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Malignant transformation of oral lichen planus and related genetic factors

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Oral lichen planus (OLP) is a chronic inflammatory disease observed in approximately 0.5–2.2% of the population, and it is recognized as a premalignant lesion that can progress into oral squamous cell carcinoma (OSCC). The rate of malignant transformation is approximately 1.09–2.3%, and the risk factors for malignant transformation are age, female, erosive type, and tongue site location. Malignant transformation of OLP is likely related to the low frequency of apoptotic phenomena. Therefore, apoptosis-related genetic factors, like p53, BCL-2, and BAX are reviewed. Increased p53 expression and altered expression of BCL-2 and BAX were observed in OLP patients, and the malignant transformation rate in these patients was relatively higher. The involvement of microRNA (miRNA) in the malignant transformation of OLP is also reviewed. Because autophagy is involved in cell survival and death through the regulation of various cellular processes, autophagy-related genetic factors may function as factors for malignant transformation. In OLP, decreased levels of ATG9B mRNA and a higher expression of IGF1 were observed, suggesting a reduction in cell death and autophagic response. Activated IGF1-PI3K/AKT/mTor cascade may play an important role in a signaling pathway related to the malignant transformation of OLP to OSCC. Recent research has shown that miRNAs, such as miR-199 and miR-122, activate the cascade, increasing the prosurvival and proproliferative signals.

Keywords: Oral lichen planus, Malignant transformation, Apoptosis and autophagy

Introduction

Oral lichen planus (OLP) is commonly observed chronic inflammatory disease of the mucous membrane surface of the mouth [1–3]. This disease is observed in about 0.5–2.2% of the populations [3–8]. Incidence rate of OLP is related with older age, female and location of the lesion. Among the patients, incidence of 30–60 year-old female is the highest [3–9]. Clinically, OLP mainly manifests three different forms: reticular, atrophic and erosive. They are generally simplified into two categories: erosive (erosive lesion) and non-erosive (reticular and atrophic lesions) [3,10,11].

The relationship of OLP and squamous cell carcinoma has attracted people's attention and studies on this subject have been performed [3,12,13]. According to the World Health Organization (WHO), OLP is categorized into the group of potentially malignant disorders, while its most severe complication is the progression into oral squamous cell carcinoma (OSCC)

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[14,15]. Possibility of the malignant transformation of OLP has been hypothesized and researchers have been searching for the evidence for malignant transformation. The OLP was recognized as pre-malignant by WHO, but the rate of malignant transformation remains unknown. Moreover, the factors involved in the malignant transformation of OLP to OSCC is not much known. Therefore, in this brief review, the malignant transformation of OLP and related genetic factors, especially in relation with apoptosis and autophagy, are discussed.

Malignant Transformation to Oral Squamous Cell Carcinoma

For many years, the possibility of malignant transformation of OLP has been discussed and reported [12,13]. Since OLP is longstanding inflammation, patients with OLP are believed to be at higher risk for OSCC. In order to elucidate the relationship between OLP and OSCC, meta-analysis studies, systematic review, and population-based studies have been performed.

A meta-analysis study was performed in order to investigate the possible risk factors for OLP malignant transformation to OSCC [16]. MEDLINE, Scopus and Web of Science were used as database. Results showed that approximately 1.1% of OLP patients develop OSCC. A higher incidence of malignant transformation was found among smokers, alcoholics, and hepatitis C virus (HCV)-infected patients compared to patients without these risk factors [3,17]. The involvement of HCV as a risk factor of OLP malignant transformation was also reported in other studies [3,17]. However, the authors reported that these associations should be further investigated.

In order to determine the malignant transformation rate of OLP and its risk factors, data bases of PubMed, Scopus and Web of Science were systemically reviewed [13]. The results of the systematic review showed that 92 of 6,559 OLP patients developed OSCC, and thus the malignant transformation rate was found to be 1.37%. This study suggested that erosive type, female and tongue site should be considered as risk factors for malignant transformation of OLP. Similar risk factors for OLP malignant transformation such as age, female and erosive form were suggested by other study [18]. These studies also suggested that to diagnose OLP, strict clinical and histological criteria to diagnose OLP and sounder methodological observation studies should be performed.

Another systematic approach was performed to evaluate the relationship between malignant transformation and OLP [12]. It was reported that among 7,806 patients with OLP, 85 developed SCC. The overall rate of transformation was 1.09 % for OLP. Average age of the patients was 60.8 years. A slight predominance of female patients among those who experienced malignant transformation was noticed. The most common subsite of malignant transformation was the tongue. The average time from diagnosis of OLP to transformation was 51.4 months.

A population-based retrospective cohort study showed that among the 303 OLP patients 7 had OSCC at 20 years after OLP incidence with malignant transformation rate of 2.3% [19]. The median time for the development of OSCC in OLP patients was 2.9 years which was 14.7 years earlier than the reference group. Patients with OLP, particularly the erosive type, have an increased incidence of OSCC development.

These studies showed that the malignant transformation rate of OLP to OSCC was approximately 1.09–2.3%. The high-risk group is older age, female, erosive type, and tongue site location. Patients with other inflammatory disease such as HCV can be categorized as a high-risk group. The OLP patients in these categories need to be monitored carefully with regular observation and continued follow-up should be done.

Genetic Factors Related to Oral Lichen Planus

1. Apoptosis related genetic factors

Apoptosis, a form of programmed cell death, is a selective physiological process that plays an important role in the balance between cell replication and cell death [20]. A wide range of stimuli can be integrated to trigger the irreversible decision of cell death. The low frequency of apoptotic phenomena in epithelial cells of OLP suggests the possibility of it creating a favorable substrate for malignant transformation [21].

Protein p53 is a transcription factor involved in DNA repair and destruction of defective cells through the induction of apoptosis and cell cycle arrest [22-24]. Increased expression of p53 in keratinocytes in OLP and the suprabasal layer localization of p53 in 20% of OLP cases was reported [25]. The association between suprabasal expression of p53 and increased risk of malignant transformation was suggested in other studies [26,27]. Protein p53 is confined to the basal cell layer in benign lesion and normal mucosa. Out of 35 patients with premalignant lesion, 7 patients showed p53 expression above the basal cell layer and 6 of these 7 developed carcinomas. In some cases, both p53 and MDM-2 was overexpressed in OLP

compared to normal mucosa [27]. MDM-2 acts as an E3 ubiquitin ligase of p53 and functions as a major negative regulator of p53 [28].

Immunohistochemical expression of p53 was compared between normal mucosa and OLP. The positive ratio of p53 in OLP patients was reported to be 69.9% [29] and 64% [30]. In some studies, even higher positive ratio of p53 was reported; 86.7% [31] and 90.9% [32], respectively. These studies, showing relatively high positive ratio of p53, claimed that mutant form of p53 was reacted. Thus revealing the presence of the mutation in the p53 protein and hence OLP has potential malignant transformation.

A follow up study was done with OLP patients who exhibited increased p53 expression. After 96 months of follow-up, enhanced p53 expression was observed in patients progressed to OSCC [33]. This observation suggested the involvement of p53 in malignant transformation to OSCC. A recent study showed that the level of unstimulated whole salivary p53 in subjects with OLP and OSCC was higher (5.63 ± 1.08) compared to only OLP (0.94 ± 0.31) [34]. All of these studies suggest the involvement of p53 in malignant transformation of OLP to OSCC.

Proteins of B-cell lymphoma-2 (BCL-2) control the intrinsic mitochondrial apoptosis pathway [35,36]. Among programmed cell death, intrinsic apoptosis is known as the most common type of cell death [37]. BCL-2 proteins with anti-apoptotic properties were discovered, which includes B-cell lymphoma-extra-large (BCL-XL), myeloid cell leukemia-1 (MCL-1), and BCL-2-like protein 2 (BCL-W) [36,38,39]. BCL-2 associated X protein (BAX) is a homologous binding partner of BCL-2. BAX has a pro-apoptotic property unlike other anti-apoptotic BCL-2 proteins. Among pro-apoptotic proteins, BAX, BCL-2 antagonist killer 1 (BAK), and BCL-2-related antagonist killer 1 (BOK) belong to the effector protein sub-class [23,36,39-41].

The altered expression of BCL-2 and BAX, and increase in capase-3, an executor protease of apoptosis were observed in lichen planus biopsy samples [42]. In OLP cases, higher rate of positive expression for BCL-2 (97%) was observed. It was suggested that overexpression of BCL-2 is associated with OLP and appears to play a role in malignant transformation [43]. In addition, an increased expression of BCL-2 was found in the lymphocytic infiltrate which is characteristically encountered in OLP lesions. The expression of BAX was elevated in epithelial basement keratin in OLP group compared to that in the control group, which includes healthy subjects [44]. In other study, 92% of OLP patients had a positive expression of BCL-2 in inflammatory infiltrate [45].

Immunohistochemical expression of BCL-2 was compared between normal mucosa and OLP. There was no positive expression in normal mucosa, but in OLP patient group, OLP positive rate was found to be 19.9% [29]. Similarly, BCL-2 positive rate of 16.7% in OLP was found in other study [46]. Strong expression of MCL-1 was observed in OLP and oral cancer cell lines. The authors suggested that MCL-1 could be a novel biomarker for the malignant potential of OLP [47]. Positive expression of BCL-2 was reported in 25 of 30 OSCC cases [48].

These data suggest that BCL-2 plays an important role in the inhibition of apoptosis of lymphocytes, while BAX is involved in the induction of apoptosis of keratinocytes. Alterations in the expression of BCL-2/BAX may be involved in malignant transformation of OLP to OSCC.

Micro RNA (miRNA) is small non-coding RNA molecule of 21–25 nucleotide that functions in RNA silencing and post-transcriptional regulation of gene expression. It usually functions by base-pairing with complementary sequences with mRNA molecules [49,50]. Recently, increasing evidence suggested that miRNAs are involved in the regulation of pathogenesis of OLP [51-53]. It was shown that miRNA-27b-3p regulates keratinocyte apoptosis through cyclinD/BCL-2 signaling [54]. Overexpression of miR-802 in OLP induces apoptosis of oral keratinocyte by targeting bcl-2 mRNA. However, vitamin D (VD)/VD receptor signaling could suppress the apoptosis by targeting miRNA-805 [55]. It was confirmed that the level of miR-26a and 26-b are decreased in OLP patients. In addition, mi-RNA 26a/b have protective action in OLP by inhibiting apoptosis of oral keratinocytes by targeting Protein Kinase C δ and cluster of the differentiation 38 (CD38) genes [56].

2. Autophagy related genetic factors

Autophagy is the major lysosomal intracellular degradation system that involves the delivery of cytoplasmic cargo to the lysosome. Autophagy is essential in survival, differentiation, development and homeostasis [57,58]. To promote cell survival or death, autophagy can be activated in response to various cellular and environmental stress conditions [59,60].

In order to investigate the role of autophagy in T cell on OLP pathogenesis, mRNA expression of autophagy-associated gene in OLP patients as analyzed [61]. Insulin-like growth factor 1 (IGF1) gene expression in the blood of OLP patients

was significantly higher than that in controls. The high expression was observed specially in female and middle-aged OLP patients compared to males and other age groups. IGF1 signaling could reduce cell death and possibly inhibit the autophagic response under the condition of nutritional stress [62,63]. Autophagy related 9 homolog B (ATG9B) mRNA level was significantly lower in OLP patients. Other genes such as hepatocyte growth factor-regulated tyrosine kinase substrate (HGS), estrogen receptor 1 (ESR1) and synuclein alpha (SNCA) showed no significant difference between experimental and control groups. These data suggest that dysregulation of T cell autophagy is involved in immune response of OLP.

IGF1 signaling, initiated from activation of IGF1 receptor (IGF1R), plays critical role in regulation of cell growth and survival [64,65]. IGF1 signaling pathway has been identified to be one of the regulators of the autophagy [66]. Phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTor) cascade is an important intracellular signaling pathway in cell quiescence, proliferation, protein synthesis, cancer and autophagy. And it is activated after the phosphorylation of IGF1R. The expression of p-IGF1R was observed to be increased in OLP patients [67]. It is also reported that the expression of pAkt, p-mTor, ULK1 and LC3B are significantly increased in local T cells of OLP patients compared with that in controls [68]. The level of microtubule associated protein 1 light chain 3β (LC3B) was higher in non-erosive OLP than in erosive OLP and control group. Thus, LC3B may be used as a marker to monitor the disease severity [68]. Taken together, these results suggest that activated IGF1-PI3K/Akt/mTor-autophagy pathway may have a critical role in local T-cell mediated immunoregulatory mechanism of OLP.

Recently, Wang et al. [69] used miRNA microarray and found that miR-122 and miR-199 demonstrated significant decrease in OLP patient group. By searching online data base, it was predicted that mTor was the target of miR-199 and Akt1 was the target of miR-122. These miRNAs may serve as potential therapeutic targets [69]. These results demonstrated that PI3K/Akt/mTor signaling pathway is activated in OLP patients. As a result, a cascade of pro-survival and pro-proliferative signals are triggered, a transduction that may affect the basal cells in OLP patients. Thus, the lifetime of these cells may be extended, which may cause dysplastic variations and may increase the risk of malignant transformation during OLP [69,70].

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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