkers for diagnosis and prognosis. These important molecules are regulated in many ways to achieve a gain in function and are involved in promoting neoplastic growth. While the causes of most cyclin overexpression are varied, these cyclins may be induced by buccal mucosal insult mainly with carcinogens that alter various pathways propelling oral cancer. Substantial experimental evidences support a link between oncogenic signaling pathways and the deregulation of cyclins in oral cancer. This review focuses on the mechanisms by which cyclins are regulated and promote oral oncogenesis.

Introduction

Oral cancer accounts for one-sixth of the total cancer cases worldwide; thus, it is a major human neoplasm [1]. Oral cancer begins with a long phase of hyperplasia, which then transforms into dysplasia and subsequently becomes carcinoma [2,3]. The overall poor survival and prognosis, which have not improved for several decades, indicate the failing of many current therapeutic strategies and a poor understanding of the disease [4]. Enormous overexpression of the cell cycle-related cyclin proteins suggests that it is rapid cell division rather than an apoptosis blockade that is the root cause of this neoplasm. Hence, a detailed analysis of cell cycle regulatory molecules may be helpful for better understanding this devastating disease.

Aberrantly expressed cell cycle-related cyclins are highly associated with mouth neoplasms [3,5–7]. Although these cyclins have been reported for the last two decades, their value is just beginning to be understood. Cyclins are an important group of proteins that regulate normal cell division. Their periodic synthesis and degradation is linked with different phases of cell division. D-type cyclins are regulatory components of cyclin dependent kinase-4/6 (CDK4/6) and are important in the G1-phase of the cell cycle [8]. E- and A-type cyclins, along with their partner, CDK2, are important for the G1-S phase transition and S-phase progression, respectively [9,10]. Cyclins A and B (with CDC2) are important for entry into the M-phase of the mammalian cell cycle [10]. Cyclin A begins to degrade in early pro-metaphase and is completely gone at metaphase [11,12]. The degradation of mitotic cyclin A is important (as is the overexpression of the S-phase cyclin A) for cell cycle progression, whereas the overexpression of cyclin B, which regulates CDC2 activity, leads to mitotic progression. In addition to its overexpression, cyclin B degradation is required for CDK1 inactivation and exit from mitosis [13]. Many cyclins are also involved in CDK-independent functions, including transcription and gene activation, but these functions are not discussed here.

The importances of the cell cycle-related cyclins and their deregulation in neoplastic growth have been established in other tumors types. Cyclin deregulation in oral cancer has been undermined because cyclins are deregulated not only in oral cancer. Additional studies on cyclins may lead to their identification as important cancer diagnostic and prognostic indicators as well as their use as possible therapeutic tools for oral cancer intervention in the future. This review mainly focuses on the mechanisms of cyclin deregulation in oral cancer to indicate areas for future investigation for better understanding of this disease.

Cyclins and their status in oral cancer

There are three major isoforms of D-type cyclins (i.e., D1, D2 and D3), and only cyclin D1 is expressed in oral cancer [14]. A number of studies have demonstrated that the cyclin D1 protein is overexpressed and accumulates in oral tumor cells [15,16]. Immunostaining results have shown the nuclear accumulation of this protein in oral cancer. An increase in the mRNA levels of cyclin D1 has also been reported in oral squamous cell carcinoma (OSCC), and its expression is

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stage-specific [3]. Cyclin D1 overexpression is correlated with disease severity, including tumor stage, lymph node involvement and OSCC aggressiveness [17,18]. Cyclin D1 amplification and overexpression in patients results in poor outcome and survival [19,20].

Cyclin E is an unstable protein, and its upregulation has been reported in dysplasia/OSCC when compared with normal oral epithelium [5,6,21–23]. Moreover, a 19q12 copy number gain provides evidence for cyclin E gene amplification, and this amplification is correlated with OSCC disease severity [21]. The oncopotential of cyclin E is further supported by its positive correlation with centrosome amplification [5] and its inverse correlation with p27 expression in OSCC [24]. Cyclin E overexpression correlates with disease severity in larynx cancer [25], and its expression is also correlated with advanced tumor stage [26]. Although more than six isoforms of this protein are reported to have, the lower molecular weight isoforms have more oncopotential.

Cyclin A has two main isoforms, A1 and A2 [10]. Cyclin A2 is produced in somatic cells while A1 in germ cells, but there are reports indicating that cyclin A1 is overexpressed in a subpopulation of OSCC and laryngeal SCC cells [27,28]. The aberrant expression of cyclin A in oral cancer has been reported [7,29,30]; for example, cyclin A is often overexpressed in oral dysplastic lesions [30–32], and it has been reported to be a marker for S phase in HNSCC [33]. Cyclin A is mainly expressed in the basal layer of the oral epithelium, and its expression gradually increases in the suprabasal layer with advancing dysplasia. Cyclin A is also correlated with advanced tumor stage [26] and the chemotherapeutic response in HNSCC [6]. Cyclin A expression has strong predictive value for the clinical outcome of patients undergoing oral pre-cancer treatments [34].

Cyclin B expresses many isoforms, including cyclin B1, B2 and B3. The aberrant expression of cyclin B1 has been observed in OSCC [6,7,30,35], and its expression correlates with the advanced tumor stages of this disease [26]. Cyclin B1 overexpression and radiotherapy resistance have also been reported in HNSCC [35]. Cyclin B1 is overexpressed in tongue carcinomas and is associated with more aggressive biological behavior [36]. The overexpression of cyclin B1 is considered a reliable marker for indicating the degree of tumor proliferation in OSCC [37] and is a useful prognostic marker for the lymph node metastasis of tongue carcinomas [38]. It also strongly predicts the clinical outcome of patients who have undergone oral pre-cancer treatments [34].

Evidence supporting cyclin deregulation

Changes at the DNA level

The cyclin D1 gene is located on chromosome 11q13, and it is commonly amplified in OSCC [15,21,39–41]. Cyclin D1 amplification in OSCCs results in overall poor survival [42]. Mutations in the DNA encoding the cyclin D gene may increase the stability of cyclin D1 mRNA/protein. Many studies have correlated cyclin D1 gene polymorphisms (CCND1 genotypes), including A870G (GG) and C1722G (CC), with poor survival and oral cancer development [43–45]. A cyclin D1 3′UTR (C1722G) polymorphism found in patients with oral cancer [43] may also stabilize cyclin D1 mRNA, possibly by disrupting its regulation by microRNAs [46].

Amplification of the cyclin E gene is known to occur in various types of human tumors [47–49], including human osteosarcoma and breast tumors [50,51]; however, few studies have examined cyclin E gene alterations in OSCC. A chromosome 19q12 copy number gain has been shown, suggesting cyclin E gene amplification in OSCC [21], but the results need to be confirmed in a larger cohort. The cyclin E promoter has consensus sequences for IE86 binding, and the gene is often activated by a viral protein (a cytomegalovirus 86-kDa protein) [52]; such opportunistic pathogen infections are commonly reported in periodontitis lesions [53].

Unlike other cyclins, changes in cyclins A and B at the DNA level have been reported in human tumors [54], but not in OSCC, which requires investigation. Promoter methylation in somatic cells leads to cyclin A1 gene silencing [55], and insertional mutations by viral DNA (HBV) are common in liver cancer [56]. Although mutations/epigenetic modifications in the promoter/enhancer regions of cyclins can alter their expression, these mutations/modifications have not been meticulously investigated in OSCC.

Overexpression and regulation at the RNA level

Cyclin D1 mRNA expression is stage-specific in OSCC [3], suggesting active transcriptional regulation of this gene. Cyclin D1 transcription is controlled by several transcription factors (TFs), including signal transducer and activator of transcription-3/5A (STAT3/5A), NFκB, ETS1, β-Catenin, c-Myc and AP-1. The overexpression of these TFs has been shown to be important in oral tumorigenesis. A recent report suggests that a cyclin D1 polymorphism in the 3'UTR in patients with oral cancer [43] may provide mRNA stability by disrupting cyclin D1 regulation by microRNAs [46]. Certain microRNAs, such as miR-17/20, are upregulated by c-Myc and cyclin D1 itself. Transcribed miR-17/20 plays a role in cyclin D1 mRNA degradation [46]. c-Myc overexpression in OSCC has been reported. Together, these studies provide evidence for the deregulation of cyclin D1 mRNA in OSCC.

Cyclin E mRNA expression has been demonstrated in human carcinomas [57]. The transcriptional upregulation of the cyclin E gene by c-ETS1 and c-Myc [58,59] has been reported, and these are important oncogenic TFs in OSCC. The cyclin E gene is also regulated by the Wnt signaling pathway, which plays a decisive role in the transformation of epithelial cells, including those in OSCC [59]. Cyclin E mRNA deregulation by various microRNAs (mir-29c, miR-15 and miR-16) in different cancers, including ESCC, has been demonstrated, and this process promotes carcinogenesis [60,61]. The estrogen-mediated regulation of the cyclin E (isoform 2) protein and mRNA has been reported [62].

Cyclin A transcription is actively regulated by various TFs, including E2F [63]. The cyclin A gene promoter is recognized by E2F, a finding that has been confirmed in OSCC [64]. Moreover, the cyclin A gene promoter is regulated by wild-type (wt) p53. p53 is inactivated by mutation in nearly half of the oral cancer population [65]. wt-p53 is known to be degraded by the action of MDM2 in OSCC. Impaired p53 can no longer suppress cyclin A, and this mechanism may be operational in OSCC. p53 activation or the ectopic expression of wt-p53 can cause G2 arrest in SCC97 cells by decreasing the levels of cyclin A [66]. This finding is supported by reports of an inverse correlation between p53 and cyclin A expression in OSCC [29]. Cyclin A gene promoter is having ATF/CREB binding sites and suppressed by activation of PP2A [67]. Recently, the expression of the cancerous inhibitor of PP2A (CIP2A) has been detected in oral dysplasia and OSCC [68]. CIP2A supports c-myc stabilization [69], an event that is highly prevalent in oral tumors [70,71], and it frequently activates cyclin A. Further the RNA binding protein, HuR (ASHuR), can bind cyclin A mRNA and increase its stability. The increased cytoplasmic expression of HuR has been reported in OSCC [72,73]. Moreover, a recent report suggests that HuR knockdown can change the oncogenic potential of oral cancer cells by decreasing the stability of many genes, including cyclin A [74]. All of these evidences suggest possible explanation of cyclin A mRNA upregulation in oral cancer.

Cyclin B1 transcription is mediated by STAT3 [75], and this pathway is one of the most important in OSCC [76]. Cyclin B1 mRNA synthesis is regulated by various TFs, such as E2F1 and E2F4, and its expression is often stimulated by the androgen receptor (AR) [77]. Although oral cancer more commonly occurs in the male population, the role of AR has not been resolved. Unlike AR,