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·综述·

锌指蛋白在口腔癌发生发展中的作用研究进展

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【摘要】 口腔癌是头颈部最常见的恶性肿瘤之一，治疗效果常欠佳。锌指蛋白（zinc finger proteins，ZNFs）是人类基因组中最大的转录因子家族蛋白之一，通过锌离子折叠形成独特的三维结构，能够与DNA、RNA及蛋白质结合，调控转录、RNA包装、蛋白质折叠等生物学过程。近年来，关于ZNFs参与调控口腔癌进展的功能机制研究日益增多。目前已报道的ZNFs包括：①调控肿瘤细胞侵袭转移的ZNF677、ZNF460、ZNF154和ZNF132、ZNF281、Kaiso、ZNF582；②调控细胞周期的ZNF750和含PEST的核蛋白（PEST-containing nuclear protein，PCNP）；③参与肿瘤免疫微环境形成的ZNF71和髓指锌指1（myeloid zinc finger 1，MZF1）。其中，甲基化修饰介导ZNF677在口腔癌中的低表达，ZNF677通过抑制丝氨酸/苏氨酸激酶/叉头盒转录因子O3a（protein kinase B/forkhead box O3a，AKT/FOXO3a）通路减少口腔癌细胞的增殖、迁移和侵袭；ZNF460通过microRNA-320a/X连锁α-地中海贫血精神发育迟滞（alpha thalassemia/mental retardation，X-linked，ATRX）轴促进口腔癌细胞的增殖、迁移和侵袭。此外，ZNF750通过抑制细胞周期转录因子活性抑制口腔癌的生长和转移。而ZNF71可通过减少肿瘤免疫细胞的浸润来促进口腔癌的进展。本文对ZNFs参与口腔癌进展的分子机制、调控关系以及促瘤/抑瘤等方面的研究进展进行综述，以期为口腔癌的诊疗提供新思路。

【关键词】 锌指蛋白；　口腔癌；　肿瘤细胞；　肿瘤微环境；　肿瘤免疫；　肿瘤治疗

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Research progress on the role of zinc finger proteins in the development of oral cancer

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【Abstract】 Oral cancer is one of the most common malignancies in the head and neck regions. few patients benefit from current clinical therapy. Zinc finger proteins (ZNFs) are one of the largest transcription factor family proteins in the human genome. ZNFs bind to DNA, RNA, and proteins through their unique three-dimensional structure created by zinc

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ions to regulate gene transcription, RNA packaging, and protein folding. In recent years, the number of studies focused on the functional mechanism of ZNFs in regulating the progression of oral cancer has been increasing, with focuses on: ① ZNF677, ZNF460, ZNF154, ZNF132, ZNF281, Kaiso, and ZNF582, which regulate the invasion and metastasis of tumor cells; ② ZNF750 and PEST-containing nuclear protein (PCNP), which regulate the cell cycle; ③ ZNFs, which are involved in forming the tumor immune microenvironment, such as ZNF71 and myeloid zinc finger 1 (MZF1). For example, methylation modification modulates the reduction of ZNF677 in oral cancer and reduces the proliferation, migration, and invasion of oral cancer cells by inhibiting the protein kinase B/forkhead box O3a (AKT/FOXO3a) pathway; and ZNF460 promotes the proliferation, migration, and invasion of oral cancer cells by regulating microRNA-320a/alpha thalassemia/mental retardation, X-linked (ATRX) axis. In addition, ZNF750 inhibits the growth and metastasis of oral cancer by suppressing cell cycle transcription factor activity. Further, ZNF71 promotes the progression of oral cancer by reducing the infiltration of tumor immune cells. In this review, we will summarize the molecular mechanism, regulatory meshwork, and pro-tumor and anti-tumor roles of ZNFs in the pathogenesis of oral cancer. Our study may provide a new strategy for the diagnosis and treatment of oral cancer.

【Key words】 zinc finger protein; oral cancer; tumor cells; tumor microenvironment; tumor immunity; tumor therapy

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口腔癌是头颈部最常见的恶性肿瘤之一，影响患者美观、进食和牙颌功能[1]。近年来，口腔癌在中国的发病率呈上升趋势并且成为重要的公共卫生问题[2]。口腔癌最常见的病理分类是鳞状细胞癌，占口腔恶性肿瘤的90%[3]。口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）的局部浸润性和侵袭性较强，患者预后较差，5年生存率在50%左右[4-5]。口腔癌的治疗方法主要包括手术、放疗和化疗，治疗效果不理想和药物的毒副作用是口腔癌临床治疗的主要难点[6-8]。因此寻找新的特异性分子靶点对口腔癌的防治具有重要意义。

锌指蛋白（zinc finger proteins，ZNFs）是真核生物基因组中最丰富的蛋白质之一，也是人类基因组中最大的转录因子家族蛋白之一。ZNF最初是被用来描述非洲爪蛙具有手指状结构域的转录因子IIIA[9]。迄今为止，已经报道了8种不同类型的ZNFs，包括类C2H2型、Zn2Cys6型、高音谱号型、带状型、塞结状型、类TAZ2型、锌离子结合短环型和金属硫蛋白型[10]。锌离子与肽序列中的半胱氨酸和组氨酸残基络合，为ZNFs提供了手指状的三维构型[11]。而ZNFs通过三维功能结构决定其功能分类[12]。ZNFs参与调控包括细胞发育、分化、代谢和凋亡等多种多样的生物过程[13]。目前大量研究报道了ZNFs在肿瘤进展和转移中的作用[14]。目前报道的参与口腔癌进展的ZNFs包括：①调控肿瘤细胞侵袭转移的ZNF677、ZNF460、ZNF154和ZNF132、ZNF281、Kaiso和ZNF582；②调控细胞周期的ZNF750和含PEST的核蛋白（PEST-containing nuclear protein，PCNP）；③参与肿瘤免疫微环境形成的ZNF71和髓指锌指1（myeloid zinc finger 1，MZF1）。因此，基于上述ZNFs的功能调控分类，本文对ZNFs参与口腔癌进展的作用机制进行综述。

1　调控肿瘤细胞侵袭和转移的ZNFs

1.1　ZNF677

ZNF677是KruppelC2H2型ZNFs家族的一员。ZNF677作为肿瘤抑制因子通过抑制AKT磷酸化抑制甲状腺癌的发生，ZNF677在原发性甲状腺癌中下调与侵袭性临床病例特征显著相关[15]。在肾细胞癌中，ZNF677通过抑制周期蛋白依赖激酶抑制因子3（cyclin-dependent kinase inhibitor 3，CDKN3）转录发挥抗肿瘤功能，m6A修饰介导ZNF677在肾细胞癌组织中的低表达并与预后不良相关[16]。ZNF677在OSCC中低表达，具有高甲基化水平，ZNF677通过抑制丝氨酸/苏氨酸激酶/叉头盒转录因子O3a（protein kinase B/forkhead box O3a，

AKT/FOXO3a）通路减少OSCC细胞的增殖、迁移和侵袭[17]，AKT/FOXO3a通路的异常激活可能通过促进增殖和抑制凋亡加剧肿瘤的恶性程度；此外，AKT/FOXO3a通路还可能与其他信号通路或分子相互作用[18-19]。因此，靶标AKT/FOXO3a通路的治疗策略是口腔癌治疗的新方向，进一步深入探索口腔癌中ZNF677与AKT/FOXO3a通路之间的相互作用关系，以及它们对肿瘤进展的调控将有助于更全面地理解口腔癌的发病机制，为开发靶向治疗提供重要的理论依据。

1.2　ZNF460

ZNF460被报道与胃癌、急性髓系白血病、乳腺癌及结肠癌的进展有关[20-23]。在OSCC中，ZNF460可以诱导环状RNA线粒体翻译优化1同源物（Circ-cRNA mitochondrial tRNA translation optimization 1，CircMTO1）表达上调，通过microRNA-320a/X连锁α-地中海贫血精神发育迟滞（alpha thalassemia/mental retardation，X-linked，ATRX）轴促进OSCC细胞的增殖、迁移和侵袭[24]。此外，牙周炎是OSCC的危险因素，牙周炎中ZNF460 miRNA的失调可能参与促进OSCC[25]。

1.3　ZNF154和ZNF132

在头颈部鳞状细胞癌（head and neck squamous cell carcinoma，HNSCC），甲基化降低ZNF154和ZNF132在HNSCC肿瘤组织中的表达并与患者的总体生存率缩短正相关[26]。ZNF154是位于染色体19q13上的Kruppel型ZNFs基因。在许多恶性肿瘤中，DNA甲基化会下调ZNF154的表达[26-28]。ZNF154作为鼻咽癌肿瘤抑制因子，通过抑制Wnt/β-catenin信号通路的激活阻断上皮细胞间充质转化（epithelial-mesenchymaltransition，EMT）介导的肿瘤细胞的迁移和侵袭[29]。在食管鳞状细胞癌（esophageal squamous carcinoma，ESCC）中，ZNF154通过参与调控细胞周期、p53信号转导和Wnt/β-catenin信号通路在细胞的增殖和迁移过程中发挥重要作用[28]。

ZNF132位于染色体19q13.4上。高甲基化抑制锌指转录因子特异性蛋白1（specificity protein 1，Sp1）与ZNF132启动子区域的结合，破坏ZNF132的反式激活，从而降低ESCC中ZNF132表达，而ZNF132低表达可以显著升高ESCC细胞的生长、迁移和侵袭能力，显著升高细胞的致瘤性[30]。

ZNF154和ZNF132在HNSCC中的潜在分子机制及作为诊断和预后标志物的潜力尚未明确。鉴于甲基化检测技术具有高度灵敏性和特异性，通过检测肿瘤相关基因的甲基化水平，ZNF154和ZNF132可能作为口腔癌侵袭转移的标志，为口腔癌的干预和治疗提供依据。

1.4　ZNF281

ZNF281在结构上有四个C2H2型锌指结构域。许多研究发现ZNF281基因的上调与肿瘤的发生、转移和不良预后相关。在肝细胞癌中，ZNF281通过靶向核呼吸因子1/过氧化物酶体增殖物激活受体-γ共激活因子1α/线粒体转录因子A（nuclear respiratory factor 1/peroxisome proliferator-activated receptor γ coactivator-1α/mitochondrial transcription factor A，NRF1/PGC-1α/TFAM）轴负调控线粒体生物功能促进肿瘤的侵袭和转移[31]。ZNF281在结直肠癌组织中高表达并通过Wnt/β-catenin通路促进肿瘤细胞的增殖、迁移和侵袭[32]。在乳腺癌中，ZNF281通过抑制X线修复交叉互补基因2（X-ray repair cross complementing 2，XRCC2）和X线修复交叉互补基因4（X-ray repair cross complementing 4，XRCC4）的表达促进DNA损伤反应参与细胞对遗传毒性应激的反应[33]。然而，目前仅对ZNF281在OSCC组织中的表达水平进行了报道，其调控机制尚不明确[34]。NRF1/PGC-1α/TFAM轴是一个关键的调控网络，主要涉及线粒体功能、能量代谢以及细胞应激反应，对维持细胞稳态和应对环境压力至关重要。线粒体功能失调、能量代谢异常和DNA损伤修复缺陷等都可能是口腔癌重要的诱发因素[35]。ZNF281是否通过NRF1/PGC-1α/TFAM轴介导口腔癌的进展有待进一步研究。Wnt/β-catenin通路的异常激活可能通过调控细胞增殖、迁移参与肿瘤的形成[36]。多项研究指出Wnt/β-catenin通路参与口腔癌的进展，而ZNF281介导口腔癌进展的机制是否受到Wnt/β-catenin通路的调控有待进一步探索。XRCC2和XRCC4作为DNA损伤修复相关的基因，在维持细胞稳定和防止基因突变方面发挥关键作用。许多研究报道了XRCC2和XRCC4参与多种肿瘤的进展过程，但其是否参与口腔癌的进展尚有待论证。因此，从XRCC2和XRCC4的基因功能出发，探讨ZNF281与口腔癌侵袭与转移之间的关联，可能为口腔癌的治疗和预防提供新策略。

1.5　Kaiso

Kaiso蛋白是一种经典的转录抑制因子，由一个锌指蛋白结构域和一个BTB/POZ结构域组成，参与介导肿瘤的侵袭、转移、凋亡、增殖和炎症等

过程[37]。Kaiso具有抑癌和致癌的双重作用，具体取决于不同恶性肿瘤中靶基因的定位和甲基化状态。Kaiso可作为前列腺癌EMT和转移的调节因子促进前列腺癌细胞的迁移和侵袭[38]。在宫颈癌组织和细胞系中，Kaiso表达增加，miR-4262可通过直接下调Kaiso来抑制宫颈癌细胞的增殖和EMT[39]。而Kaiso可因磷酸化降低导致胃肠道癌的发展[40]。在口腔癌中的研究发现，与正常患者相比，Kaiso在口腔癌患者黏膜中的表达显著下调[41]。Kaiso在口腔癌中的特定靶点需要在未来的研究中确定。

1.6　ZNF582

既往报道在多种肿瘤中发现ZNF582的甲基化，并与肿瘤进展及不良预后有关。在ESCC中，ESCC肿瘤组织中的ZNF582甲基化水平显著高于癌旁组织[42]。此外，在鼻咽癌中，ZNF582甲基化可以通过调节黏附分子Nectin-3的转录促进鼻咽癌的转移[43]。在口腔癌中，ZNF582甲基化与口腔癌的侵袭性进展和不良预后有关[44-46]。未来的研究可以进一步探讨ZNF582在口腔癌进展和转移中的分子机制。

2　调控细胞周期的ZNFs

2.1　ZNF750

ZNF750是一种潜在的抑癌基因，在OSCC中发挥抗肿瘤作用。ZNF750通过抑制细胞周期转录因子活性抑制OSCC的生长和转移[47]；ZNF750可以通过抑制血管生成素、血管内皮生长因子、细胞黏附分子和CD44等调节肿瘤微环境抑制OSCC的恶性进展[48]；ZNF750还可通过直接抑制层粘连蛋白亚基γ2（laminin subunit gamma 2 gene，LAMC2）的反式激活来抑制鳞状细胞癌细胞的迁移，包括HNSCC[49]；此外，ZNF750可消除OSCC干细胞样表型从而抑制肿瘤复发和转移[50]。肿瘤的发生发展受到多个信号通路的调控，因此，在研究ZNF750对口腔癌的影响时，可能需要综合考虑相关通路的相互影响，深入探讨它们之间的相互作用机制，这将有助于更全面地理解其调控机制。

2.2　含PEST的核蛋白

含PEST的核蛋白（PEST-containing nuclear protein，PCNP）是一种新型的ZNFs，参与调控细胞周期[51]。在人甲状腺癌中，PCNP的过表达可通过激活甲状腺癌细胞中的ERK/JNK/p38通路调控细胞凋亡，还可通过抑制甲状腺癌细胞中Wnt/β-catenin通路来促进细胞自噬，从而减少了肿瘤细胞的增殖、迁移和侵袭[52]。然而在卵巢癌中，PCNP通过激活Wnt/β-catenin信号通路和EMT促进卵巢癌进展，其过表达与预后不良相关[53]。Zhang等[54]研究表明，PCNP的表达与OSCC的分化程度和淋巴结转移负相关。正常情况下，Wnt/β-catenin通路调控细胞增殖、分化和凋亡，然而该通路的异常激活导致细胞的异常增殖和恶性转化[55]。而在OSCC中，对Wnt/β-catenin通路的抑制可能实现PCNP的下调，针对该通路的肿瘤抑制策略包括抑制Wnt配体的表达、阻断受体的功能、干扰β-catenin的稳定性或活性等。因此，深入了解这一通路的调控机制及其在口腔癌发生中的作用，对于口腔癌的治疗和预防具有重要的意义。

3　参与肿瘤免疫微环境形成的ZNFs

3.1　ZNF71

ZNF71由肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）诱导表达并参与多种肿瘤的发生发展。ZNF71在人喉鳞状细胞癌（laryngeal squamous cell carcinoma，LSCC）组织中表达下调，通过介导肿瘤细胞之间的紧密连接和中性粒细胞的浸润来调控LSCC的发展[56]。Kruppel相关盒（Kruppel-associated box，KRAB）是存在于ZNFs转录因子中的转录抑制结构域[13]，ZNF71 KRAB在非小细胞肺癌（non-small cell lung cancer，NSCLC）中表达水平升高，与EMT的进程相关，并通过介导肿瘤耐药促进NSCLC的进展[57]。研究发现ZNF71在OSCC组织中的表达显著降低，可同时发挥促瘤/抗瘤作用；一方面可减少Ⅰ型单纯疱疹病毒（herpes simplex virus 1，HSV1）的感染抑制OSCC进展；另一方面可减少肿瘤免疫细胞的浸润促进OSCC的进展，然而其具体调控机制仍未阐明[58]。在口腔癌中，ZNF71是否通过调控肿瘤细胞与肿瘤基质细胞及其相关信号分子的相互作用参与口腔癌的进展尚不清楚。ZNF71是否通过EMT调控口腔癌的迁移和侵袭尚有待进一步研究。在口腔癌进展调控机制中，除了ZNF71在肿瘤细胞中的异常表达水平，ZNF71的高甲基化也发挥重要作用。与正常样本相比，口腔癌癌前病变和肿瘤患者的唾液和组织样本中ZNF71的甲基化水平明显升高[59]。因此，基于唾液样本进行ZNF71甲基化分析可作为口腔癌临床管理的一种非侵入性检测手段。

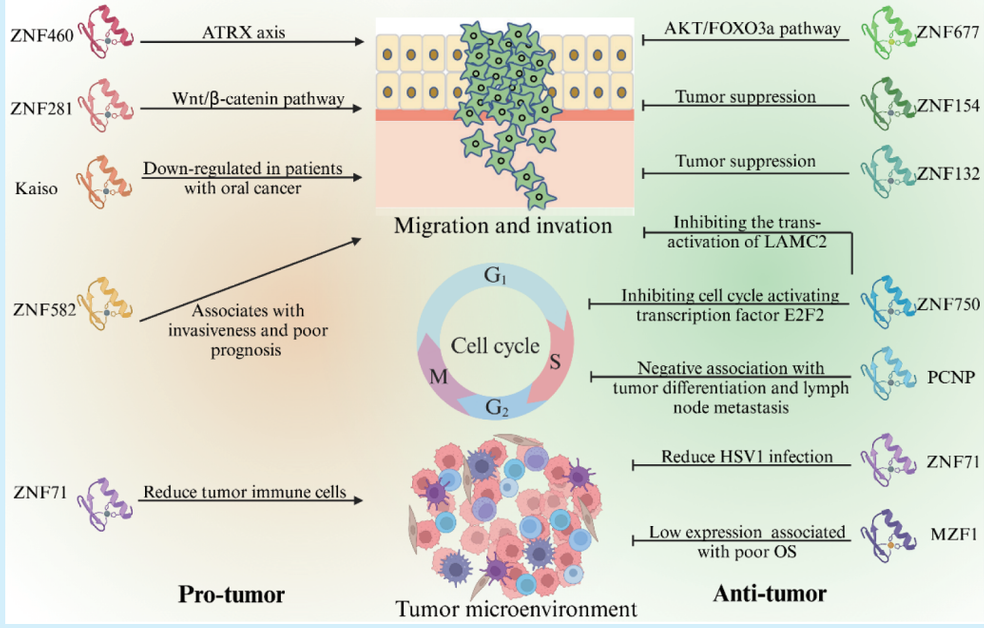
3.2　MZF1

髓指锌指1（MZF1）是SCAN结构域含锌指蛋

白转录因子家族的成员，该家族是ZFP的一个亚家族[60]。MZF1的表达上调和/或激活可诱导细胞生长、迁移和侵袭[60]。MZF1过表达的肝细胞癌呈现免疫抑制微环境，并可通过激活细胞周期依赖性激酶4（cyclin-dependent kinase 4，CDK4）加速PD-L1泛素化[61]。多项研究表明MZF1可以促进乳腺癌、宫颈癌、结直肠癌、肝癌、肺癌和前列腺癌的发生[61-65]。然而在舌鳞状细胞（tongue squamous cell carcinoma，TSCC）中，有研究指出高表达MZF1的TSCC患者预后较好，反之预后较差[66]。免疫治疗通过激活机体的免疫系统来攻击肿瘤细胞，是近年来备受关注的一种治疗策略。正常情况下，免疫细胞能够保持适度的增殖能力，以应对体内可能出现的病原体或免疫攻击。在抗肿瘤免疫中，免疫细胞释放肿瘤毒性细胞因子识别并杀伤肿瘤细胞。然而，肿瘤细胞往往能够通过各种机制逃避免疫细胞的监视和攻击，包括影响免疫细胞的细胞周期调控。反之，肿瘤细胞可以通过分泌免疫抑制因子、诱导免疫细胞凋亡或功能耗竭等方式干扰免疫细胞的细胞周期进程，导致免疫细胞增殖受到抑制、功能下降，从而无法有效地清除肿瘤细胞。CDK4作为细胞周期调控的关键分子，与细胞增殖、分化及凋亡等生物学过程紧密相关。因此，CDK4的活性可能影响免疫治疗的效果。然而，MZF1与CDK4以及免疫治疗之间的相互作用机制尚未完全明确，不同的肿瘤类型和个体差异也可能影响CDK4在免疫治疗中的作用。因此，未来的研究可以深入全面地构建MZF1和CDK4及其他细胞周期蛋白与免疫治疗之间的调控网络，并为其在肿瘤治疗中的应用提供更有力的支持。

4　小　结

ZNFs作为转录因子大家族的关键蛋白之一。不同的ZNFs在口腔癌的发生中发挥不同的作用，参与不同的肿瘤调控机制，可发挥促瘤或抑瘤作用（图1）。其中，ZNF677、ZNF460、ZNF154和ZNF132、ZNF281、Kaiso和ZNF582通过参与调控肿瘤细胞侵袭和转移影响口腔癌的进展。而ZNF750和PCNP主要通过调控细胞周期影响口腔癌细胞的增殖、分化及凋亡等过程。此外，ZNF71和MZF1通过调控肿瘤相关免疫细胞的增殖和浸润参与肿瘤免疫微环境形成影响口腔癌的发生发展。ZNFs



ZNFs play both pro-tumor and anti - tumor roles in the development of oral cancer. (1) ZNF460, ZNF281, Kaiso, and ZNF582 regulate the invasion and metastasis of tumor cells to promote the development of oral cancer; however, ZNF677, ZNF154, ZNF132, and ZNF750 suppress the invasion and metastasis of oral cancer. (2) ZNF750 and PCNP regulate the cell cycle by inhibiting the progression of oral cancer. (3) ZNF71 promotes oral cancer by reducing the infiltrating immune cells, while ZNF71 and MZF1 inhibit tumor progression by modulating the tumor immune microenvironment. ZNFs: zinc finger proteins; ATRX: alpha thalassemia/mental retardation, X-linked; FOXO3a: Forkhead box O3a; LAMC2: laminin subunit gamma 2 Gene; E2F2: E2F transcription factor 2; PCNP: PEST-containing nuclear protein; HSV1: Herpes simplex virus 1; OS: overall survival; MZF1: myeloid zinc finger 1

Figure 1　The roles of ZNFs in the development of oral cancer

图1　锌指蛋白在口腔癌进展中的作用

具有复杂性和多样性，为了进一步理解它们与口腔癌的关联，后续可深入探究ZNFs在口腔癌细胞和肿瘤组织中的表达分布、功能调控以及与口腔癌药物治疗及其相关的肿瘤耐药机制之间的关联。此外，通过研究ZNFs与细胞周期、黏附和侵袭及其相关信号通路的相互作用机制，将有助于揭示ZNFs在口腔癌发病中的综合作用。

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