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微生物与巨噬细胞相互调控并介导口腔癌发生发展的研究进展

代东跃，李博磊，李明云，程　磊△
口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院 牙体牙髓病科（成都 610041）

【摘要】 口腔鳞状细胞癌是世界第六大常见的恶性肿瘤，目前临床治疗效果并不理想。由于其所在部位的特殊性，口腔癌与多种微生物关系密切，且其发生发展极易受到微生物的调控。免疫系统的介导作用在肿瘤发生发展过程中也不可或缺，尤其是肿瘤相关巨噬细胞，其具有放大微生物调控作用的能力，并反过来调控微生物种群组分及数量，相辅相成，共同加剧口腔癌的恶化。本文旨在总结目前微生物和巨噬细胞之间的相互关系，以及微生物、巨噬细胞对口腔癌发生发展的调控作用等相关工作，并对于微生物、巨噬细胞以及口腔癌之间的深层次关系的研究现状与不足进行讨论。微生物和巨噬细胞都被认为是有前景的预后指标，有望成为新的治疗靶点。尽管目前已有学者关注着微生物及巨噬细胞在口腔癌中的作用，但少有研究将其与口腔癌前病变联系起来，微生物与巨噬细胞间相互调控关系也仍不明晰。因此，对于微生物、巨噬细胞、口腔癌三者关系网络的深度探索有望为肿瘤的早期诊断及治疗提供更多的可能性。

【关键词】 微生物　肿瘤相关巨噬细胞　肿瘤　口腔鳞状细胞癌

Research Progress on the Interaction Between Microorganisms and Macrophages and Their Role in the Mediation of the Onset and Development of Oral Cancer

DAI Dong-yue, LI Bo-lei, LI Ming-yun, CHENG Lei△. *State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Department of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University*, Chengdu 610041, China
△ Corresponding author, E-mail: chengleidentist@163.com

【**Abstract**】 Oral squamous cell carcinoma is the sixth most common malignant tumor in the world, and the clinical treatment effect is not satisfactory. Because of the special nature of its location, oral cancer is inextricably linked with a wide variety of microorganisms, and its pathogenesis and development are also extremely susceptible to microbial regulation. In addition, the mediating role of the immune system is also indispensable to the course of tumor pathogenesis and development, especially tumor-associated macrophages, which amplify the regulatory role of microorganisms, and in turn regulate the microbial population components--two complementary effects that jointly exacerbate oral cancer. Herein, we summarized the existing research on the relationship between microorganisms and macrophages, as well as the regulatory role of microorganisms and macrophages in the pathogenesis and development of oral cancer. We also discussed the current status of and gaps in research on the relationship between microorganisms and macrophages and oral cancer. Both microorganisms and macrophages are considered promising indicators for prognosis, showing potentials to be used as new therapeutic targets. Despite some research interest in the role of microorganisms and macrophages in oral cancer, very few studies have linked them to oral precancerous lesions, and the mutual regulatory relationship between microorganisms and macrophages remains unclear. Therefore, in-depth exploration of the relationship network of microorganisms, macrophages and oral cancer is expected to provide more possibilities for the early diagnosis and treatment of tumors.

【**Key words**】 Microorganisms　Tumor-associated macrophages　Tumor　Oral squamous cell carcinoma

口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）是头颈部最常见的恶性肿瘤，约占口腔恶性肿瘤的90%[1]，2020年全球口腔癌新发病例数有377 713例，同年死亡人数为177 757例[2]。OSCC通常首选手术切除，临床治疗手段有限。尽管对口腔癌致病因素、风险因素的认识及其治疗手段都有所提高和改进，其预后仍不理想，甚至在全球大部分国家和地区中，口腔癌5年生存率低于50%[3]。OSCC的主要风险因素包括吸烟、嚼槟榔等，但仍有多达15%的无法用这些因素来解释[4]。因此，进一步解析OSCC病因、扩充风险因素，并探究其发生发展机制依旧意义重大。

自从世界卫生组织将幽门螺杆菌归类为明确致癌物以来，对细菌与癌症之间潜在关系的研究也逐年增加，其深层关系的探究也使其相互之间的作用机制逐渐趋于清晰[5]。人类口腔中有超过700种细菌[6-7]，是人体最复杂的微生物群落之一。即便口腔菌群失调与口腔癌发生发展之间的关系已得到广泛认可[8]，然而口腔微生物在OSCC中的作用机制仍无明确结论。关于两者的关系，大致为两种观点，即认为某些细菌具有强致病性，调控口腔癌发

△ 通信作者，E-mail：chengleidentist@163.com

生发展;或是认为口腔菌群失衡加剧肿瘤的恶化[9]。

除此之外,免疫系统的作用也不可或缺。巨噬细胞是先天免疫系统中重要组成成分之一,可吞噬病原体,抑制炎症,协调组织修复[10]。无独有偶,肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)也是肿瘤中最常见的炎症细胞之一,在肿瘤发生发展中具有多重作用。目前的研究表明,这些巨噬细胞能够根据不同微环境表现出包括经典活化M1型和交替活化M2型等在内的多种表型,能够起到抗肿瘤反应或促肿瘤作用[11]。

基于此,本文介绍了目前口腔癌中微生物的变化特征、巨噬细胞的表型,并讨论了微生物在调控巨噬细胞并介导口腔癌发生发展中的作用。

1 口腔癌中的微生物

越来越多的研究显示,口腔微生物在口腔癌发生发展中起着重要作用。得益于高通量测序技术的发展,许多针对口腔癌患者不同口腔部位微生物变化的研究得以开展,意图找到生态失调与肿瘤发病机制之间的潜在联系。虽然因数据表示及实验设置存在的差异使得微生物变化与口腔癌发生发展之间难以总结出确切的规律,但许多研究都显示,OSCC患者黏膜表面、肿瘤组织和唾液中的细菌组成与健康个体明显不同,其深层关系也值得进一步探索。

1.1 口腔癌中微生物种群的变化

在口腔癌中,微生物种群数量及占比在肿瘤不同阶段以及口腔不同部位上均存在较大差异。YANG等[8]分析了OSCC患者正常瘤周组织、肿瘤组织以及唾液的微生物组成,发现产线菌属和消化链球菌属在肿瘤中丰度最高,唾液中丰度最低,而奈瑟菌属则相反。SARKAR等[12]也发现,相较于正常瘤周组织,普雷沃菌属、棒状杆菌属在肿瘤中丰度显著增加。LI等[13]发现在健康人群和OSCC中,中间普氏菌、消化链球菌差异显著且在肿瘤样本中明显富集,其中中间普氏菌丰度增加可能与患者体内C反应蛋白升高有关。研究发现口腔微生物与肿瘤临床分期也存在潜在联系:在肿瘤早期,密螺旋体在肿瘤中丰度较高,普雷沃菌和嗜二氧化碳纤维菌在唾液中富集;而到了晚期,莫雷梭菌在肿瘤组织中富集,唾液中弯曲杆菌富集[8]。

牙周病也会增加OSCC的发病风险[14],这也从侧面表明口腔微生物引起的炎症与口腔癌关系密切。ZHANG等[15]证实在OSCC中具核梭杆菌(*Fusobacterium nucleatum*, *F. nucleatum*)的丰度明显增加。有研究对正常组织、癌前病变和口腔癌中的*F. nucleatum*进行检测后发现,三个组中其丰度依次增加[8, 16]。无独有偶,牙周炎致病菌——牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P. gingivalis*)也与OSCC关系密切[17-18]。在一项比较牙龈鳞状细胞癌与牙周炎的微生物研究中,梭杆菌属,肽链球菌和普雷沃菌属在肿瘤中丰度明显更高[19]。

1.2 微生物调控口腔癌发生发展的潜在机制

口腔癌中,微生物通过产生细胞因子或趋化因子诱导炎症反应,促进肿瘤细胞增殖;也可以产生细胞因子并促进上皮间充质转化(epithelial mesenchymal transformation, EMT),提高肿瘤迁移和侵袭能力[17, 20]。*F. nucleatum*和*P. gingivalis*慢性感染可增加舌部肿瘤严重程度,该研究中实验组小鼠肿瘤体积较对照组约大2.5倍[20-21]。

究其原因,*F. nucleatum*促进OSCC进展,并与其不良预后密切相关[20, 22]。其可定植、黏附和侵入组织,加剧肿瘤细胞的增殖和迁移,在其他微生物作用下,进一步调控机体的免疫功能,最终促进炎症及肿瘤微环境(tumor microenvironment, TME)的形成[23]。进一步研究显示,*F. nucleatum*通过调节lncRNA MIR4435-2HG/miR-296-5p/Akt2/SNAI1信号通路促进EMT[24]。在结直肠癌(colorectal cancer, CRC)中,*F. nucleatum*激活STAT3上调EMT相关基因和蛋白表达。同样,*F. nucleatum*感染的OSCC细胞中也可以观察到部分EMT基因上调[25]。

*P. gingivalis*可激活ERK1/2-Ets1、p38/HSP27和PAR2/NF-κB通路促进基质金属蛋白酶(matrix metalloproteinase, MMP)表达,提高肿瘤侵袭能力[26]。*F. nucleatum*和*P. gingivalis*也可以激活TLR/MyD88触发的整合素/FAK通路增强肿瘤侵袭性[27]。

越来越多的研究证实,微生物在口腔疾病的恶化甚至口腔癌的发生发展中起到不可比拟的作用,甚至是主导作用[28]。

2 口腔癌中的巨噬细胞

肿瘤中,除癌细胞外,还有成纤维细胞、免疫细胞等非癌细胞,它们是构成TME的重要组分[29]。实体瘤中,TAMs释放细胞因子、趋化因子或生长因子于TME中,提高肿瘤活性[30]。

巨噬细胞可分化为M1型和M2型,并在不同疾病中表现出截然不同的作用效果[31]。TAMs同理,根据不同微环境可以促进肿瘤排斥反应或调控肿瘤发生发展。然而M1和M2只是巨噬细胞极化状态的两个极端描述,并没有涵盖广泛的巨噬细胞亚群[32]。其中M2型包含四种表型,分别是白细胞介素-4(interleukin, IL-4)和IL-13诱导的M2a巨噬细胞;免疫化合物和脂多糖(lipopolysaccharide,

LPS)诱导的M2b巨噬细胞; 糖皮质激素、IL-10等诱导M2c亚型[33]; 以及IL-6和腺苷诱导的M2d亚型[34]。而目前M1亚型的分类尚未明确, 这两个亚型之间可以随着内部环境的变化而相互转化。

M1巨噬细胞在肿瘤早期作用显著[35]。M1分泌肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等促进炎症反应, 分泌趋化因子9(C-X-C motif chemokine 9, CXCL9)和CXCL10增强Th1细胞向炎症部位聚集[36]。其次, M1巨噬细胞释放具有肿瘤杀伤作用的物质如一氧化氮合酶(inducible nitric oxide synthase, iNOS)和活性氧(reactive oxygen species, ROS)清除肿瘤细胞[37], 并且介导机体对病原体的防御反应, 在抗肿瘤免疫中起到关键作用。

M2巨噬细胞具有促进肿瘤慢性炎症、基质重塑、肿瘤细胞迁移、侵袭和血管生成等能力[30]。其可以通过释放血小板衍生生长因子(platelet derived growth factor, PDGF)、转化生长因子-β(transforming growth factor-β, TGF-β)等来诱导肿瘤细胞增殖和转移。肿瘤细胞分泌的细胞因子, 包括IL-6、TGF-β1和前列腺素E2(prostaglandin E2, PGE2)等, 可反过来调控肿瘤的发展进程[38]。

M2a细胞分泌TGF-β、纤连蛋白来促进组织修复。M2b能够调节免疫反应和炎症反应, 除了分泌促炎因子如IL-6外, 还能产生大量抗炎细胞因子。研究表明, 肝癌患者中分离出来的巨噬细胞更多地显示M2b表型[39]。M2c释放大量IL-10发挥抗炎作用, 参与免疫抑制等过程。M2d促进IL-10、TGF-β以及少量IL-12、TNF-α等产生, 促肿瘤血管生成和转移[40]。TAMs具有M2a、M2c和M2d的表型, 而M2b表型的作用更接近M1型巨噬细胞, 这些表型均在肿瘤发生发展中起到不可忽视的作用。

3　微生物与巨噬细胞相互调控并介导口腔癌的发生发展

3.1　口腔微生物与巨噬细胞间的相互调控作用

口腔微生物、免疫细胞和上皮屏障的平衡有利于口腔微生态稳定。而当平衡被打破, 免疫系统在致病菌作用下产生不同程度的炎症反应, 诸如黏膜屏障的破坏, 诱发多种口腔疾病(如牙周炎等), 甚至最终诱发口腔癌。

牙周炎作为世界第六大流行疾病[41], 细菌感染及免疫紊乱是其发生发展的重要因素。*P. gingivalis*、*F. nucleatum*、福赛坦氏菌(*Tannerella forsythia, T. forsythia*)等多种细菌在牙周炎模型中已得到充分研究[42], 免疫细胞诸如巨噬细胞在牙周炎的发生发展中也起到关键作用, 巨噬细胞可通过多种作用响应牙周致病菌而极化为牙周炎主要浸润型——M1巨噬细胞[43]。

牙周炎中, 巨噬细胞在微生物的诱导下能够发挥多重作用。*P. gingivalis*通过抑制α-酮戊二酸(α-ketoglutarate, α-KG)的表达来抑制M2巨噬细胞的产生, 并诱导M1巨噬细胞极化来维持局部炎症状态[44]。*P. gingivalis*诱导M1浸润到深层牙周组织中, 分化为破骨细胞, 促进牙龈炎症和牙槽骨吸收[44-45]。巨噬细胞与口腔共生菌之间的相互作用也可以改变, 如IFN-γ/LPS刺激巨噬细胞后增加了共生链球菌存活能力, 促进疾病的进展[46]。TME中, 口腔微生物促进巨噬细胞M2极化。研究表明, 牙周炎致病菌可以直接激活IL-17阳性γδ T细胞, 并促进OSCC中M2型TAMs浸润[47]。本课题组前期研究证实, *P. gingivalis*保护OSCC肿瘤细胞免受巨噬细胞吞噬, 并诱导巨噬细胞极化为促肿瘤的M2型巨噬细胞[48]。除*P. gingivalis*外, 口腔中其他细菌, 如*T. forsythia*产生胞外囊泡(outer membrane vesicles, OMVs), 当OMVs被巨噬细胞吞噬后诱导NF-κB活化, 并上调TNF-α、IL-8和IL-1β表达[49], 而*P. gingivalis*也可以上调巨噬细胞中的miR-155以促进巨噬细胞NLRP3炎症小体活化, 诱导巨噬细胞焦亡[50]。

3.2　微生物与巨噬细胞间的调控对口腔癌发生发展的影响

口腔黏膜、微生物和免疫系统之间的平衡被破坏时, 可诱发多种口腔疾病。无菌小鼠的肠壁黏膜萎缩和巨噬细胞显著减少, 菌群定植1周后, 肠道形态大体恢复, 巨噬细胞数量在5周后能完全恢复[51]; 在肠道菌群失调的小鼠中, 巨噬细胞释放IL-6等细胞因子, 促进CRC增殖及EMT, 将巨噬细胞耗尽后, 菌群失调导致的促肿瘤效应几乎完全解除[52]; 更有研究显示, 粪肠球菌与巨噬细胞共同培养后, 可诱导肠道上皮细胞重组及形态改变[53], 可见三者的调控关系密不可分。

菌群失调削弱黏膜屏障而有利于细菌易位, 进而促巨噬细胞活化, 产生慢性炎症。有研究发现, 微生物及其产物可上调粒细胞、巨噬细胞、单核细胞等活性, 促进活性氧、活性氮(NO)和MMP等的产生[16]。这些物质可以导致上皮细胞的DNA损伤, 也可以诱导产生细胞因子、趋化因子等, 在肿瘤细胞增殖、迁移和凋亡抑制中发挥调控作用[54]。

F. nucleatum 在OSCC发生发展中发挥重要作用。早期, *F. nucleatum*促进M2型TAMs在瘤内聚集, 并通过抑制巨噬细胞、T细胞等诱导免疫抑制[55], 同时, *F. nucleatum*的细胞表面蛋白(如FadA)破坏上皮细胞间连接, 加剧CRC。*F. nucleatum*感染的巨噬细胞能够通过上调免疫调节酶吲哚胺2, 3-双加氧酶(indoleamine 2, 3-dioxygenase, IDO)表达, 这可能是免疫抑制的一种潜在机制[56]; 其次,

*F. nucleatum*也可通过NF-κB/miR-1 322轴上调CCL20表达,促进巨噬细胞局部浸润,并诱导M2巨噬细胞极化来促进CRC的转移;除此之外,还可能激活TLR4/IL-6/p-STAT3/c-MYC通路来促进肿瘤中M2巨噬细胞极化,发挥免疫抑制的作用[56-58]。在口腔癌的发生发展中,除了*F. nucleatum*外,粪肠球菌、大肠杆菌等感染的巨噬细胞也可以调控COX-2和PGE2,实现促进肿瘤的发生和生长的效果[59]。除此之外,本课题组相关研究也证实,*P. gingivalis*可以诱导巨噬细胞极化为M2型,并实现OSCC免疫逃避[48]。不可否认,微生物感染的巨噬细胞在肿瘤发生发展中起到至关重要的作用,对口腔癌的早期诊断和治疗提供了新的思路。

4 讨论和展望

肿瘤作为影响人类健康及生存的一个重大疾病,其早期的诊断及治疗对于患者的生存至关重要。口腔癌作为口腔中的一种常见疾病,其自身微环境的特殊性、致病因素的复杂性等特征为其治疗设置了不少障碍。口腔癌中微生物种群组分和数量变化对于疾病的调控作用在包括口腔癌在内的多数口腔疾病中均占据着不可忽视的作用。而在这个过程中,免疫系统中的巨噬细胞对其的响应也尤为敏感,并在多数疾病中作为调控肿瘤发生发展的直接或间接因素而得到广泛研究。微生物群可以影响宿主的成熟和稳态,以及某些疾病的进展;反过来,免疫细胞也可以接收来自微生物群的信号,以维持菌群平衡和加强宿主防御功能,甚至影响到某些疾病进展。

目前已有多种证据表明微生物、巨噬细胞和肿瘤之间存在密切的相互作用,且三者之间互联交互,彼此影响,并为口腔疾病的诱发提供了适宜的环境。

尽管目前已有学者关注着巨噬细胞在癌症发展中的作用,但仅有少数研究将巨噬细胞与癌变,特别是与口腔癌前病变联系起来。因此,口腔癌中微生物以及巨噬细胞的特性变化及其相互之间的调控关系的研究,为其成为一种潜在的早期诊断及预后生物标志物、亦或是作为免疫治疗的基础创造了可能,并且对微生物群、巨噬细胞、肿瘤之间关系网络的深度挖掘有望为肿瘤的早期诊断及治疗提供更多的可能性。

* * *

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参 考 文 献

[1] SUNG H, FERLAY J, SIEGEL R L, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2021, 71(3): 209–249. doi: 10.3322/caac.21660.

[2] Global cancer observatory: Cancer today. International Agency for Research (2021). [2022-09-19].https://gco.iarc.fr/today/fact-sheets-cancers.

[3] SKLENICKA S, GARDINER S, DIERKS E J, *et al*. Survival analysis and risk factors for recurrence in oral squamous cell carcinoma: does surgical salvage affect outcome? J Oral Maxillofac Surg, 2010, 68(6): 1270–1275. doi: 10.1016/j.joms.2009.11.016.

[4] PERERA M, Al-HEBSHI N N, PERERA I, *et al*. Inflammatory bacteriome and oral squamous cell carcinoma. J Dent Res, 2018, 97(6): 725–732. doi: 10.1177/0022034518767118.

[5] KHATOON J, RAI R P, PRASAD K N. Role of *Helicobacter pylori* in gastric cancer: updates. World J Gastrointest Oncol, 2016, 8(2): 147–158. doi: 10.4251/wjgo.v8.i2.147.

[6] DEWHIRST F E, CHEN T, IZARD J, *et al*. The human oral microbiome. J Bacteriol, 2010, 192(19): 5002–5017. doi: 10.1128/JB.00542-10.

[7] DEO P N, DESHMUKH R. Oral microbiome: unveiling the fundamentals. J Oral Maxillofac Pathol, 2019, 23(1): 122–128. doi: 10.4103/jomfp.JOMFP_304_18.

[8] YANG K, WANG Y, ZHANG S, *et al*. Oral microbiota analysis of tissue pairs and saliva samples from patients with oral squamous cell carcinoma--a pilot study. Front Microbiol, 2021, 12: 719601. doi: 10.3389/fmicb.2021.719601.

[9] 刘塬, 张凌. 口腔微生物与口腔鳞状细胞癌关系的研究进展. 中国口腔颌面外科杂志, 2020, 18(3): 278–267. doi: 10.19438/j.cjoms.2020.03.018.

[10] KIM S Y, NAIR M G. Macrophages in wound healing: activation and plasticity. Immunol Cell Biol, 2019, 97(3): 258–267. doi: 10.1111/imcb.12236.

[11] AVILA-PONCE DE LEÓN U, VÁZQUEZ-JIMÉNEZ A, MATADAMAS-GUZMAN M, *et al*. Transcriptional and microenvironmental landscape of macrophage transition in cancer: a boolean analysis. Front Immunol, 2021, 12: 642842. doi: 10.3389/fimmu.2021.642842.

[12] SARKAR P, MALIK S, LAHA S, *et al*. Dysbiosis of oral microbiota during oral squamous cell carcinoma development. Front Oncol, 2021, 11: 614448. doi: 10.3389/fonc.2021.614448.

[13] LI Z, CHEN G, WANG P, *et al*. Alterations of the oral microbiota profiles in chinese patient with oral cancer. Front Cell Infect Microbiol, 2021, 11: 780067. doi: 10.3389/fcimb.2021.780067.

[14] KOMLÓS G, CSURGAY K, HORVÁTH F, *et al*. Periodontitis as a risk for oral cancer: a case-control study. BMC Oral Health, 2021, 21(1): 640. doi: 10.1186/s12903-021-01998-y.

[15] ZHANG L, LIU Y, ZHENG H J, *et al*. The oral microbiota may have influence on oral cancer. Front Cell Infect Microbiol, 2019, 9: 476. doi: 10.

3389/fcimb.2019.00476.

[16] GANLY I, YANG L, GIESE R A, *et al*. Periodontal pathogens are a risk factor of oral cavity squamous cell carcinoma, independent of tobacco and alcohol and human papillomavirus. Int J Cancer, 2019, 145(3): 775–784. doi: 10.1002/ijc.32152.

[17] OLSEN I, YILMAZ Ö. Possible role of *Porphyromonas gingivalis* in orodigestive cancers. J Oral Microbiol, 2019, 11(1): 1563410. doi: 10.1080/20002297.2018.1563410.

[18] WEN L, MU W, LU H, *et al*. *Porphyromonas gingivalis* promotes oral squamous cell carcinoma progression in an immune microenvironment. J Dent Res, 2020, 99(6): 666–675. doi: 10.1177/0022034520909312.

[19] LI Y, TAN X, ZHAO X, *et al*. Composition and function of oral microbiota between gingival squamous cell carcinoma and periodontitis. Oral Oncol, 2020, 107: 104710. doi: 10.1016/j.oraloncology.2020.104710.

[20] HARRANDAH A M, CHUKKAPALLI S S, BHATTACHARYYA I, *et al*. Fusobacteria modulate oral carcinogenesis and promote cancer progression. J Oral Microbiol, 2020, 13(1): 1849493. doi: 10.1080/20002297.2020.1849493.

[21] BINDER GALLIMIDI A, FISCHMAN S, REVACH B, *et al*. Periodontal pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum* promote tumor progression in an oral-specific chemical carcinogenesis model. Oncotarget, 2015, 6(26): 22613–22623. doi: 10.18632/oncotarget.4209.

[22] NEUZILLET C, MARCHAIS M, VACHER S, *et al*. Prognostic value of intratumoral *Fusobacterium nucleatum* and association with immune-related gene expression in oral squamous cell carcinoma patients. Sci Rep, 2021, 11(1): 7870. doi: 10.1038/s41598-021-86816-9.

[23] NOSHO K, SUKAWA Y, ADACHI Y, *et al*. Association of *Fusobacterium nucleatum* with immunity and molecular alterations in colorectal cancer. World J Gastroenterol, 2016, 22(2): 557–566. doi: 10.3748/wjg.v22.i2.557.

[24] ZHANG S, LI C, LIU J, *et al*. *Fusobacterium nucleatum* promotes epithelial-mesenchymal transiton through regulation of the lncRNA MIR4435-2HG/miR-296-5p/Akt2/SNAI1 signaling pathway. FEBS J, 2020, 287(18): 4032–4047. doi: 10.1111/febs.15233.

[25] SHAO W, FUJIWARA N, MOURI Y, *et al*. Conversion from epithelial to partial-EMT phenotype by *Fusobacterium nucleatum* infection promotes invasion of oral cancer cells. Sci Rep, 2021, 11(1): 14943. doi: 10.1038/s41598-021-94384-1.

[26] INABA H, SUGITA H, KUBONIWA M, *et al*. *Porphyromonas gingivalis* promotes invasion of oral squamous cell carcinoma through induction of proMMP9 and its activation. Cell Microbiol, 2014, 16(1): 131–145. doi: 10.1111/cmi.12211.

[27] KAMARAJAN P, ATEIA I, SHIN J M, *et al*. Periodontal pathogens promote cancer aggressivity via TLR/MyD88 triggered activation of Integrin/FAK signaling that is therapeutically reversible by a probiotic bacteriocin. PLoS Pathog, 2020, 16(10): e1008881. doi: 10.1371/journal.ppat.1008881.

[28] JEBRANE BOUAOUD J P F, TORTEREAU A, MICHON L. Early changes in the immune microenvironment of oral potentially malignant disorders reveal an unexpected association of M2 macrophages with oral cancer free survival. Oncoimmunology, 2021, 27(10): 1944554. doi: 10.1080/2162402X.2021.1944554.

[29] CHANMEE T, ONTONG P, ITANO N. Hyaluronan: a modulator of the tumor microenvironment. Cancer Lett, 2016, 375(1): 20–30. doi: 10.1016/j.canlet.2016.02.031.

[30] CHEN Y, JIN H, SONG Y, *et al*. Targeting tumor-associated macrophages: a potential treatment for solid tumors. J Cell Physiol, 2021, 236(5): 3445–3465. doi: 10.1002/jcp.30139.

[31] XU T, YU S, ZHANG J, *et al*. Dysregulated tumor-associated macrophages in carcinogenesis, progression and targeted therapy of gynecological and breast cancers. J Hematol Oncol, 2021, 14(1): 181. doi: 10.1186/s13045-021-01198-9.

[32] MURRAY P J. Macrophage polarization. Annu Rev Physiol, 2017, 79: 541–566. doi: 10.1146/annurev-physiol-022516-034339.

[33] ARORA S, DEV K, AGARWAL B, *et al*. Macrophages: their role, activation and polarization in pulmonary diseases. Immunobiology, 2018, 223(4/5): 383–396. doi: 10.1016/j.imbio.2017.11.001.

[34] HUANG X, LI Y, FU M, *et al*. Polarizing macrophages *in vitro*. Methods Mol Biol, 2018, 1784: 119–126. doi: 10.1007/978-1-4939-7837-3_12.

[35] SWANN J B, VESELY M D, SILVA A, *et al*. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. Proc Natl Acad Sci U S A, 2008, 105(2): 652–656. doi: 10.1073/pnas.0708594105.

[36] Van DALEN F J, Van STEVENDAAL M, FENNEMANN F L, *et al*. Molecular repolarisation of tumour-associated macrophages. Molecules, 2018, 24(1): 9. doi: 10.3390/molecules24010009.

[37] BERNSMEIER C, Van Der MERWE S, PÉRIANIN A. Innate immune cells in cirrhosis. J Hepatol, 2020, 73(1): 186–201. doi: 10.1016/j.jhep.2020.03.027.

[38] POTAS J R, HAQUE F, MACLEAN F L, *et al*. Interleukin-10 conjugated electrospun polycaprolactone (PCL) nanofibre scaffolds for promoting alternatively activated (M2) macrophages around the peripheral nerve *in vivo*. J Immunol Methods, 2015, 420: 38–49. doi: 10.1016/j.jim.2015.03.013.

[39] ASAI A, TSUCHIMOTO Y, OHAMA H, *et al*. Host antitumor resistance improved by the macrophage polarization in a chimera model of patients with HCC. Oncoimmunology, 2017, 6(4): e1299301. doi: 10.1080/2162402X.2017.1299301.

[40] WU H, XU J B, HE Y L, *et al*. Tumor-associated macrophages promote angiogenesis and lymphangiogenesis of gastric cancer. J Surg Oncol, 2012, 106(4): 462–468. doi: 10.1002/jso.23110.

[41] SLOTS J. Periodontitis: facts, fallacies and the future. Periodontology, 2000, 2017,75(1): 7–23. doi: 10.1111/prd.12221.

[42] SÖDER B, KÄLLMÉN H, YUCEL-LINDBERG T, *et al*. Periodontal microorganisms and diagnosis of malignancy: a cross-sectional study. Tumour Biol, 2021, 43(1): 1–9. doi: 10.3233/TUB-200066.

[43] ALMUBARAK A, TANAGALA K K K, PAPAPANOU P N, *et al*. Disruption of monocyte and macrophage homeostasis in periodontitis. Front Immunol, 2020, 11: 330. doi: 10.3389/fimmu.2020.00330.

[44] YU S, DING L, LIANG D, *et al*. *Porphyromonas gingivalis* inhibits M2 activation of macrophages by suppressing α-ketoglutarate production in mice. Mol Oral Microbiol, 2018, 33(5): 388–395. doi: 10.1111/omi.12241.

[45] YUAN G, FU C, YANG S T, *et al*. RGS12 drives macrophage activation and osteoclastogenesis in periodontitis. J Dent Res, 2022, 101(4): 448–457. doi: 10.1177/00220345211045303.

[46] CROFT A J, METCALFE S, HONMA K, *et al*. Macrophage polarization alters postphagocytosis survivability of the commensal *Streptococcus gordonii*. Infect Immun, 2018, 86(3): e00858-17. doi: 10.1128/IAI.00858-17.

[47] WEI W, LI J, SHEN X, *et al*. Oral microbiota from periodontitis promote oral squamous cell carcinoma development via γδ T cell activation. mSystems, 2022, 7(5): e0046922. doi: 10.1128/msystems.00469-22.

[48] LIU S, ZHOU X, PENG X, *et al*. *Porphyromonas gingivalis* promotes immunoevasion of oral cancer by protecting cancer from macrophage attack. J Immunol, 2020, 205(1): 282–289. doi: 10.4049/jimmunol.1901138.

[49] CECIL J D, O'BRIEN-SIMPSON N M, LENZO J C, *et al*. Outer membrane vesicles prime and activate macrophage inflammasomes and cytokine secretion *in vitro* and *in vivo*. Front Immunol, 2017, 8: 1017. doi: 10.3389/fimmu.2017.01017.

[50] LI C, YIN W, YU N, *et al*. miR-155 promotes macrophage pyroptosis induced by *Porphyromonas gingivalis* through regulating the NLRP3 inflammasome. Oral Dis, 2019, 25(8): 2030–2039. doi: 10.1111/odi.13198.

[51] SCHMIDT F, DAHLKE K, BATRA A, *et al*. Microbial colonization in adulthood shapes the intestinal macrophage compartment. J Crohns Colitis, 2019, 13(9): 1173–1185. doi: 10.1093/ecco-jcc/jjz036.

[52] WAN G, XIE M, YU H, *et al*. Intestinal dysbacteriosis activates tumor-associated macrophages to promote epithelial-mesenchymal transition of colorectal cancer. Innate Immun, 2018, 24(8): 480–489. doi: 10.1177/1753425918801496.

[53] BELOGORTSEVA N, KREZALEK M, GUYTON K, *et al*. Media from macrophages co-incubated with *Enterococcus faecalis* induces epithelial cell monolayer reassembly and altered cell morphology. PLoS One, 2017, 12(8): e0182825. doi: 10.1371/journal.pone.0182825.

[54] KARIN M, LAWRENCE T, NIZET V. Innate immunity gone awry: Linking microbial infections to chronic inflammation and cancer. Cell, 2006, 124(4): 823–835. doi: 10.1016/j.cell.2006.02.016.

[55] KOSTIC A D, CHUN E, ROBERTSON L, *et al*. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe, 2013, 14(2): 207–215. doi: 10.1016/j.chom.2013.07.007.

[56] WU J, LI Q, FU X. *Fusobacterium nucleatum* contributes to the carcinogenesis of colorectal cancer by inducing inflammation and suppressing host immunity. Transl Oncol, 2019, 12(6): 846–851. doi: 10.1016/j.tranon.2019.03.003.

[57] CHEN T, LI Q, WU J, *et al*. *Fusobacterium nucleatum* promotes M2 polarization of macrophages in the microenvironment of colorectal tumours via a TLR4-dependent mechanism. Cancer Immunol Immunother, 2018, 67(10): 1635–1646. doi: 10.1007/s00262-018-2233-x.

[58] XU C, FAN L, LIN Y, *et al*. *Fusobacterium nucleatum* promotes colorectal cancer metastasis through miR-1322/CCL20 axis and M2 polarization. Gut Microbes, 2021, 13(1): 1980347. doi: 10.1080/19490976.2021.1980347.

[59] MOLA S, PANDOLFO C, SICA A, *et al*. The macrophages-microbiota interplay in colorectal cancer (CRC)-related inflammation: prognostic and therapeutic significance. Int J Mol Sci, 2020, 21(18): 6866. doi: 10.3390/ijms21186866.

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