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Review Article

Research Advances of ENO1 Gene Products in the Oncogenesis and Development of Oral Cancer

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Abstract

ENO1 gene encodes two kinds of proteins, α- Enolase (ENO1) and c-Myc promoter-binding protein-1 (MBP-1). They are widely distributed in human tissues and play an important role in regulating cell metabolism, growth, proliferation, apoptosis and other pathophysiological processes. It has been found that the abnormal expression and function of ENO1 are closely related to the development of many types of tumors. This study summarized the structure, function, mechanism and other information of two kinds of proteins encoded by ENO1. It will provide important information for the prevention and treatment of oral cancer, and the study of regulatory mechanisms in the oncogenesis and development of oral cancer.

Keywords: ENO1; MBP-1; Oral cancer

Introduction

Oral Cancer is a malignant tumor occurring in the mouth or lips. According to the lastest epidemiological study released by GLOBOCAN in 2018, there were 354,864 new cases of oral cancer worldwide and 177,384 deaths [1]. The primary cases were mainly squamous cell carcinoma [2]. Although the diagnosis and treatment of oral cancer have improved in recent years, the 5-year survival rate is still less than 50%3, and the recurrence rate is as high as 65% [2]. Therefore, it is important to look for bio-markers that are closely related to its oncogenesis and development. It not only contributes to early diagnosis, but also plays a guiding role in treatment and prognosis.

Multiple studies suggested that the expression level of ENO1 gene and the subcellular localization of its protein products were closely related to the oncogenesis and development of oral cancer [4,5]. Compared with normal oral mucosal tissues, α-enolase (ENO1), a protein product of the ENO1 gene, aggregated in cytoplasm in oral squamous cell carcinoma tissues, which could be related to the oncogenesis of oral squamous cell carcinoma [5]. ENO1 gene had two translation initiation sites and produced two protein products: ENO1 and c-Myc promoter binding protein-1 (MBP-1), which were widely expressed in human tissues and participated in the regulation of growth, metabolism, proliferation, apoptosis and other pathological and physiological processes. In normal oral mucosal tissues, ENO1 could be randomly distributed in the cytoplasm and nuclei of epithelial layer [5]. Current research suggested that ENO1 had two main functions: One was in the cytoplasm as a key enzyme for anaerobic glycolysis. ENO1 was involved in Warburg effect [6] and affected cell proliferation by changing metabolic pathways in the cytoplasm, which might be one of the important initiating factors in the process of tumorigenesis [7]. The other was located on the surface of the cell membrane and was considered to be a tumor-associated antigen and plasminogen receptor. Previous studies had confirmed that ENO1 was involved in tumor invasion and migration. However, the role of ENO1 in the nucleus remained to be studied. MBP-1 acted as a transcription inhibitor of oncogene c-Myc, which was mainly located in the nucleus and interacted with other cytokines to weaken the proliferation and metastasis of breast, esophagus, stomach, bone, prostate, colorectal and cervical cancer cells. As we know, the role of MBP-1 in the development of oral cancer have not been reported. In this review, the biological structure and function of two protein products of ENO1 gene were presented, which was expected to bring new ideas for further research on the regulatory mechanism of ENO1 in the tumorigenesis and development of oral cancer.

Structure and function of ENO1 gene

The ENO gene family is widespread in vertebrates and three subtypes have been identified, α-enolase (ENO1), β-enolase and γ-enolase [8]. In mammals, β-enolase exists mainly in muscle tissue [9], γ-enolase is mainly found in nerve and neuroendocrine tissues [10], and α-enolase is found in most mammalian tissues. The human ENO1 gene is located on the short arm of chromosome 1 (1p35-P36) and consists of 12 exons distributed on 17718 bp genomic DNA. There are two different translation initiation sites in a single ENO1 transcript, encoding two proteins with different structure and function, ENO1 and MBP-1 respectively [11] (Figure 1).

The role of ENO1 in the tumorigenesis and development of oral cancer

It is believed that ENO1 mainly functions in cytoplasm and membrane. In the cytoplasm, ENO1 as a key enzyme in glycolysis catalyzes the formation of phosphoenolpyruvate from 2-phosphoglycerate. In the hypoxic microenvironment, lactic acid is finally produced by the catalytic action of pyruvate kinase and lactate dehydrogenase. In the cell membrane, ENO1 acted as a plasminogen receptor to degrade extracellular matrix by activating plasminogen, then promoting the invasion and metastasis of cancer cells. It can also be used as tumor-associated antigens to activate adaptive immunity and inhibit the further development of tumors. ENO1 expression was found to be higher in four different oral cancer cell lines (OEC-M1, OC-3, Cal-27, and HSC-3) than in normal oral keratinocytes4. ENO1 was mainly concentrated in the cytoplasm in moderately and highly

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differentiated tissue samples of oral squamous cell carcinoma [5]. In addition, the survival analysis of 44 patients with oral cancer found that the high expression of ENO1 predicted poor prognosis [4]. These results suggested that the location and expression level of ENO1 could be related to the stage of oral cancer.

ENO1 as a key glycolytic enzyme in cytoplasm in oral cancer

As a key enzyme in glycolysis, ENO1 is mainly located in the cytoplasm and involved in cell metabolism. Metabolic reprogramming is an important feature of cancer cells, and while the Tricarboxylic Acid Cycle (TCA) produces more ATP, cancer cells tend to use less efficient glycolytic methods for energy. Inhibition of the TCA has been demonstrated in oral cancer [12], but the specific mechanism is still unknown. Most tumor cells still produce large amounts of pyruvate and lactic acid in the presence of sufficient oxygen, which was known as the Warburg effect [13]. This phenomenon is described as metabolic reprogramming, and ENO1 may be associated with it. ENO1 was knocked down in breast cancer, lung cancer and pancreatic cancer cells, resulting in increased glucose uptake and intracellular glucose increase. Cell metabolism turned to alternative pathways, such as Pentose Phosphate Pathway (PPP). As a result, the expression level of lactic acid decreased [14]. After knockdown of ENO1 in Endometrial cancer (EC), Lactate Dehydrogenase A (LDHA) catalyzed lactic acid production decreased both in gene and protein levels, indicating that the glycolysis process was inhibited [15]. Proteomics studies found that compared with normal tissues, the expression level of ENO1 in cancer tissues was significantly different, suggesting that the up-regulation of ENO1 as glycolytic enzyme may be related to anaerobic glycolysis of cancer cells and the tumorigenesis of malignant tumors. Studies on gastric cancer cells have shown that ENO1 gene silencing leads to growth inhibition and cell cycle arrest of gastric cancer cells [16]. In hepatitis - related hepatic carcinoma studies, inhibition of ENO1 activity can reduce glucose intake and lactic acid production, and ultimately inhibit the growth of hepatoma cells [17]. In addition, ENO1 is highly expressed in various squamous cell carcinomas. For example, ENO1 expression is increased in sputum of patients with early lung cancer [18]. In lung squamous cell carcinoma samples, the expression of ENO1 was confirmed to increase at the gene level [19]. In oral cancer, ENO1 may have a similar mechanism of action.

ENO1 as plasminogen receptor on cell membrane in oral cancer

ENO1 is located in the cell membrane in monocytes U937, T cells, B cells, peripheral blood monocytes and human brain cancer cells [20], As a plasminogen receptor, it mediates the activation of plasminogen and degrades extracellular matrix. This biological behavior can increase tumor invasion and metastasis [21]. This process is regulated by post-translational modifications such as acetylation, methylation and phosphorylation. On the cell surface, ENO1 is part of a multiprotein complex which includes uPA receptors, integrins, and cytoskeleton proteins responsible for adhesion, migration, and proliferation [22]. The invasion and migration of cancer cells were closely related to the expression of ENO1 *in vivo*. Knockdown of ENO1 in tumor cells not only reduced glycolysis, but also reduced migration and invasion, which had been verified *in vivo* studies [23-26]. Overexpression of ENO1 in oral cancer cell line Cal-27, the invasion and migration of cells were enhanced4, but the mechanism remained to be further explored.

ENO1 as a tumor-associated antigen in oral cancer

ENO1 in the cell membrane is considered to be an immunogenic tumor-associated antigen. Using serological proteome analysis (SERPA), anti-ENO1 antibodies have been found in patients with a variety of cancers, such as cholangiocarcinoma, breast cancer, head and neck cancer, leukemia, lung cancer, pancreatic cancer and melanoma [27-33]. In advanced stage of lung cancer and breast cancer, the expression of anti-ENO1 autoantibody decreases, indicating that ENO1, as a tumor-associated antigen, may activate the immune system and inhibit the further development of tumors. Researchers found that the decrease of anti-ENO1 autoantibody in the circulatory system may be due to physiological absorption and the neutralization of ENO1 on the membrane surface in vitro. After lung cancer surgery, high expression of anti-ENO1 antibody always predicted better prognosis. This discovery provides a new target for tumor immunotherapy.

The Role of MBP-1 in the tumorigenesis and development of oral cancer

Structure and function of MBP-1: MBP-1 was first discovered by Ray and Miller as a transcription factor in nucleus34 with a molecular weight of 37 kDa without enzyme activity. Compared with ENO1, MBP-1 had the same C-terminal and proline rich regions in protein structure, but lack 3 β-chains in N-terminal [35]. Due to the high similarity in structure with ENO1 protein, there is no specific antibody against MBP-1. This largely limited the study of MBP-1. As promoter binding protein of the oncogene c-Myc, MBP-1 can bind to P2 promoter and inhibit the expression of oncogene c-Myc. MBP-1 is present in a variety of normal tissues, such as the brain, liver, kidney and spleen [36]. MBP-1 was susceptible to ubiquitin-mediated protease degradation, so in normal mammalian renal fibroblast cell line COS-7, the half-life of MBP-1 was only 2.5h. The protease inhibitor MG132 could enhance the stability of MBP-136.

MBP-1 in the Tumorigenesis and development of oral cancer: Due to the lack of specific anti-MBP-1 antibody, researchers indirectly reflected the change of MBP-1 by detecting the change of c-Myc protein expression level in oral cancer in previous studies. However, c-Myc protein was not detected in oral cancer samples, and the mechanism remained to be further studied5. In the study of tumorigenesis of other tumors, researchers had confirmed that MBP-1 had an impact on tumor growth, invasion and migration in vitro. In the study of two different breast cancer cell lines, it was found that MBP-1 inhibited anchorage-independent growth of McF-7 and the tumorigenicity of MDA-MB-231 [37]. In gastric cancer cell line SC-M1, overexpression of MBP-1 inhibited cell clonal formation, migration and invasion [38]; In SGC-7901, MBP-1 can inhibit cell proliferation [39]. In the study of non-small cell carcinoma, exogenous overexpression of MBP-1 inhibited cell proliferation and induced mitochondrial permeability changes [40]. MBP-1 inhibited the proliferation of prostate cancer cells through MAPK signaling pathway [41], and inhibited the synthesis of collagen and MMP-2 protein by upregulating miR-29b, thus reducing the aggressiveness of cancer cells [42]. However, recent studies reported that in esophageal cancer and osteosarcoma, inhibition of MBP-1 expression inhibited cell proliferation, promoted cell apoptosis, reduced cell invasion

ability and the expression of oncogene c-Myc [43,44].

Previous study reported that MBP-1 expression was affected by oxygen concentration in the microenvironment [45]. The hypoxic response element binded to the hypoxia-inducible factor 1 to regulate the expression of MBP-1. In bronchial endothelial cells, the mRNA level of MBP-1 was down-regulated under hypoxia conditions. In breast cancer cell McF-7, the protein level of MBP-1 was down-regulated under hypoxia conditions36. In oral cancer, anaerobic glycolysis increased [12], suggesting that the lesion site was likely to be in a hypoxic microenvironment. However, the function and related mechanism of MBP-1 remain to be studied during the tumorigenesis and development of oral cancer.

Regulation of ENO1 gene: MBP-1 was known to have three target genes, namely, c-Myc46, Cyclooxygenase-2 (COX2) 38 and ERb-B2 Receptor Tyrosine Kinase 2 (ERBB2) [47]. MBP-1 could inhibit the expression of c-Myc by binding to the P2 promoter of c-Myc, as well as the expression of COX-2 and ERBB2. In the study of breast cancer, MBP-1 inhibited the expression of ERBB2 gene in human breast cancer cell line SKBr3, then affecting the regulation of PI3K/AKT pathway and thereby inhibiting cell apoptosis [47]. Researches showed that MBP-1 could inhibit the expression of endothelin-1 (ET-1), Angiogenin (ANG), interleukin-8 (IL-8), Matrix Metallopeptidase 9 (MMP-9), and Placental Growth Factor. The activity of PGF and Vascular Endothelial Growth Factor (VEGF) promoted the apoptosis of BREAST cancer cells (McF-7) [48]. By interacting with the intracellular domain N1IC of Notch1 receptor, MBP-1 inhibited the binding of the N1IC/YY1 complex to the YY1 element on the c-Myc promoter, thereby eliminating the promotion effect of c-Myc expression [49]. Notch signaling pathway was involved in the process of cell proliferation, differentiation, apoptosis and tumorgenesis.

The expression of MBP-1/ENO1 can be regulated by miRNAs. Studies suggested that overexpression of miR-363 inhibited MBP-1/ENO1 at the protein level [50]. In the study of retinoblastoma, miR-22-3p was proved to target ENO1 and inhibit cell proliferation [51]. In addition, miR-14b and miR-29b interacted with MBP-1. Wherein, MBP-1 inhibited the expression of miR-14b, and the binding site was 5'-GAGGAAAAGACTG-3', but promoted the expression of miR-29b. MBP-1 could induce the expression of miR-29b by inhibiting the activation of MMP-2. But in oral cancer, no reports on the regulation of ENO1 gene have been found.

Conclusion

In summary, MBP-1/ENO1 may play an important role in oral cancer, including the tumorgenesis, development and metastasis. Although there are differences in biological functions among different cells, especially among different types of cancer cells, MBP-1 and ENO1 show opposite biological functions on the whole. Whether there is an antagonistic effect of intrinsic mechanism between them remains to be further studied.

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