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·综述·

诱导自噬在口腔癌治疗中的研究进展

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【摘要】 口腔癌恶性程度高,易复发、易转移,预后欠佳。自噬是细胞在应激条件下诱导的分解代谢过程。近年研究发现上皮细胞自噬激活可通过抑制哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK),激活腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)信号通路等,激活口腔癌细胞自噬,抑制口腔癌细胞存活。诱导自噬可以降解真核起始因子4E蛋白,抑制口腔癌转移。在口腔癌治疗中发现,诱导口腔癌细胞自噬能抑制口腔癌细胞增殖,促进口腔癌细胞凋亡。与单独放化疗相比,联合使用自噬诱导剂有助于提高口腔癌患者的疗效和存活率。此外诱导口腔癌细胞自噬可提高机体免疫功能,增强口腔癌免疫疗法疗效。本文就自噬与口腔癌的关系,诱导自噬与放化疗及免疫治疗联合应用治疗口腔癌的作用研究进行综述,为诱导自噬治疗口腔癌,提高口腔癌治疗效果和患者存活率提供新思路。当前诱导自噬治疗口腔癌的作用机制尚不明确,研究其作用机制,精准调控诱导自噬,提高口腔癌治疗效果及研发自噬诱导剂用于治疗口腔癌是未来的研究热点。

【关键词】 自噬；　口腔癌；　诱导自噬；　自噬诱导剂；　细胞凋亡；　化疗；　放疗；　免疫治疗
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Research progress on induced autophagy for the treatment of oral cancer

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【Abstract】 Oral cancer has a high degree of malignancy, easily recurs, readily metastasizes and poor progonsis. Autophagy is a catabolic process induced in cells under stressful conditions. In recent years, studies have found that the activation of autophagy in epithelial cells can inhibit carcinogenesis and activate pathways such as mTOR and MAPK to activate autophagy in oral cancer cells and inhibit their survival. Inducing autophagy can degrade eukaryotic initiation factor 4E protein and inhibit oral cancer metastasis. Inducing autophagy in oral cancer cells can inhibit their proliferation and promote their apoptosis. Adding autophagy inducers to the treatment can help improve its efficacy and patient survival compared with chemoradiotherapy alone. In addition, the induction of autophagy in oral cancer cells can improve the body's immune function and enhance the efficacy of oral cancer immunotherapy. This article summarizes the

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relationship between autophagy and oral cancer and the role of induced autophagy in the treatment of oral cancer with the combined application of chemoradiotherapy and immunotherapy. The goal is to provide new ideas for inducing autophagy during the treatment of oral cancer, improving the therapeutic effect of oral cancer and the survival rate of patients. At present, the mechanism of action of induced autophagy in the treatment of oral cancer is not clear. Future research should study its mechanism of action, improve its therapeutic effect on oral cancer and develop autophagy inducers to accurately regulate and induce autophagy during the treatment of oral cancer.

【Key words】 autophagy; oral cancer; inducing autophagy; autophagy inducer; apoptosis; chemotherapy; radiotherapy; immunotherapy

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口腔癌是最常见的头颈部癌症之一，好发于唇、颊、舌等部位，严重影响患者生理、心理和生活质量，并带来了巨大经济负担。口腔癌致病因素主要有：饮酒、吸烟、咀嚼槟榔和感染人类乳头瘤病毒。目前口腔癌主要治疗手段是手术治疗联合放疗或化疗，5年存活率达约50%，但早期发现并治疗存活率可达80%[1]。近年来发现自噬在口腔癌发生发展过程中有重要作用，对其进行调控有利于治疗口腔癌。

自噬是受自噬相关基因（autophagy related genes，ATG）调控的代谢和大分子物质回收的关键过程。根据包裹包浆和转运方式不同，自噬分为巨自噬、微自噬和分子伴侣介导的自噬，本文介绍的均为巨自噬[2]。在正常生理条件下，自噬基础水平对于维持细胞稳态、发育和代谢平衡至关重要，自噬针对不同刺激（如缺氧、营养和能量缺乏）的细胞适应性反应，具有细胞保护作用；在病理条件下，自噬通过回收未折叠蛋白质和受损细胞器为细胞提供必需物质，使细胞能在恶劣条件下存活，但持续诱导自噬会增加细胞质消耗从而促进细胞死亡，称为Ⅱ型细胞程序性死亡[2-3]。正常口腔上皮细胞自噬稳态失调与口腔癌发生、发展密切相关，自噬与口腔癌的关系也是近年研究热点；诱导自噬是通过使用自噬诱导剂使自噬活性上调，促进口腔癌细胞凋亡和增强口腔癌疗效。本文就现有文献对诱导自噬在口腔癌中的意义和作用机制做一综述。

1　自噬与口腔癌

1.1　自噬与口腔癌的发生发展

口腔组织发生癌变与自噬基因缺陷有密切关系。在正常生理条件下，自噬维持机体细胞内稳态；在病理条件下，通过诱导自噬可保护正常口腔上皮细胞。ATG基因缺失，可导致活性氧产生、缺陷蛋白质和细胞器等过量沉积，导致口腔上皮细胞DNA损伤，肿瘤形成[4]。Fernández-Mateos等[5]对72例口腔癌患者ATG寡核苷酸多态性的研究结果发现，当ATG16L1 rs2241880位点发生核苷酸多态性时，口腔癌发生概率明显升高，这提示自噬紊乱会增加口腔癌形成的风险。

肿瘤抑制基因TP53，主要编码P53蛋白，在营养缺乏或缺氧等应激条件下，TP53可通过抑制哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号传导促进正常上皮细胞自噬激活，抑制正常上皮细胞癌变[6]。在细胞核中P53通过死亡相关蛋白激酶1（death associated protein kinase1，DAPK-1），B细胞淋巴瘤/白血病-2（B cell lymphoma/leukemia-2，Bcl2）/beclin1复合物中的beclin1磷酸化，从而激活上皮细胞自噬，防止DNA损伤，抑制肿瘤发生[6]。口腔癌中TP53突变率高达76%～80%，突变后TP53使口腔癌细胞自噬稳态紊乱，从而促进口腔癌进展[6]。Liu等[7]通过对仓鼠口腔癌模型不同时期检测发现，不良增生的上皮细胞自噬被显著激活，DNA损伤标志物含量低；口腔癌细胞自噬活性降低，DNA损伤标志物含量较多。这表明在口腔癌早期诱导自噬可以防止

DNA损伤,抑制口腔癌的进展。

1.2　自噬与口腔癌的转移

口腔癌转移主要以颈淋巴结为主。转移相关蛋白2(metastasis-associated protein 2 ,MTA2)可以促进肿瘤转移,在口腔癌细胞中发现通过短发夹RNA抑制MTA2的表达增强自噬相关蛋白LC3-Ⅱ的表达,抑制口腔癌细胞的转移[8]。这提示通过诱导口腔癌细胞自噬抑制其转移是一种可行的方法。

肿瘤上皮间充质转化可以为肿瘤细胞的黏附、增殖和迁移提供框架,是肿瘤浸润和转移的重要一步。研究表明自噬可影响肿瘤上皮间充质转化,并可减少肿瘤纤维化[9]。Wang等[10]发现在雷帕霉素诱导口腔癌细胞自噬模型中甲基转移酶样蛋白14高表达,抑制口腔癌上皮间充质转化,从而降低口腔癌侵袭性和减少其转移;而高表达甲基转移酶样蛋白14通过降解自噬抑制真核起始因子4E蛋白,促进自噬溶酶体形成,增强口腔癌细胞自噬。诱导口腔癌细胞自噬可抑制其转移,但具体机制尚不明确。

2　诱导自噬与口腔癌的治疗

目前通过诱导自噬辅助放化疗及免疫治疗口腔癌已有相关报道。激活腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase,AMPK)信号通路或抑制丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)、mTOR信号通路可诱导口腔癌细胞自噬,提高口腔癌治疗效果。

2.1　诱导自噬与口腔癌化疗

化疗通过诱导癌细胞凋亡从而达到治疗效果,通过化学药物或者自噬诱导剂诱导癌细胞过度自噬也会促进癌细胞Ⅱ型程序性死亡,从而提高化疗效果[11]。诱导自噬治疗癌症已经在胶质母细胞瘤、子宫内膜癌细胞、肺细胞癌、乳腺癌细胞等取得较好的疗效[12-13]。通过药物诱导自噬治疗口腔癌已有相关研究,重楼皂苷G在干预口腔癌细胞24 h后发现,通过介导ERK和JNK信号通路上调自噬相关蛋白(Beclin-1和LC3-Ⅱ)和降低P62蛋白表达,诱导口腔癌细胞自噬促进口腔癌细胞死亡,提高化疗效果[14]。姜黄素及其衍生物MTH-3通过结合转录因子EB抑制EGFR/AKT/mTOR信号通路上调自噬相关蛋白(LC3B-Ⅱ和p62)和减低P38蛋白表达,诱导舌鳞状细胞癌细胞自噬降低舌鳞状细胞癌细胞活性[15]。紫檀芪在顺铂耐药的口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)细胞中发现,通过介导AKT信号通路上调自噬相关蛋白(Atg5、Atg7、Atg12、Beclin-1和LC3-Ⅱ)诱导OSCC细胞自噬,促进OSCC细胞死亡[16]。潜在抗肿瘤药物氯丙嗪在细胞和动物实验中通过提高自噬相关蛋白(Atg5、Atg7、Atg12、Beclin-1和LC3A/B-Ⅱ)表达和降低自噬负相关信号通路(mTOR、PI3K、Akt和p70S6K)磷酸化水平,诱导牙龈癌细胞自噬,促进牙龈癌细胞死亡和抑制牙龈癌细胞生长的作用[17]。研究表明5′ AMP激活蛋白激酶激活剂可增加微管相关蛋白1A/1B-轻链3(microtubule-associated protein 1 light chain 3,LC3)和P62积累,诱导自噬体在SCC2095细胞中积累,促进SCC2095细胞凋亡[18]。乌苏酸诱导半胱氨酸蛋白酶依赖性细胞凋亡,同时调节多种生物标志物,包括下调蛋白激酶B、mTOR、NF-κB信号转导、细胞外信号激酶和p38 MAPK等蛋白表达,通过LC3B-Ⅱ转化、增加p62蛋白表达和自噬体积累来诱导口腔癌细胞自噬,促进口腔癌细胞凋亡[19]。

2.2　诱导自噬与口腔癌放疗

放疗是一种成熟的癌症治疗方法,放疗敏感性是影响放疗疗效的主要因素之一。研究发现,柴胡皂苷联合放疗治疗肝癌更能诱导肝癌细胞中自噬体积累,促进肝癌细胞凋亡[20]。雷帕霉素诱导肺癌细胞中自噬体形成增多,使肺癌细胞对放疗敏感性增强[21]。诱导自噬可抑制喉癌生长,促进放疗敏感性[22]。在口腔癌中也有研究显示诱导口腔癌细胞自噬可增强口腔癌放疗敏感性[23]。丹参酮ⅡA处理SCCO9O细胞中发现,增强放疗敏感性与自噬密切相关,SCC090细胞中自噬相关蛋白Beclin 1、ATG5与LC3-Ⅱ蛋白表达增高[24]。与单独放疗相比,虫草素联合放疗使舌鳞状细胞癌细胞自噬相关蛋白(p62、LC3-Ⅱ)和基因(ATG5和BECN1)表达升高,增强舌鳞状细胞癌细胞自噬,促进舌鳞状细胞癌细胞周期停滞在G2/M期,提高放疗敏感性,诱导舌鳞状细胞癌细胞死亡[25]。泛素蛋白酶14(ubiquitin-specific protease 14,USP14)高表达的口腔癌患者较低表达患者的生存时间和放疗效果差;且在细胞实验中发现USP14可增强OSCC细胞放射抗性,抑制自噬相关蛋白表达;敲除USP14的小鼠较未敲除小鼠的肿瘤更小且放疗效果更好[26]。诱导口腔癌细胞自噬可减少口腔癌细胞增殖,提高口腔癌细胞放射敏感性。

2.3　诱导自噬与口腔癌的免疫治疗

在癌症进展中，部分癌细胞逃避免疫系统监视，导致肿瘤细胞存活。癌症免疫疗法是通过增强癌症免疫多个步骤来根除癌细胞，是治疗多种癌症的有效方法[8]。自噬可通过抗原提呈、调节淋巴细胞稳态、促进T细胞活化和自然杀伤细胞进入肿瘤组织等影响免疫系统[27-29]。通过自噬激活剂增强免疫已有众多研究，如亚精胺、海藻糖等可增强免疫功能[30-31]。目前，激活肿瘤免疫的方法有特异性阻断程序性细胞死亡配体1（programcell death 1，PD-L1）/程序性细胞死亡率蛋白1（programyl death ligand 1，PD-1）途径。而在自噬调控PD-L1中发现，诱导自噬可以降低其表达，促进肿瘤细胞死亡[32]。抗PD-1能激活自噬促进肺癌细胞死亡[33]。抗PD-1联合放化疗均可提高口腔癌小鼠治疗效果，延长小鼠生存期；而且自噬诱导剂雷帕霉素、二甲双胍等联合抗PD-1可增强抗肿瘤活性[34]。这些研究表明，通过诱导口腔癌细胞自噬，可促进口腔癌患者免疫功能，从而增强口腔癌疗效。

3　小　结

综上所述，自噬与口腔组织癌变密切相关，许多研究表明在口腔癌组织中均有自噬基因异常表达和缺失，在口腔癌早期，诱导异常增生的上皮细胞自噬可抑制口腔癌的进展。诱导口腔癌细胞自噬可抑制口腔癌转移，提高放化疗和免疫治疗效果。但自噬在肿瘤进展和抑制中的双重作用仍存在争议，诱导自噬在口腔癌治疗中的具体靶点和治疗时期仍需要大量基础研究和临床试验探索，还需考虑到肿瘤细胞死亡不仅是药物对肿瘤细胞的作用，还可能是肿瘤微环境改变的整体结果。明确诱导口腔癌细胞自噬联合放化疗及免疫治疗的具体机制，通过精准诱导自噬提高口腔癌疗效和减少口腔癌复发将会是一个新的突破点。

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