MFG-E8介导的骨免疫在牙周炎中的作用研究进展

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[摘要] 牙周炎是一种典型的骨免疫疾病，其特征为牙槽骨的炎症性吸收，是成年人牙齿松动和脱落的主要原因。细菌抗原可刺激破骨细胞并加重牙周炎症，因此控制炎症、阻断牙槽骨吸收对牙周炎的治疗具有重要意义。乳脂肪球表皮生长因子8(MFG-E8)作为一种细胞膜上的亲脂性糖蛋白，在多个器官和组织细胞中表达并参与骨免疫反应。MFG-E8不仅可作为诊断牙周病的新标志，还参与了包括牙周炎在内的骨炎性疾病的发展，随着骨炎性疾病的加剧，MFG-E8的表达逐渐降低，因此也具有靶向治疗牙周炎的潜能，可减少破骨细胞的形成，抑制牙槽骨的吸收。MFG-E8或可通过早期诊断和干预来控制牙周炎的病情，以减轻患者的经济负担及提高生活质量，将来可能成为治疗牙周炎和其他骨炎性疾病的热点。因此，该文对MFG-E8介导的骨免疫在牙周炎中的作用研究进展进行综述，以期为临床诊断和治疗牙周炎提供新思路。

[关键词] 乳脂肪球表皮生长因子8；骨免疫；牙周炎；骨稳态

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Research progress of MFG-E8 mediated osteoimmunology in periodontitis

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[**Abstract**] Periodontitis is a typical osteoimmune disorder characterized by inflammatory absorption of alveolar bone, and is the main cause for loose and fall off teeth in adults. Bacterial antigens stimulate the osteoclasts and aggravate periodontal inflammation, so it is of great significance for treatment of periodontitis to control inflammation and block the resorption of alveolar bone. Milk fat globule epidermal growth factor 8 (MFG-E8), as a lipophilic glycoprotein on the cell membrane, is expressed in multiple organs and histiocytes and participates in the bone immune response. MFG-E8 is involved in the development of osteoinflammatory diseases including periodontitis, so can be used as a new marker for the diagnosis of periodontal disease, and also has the potential of targeted therapy for periodontitis with the aggravation of osteoinflammatory diseases, the decreased expression of MFG-E8, reduction of osteoclasts formation and inhibition of alveolar bone resorption. MFG-E8 may be committed to early diagnosis and intervention to control the disease in order to reduce the economic burden of patients and improve the quality of life, and may become a hot spot for the treatment of periodontitis and other osteoinflammatory diseases in the future. Therefore, the research progress of MFG-E8-mediated osteoimmunology in periodontitis has reviewed in present paper to provide new ideas for clinical diagnosis and treatment of periodontitis.

[**Key words**] milk fat globule epidermal growth factor 8; osteoimmunology; periodontitis; bone homeostasis

牙周炎(periodontitis，PD)在中国≥55岁人群中的患病率为69.3%，是该年龄段患病率最高的口腔疾病，也是牙齿脱落的最主要病因[1-2]。在未经治疗的牙周炎易感者中，宿主的免疫功能失调促进了牙槽骨的吸收，最终导致牙齿松动、脱落，进而又加剧了口腔内的免疫失调[3-4]。研究发现，乳脂肪球表皮生长因子8(milk fat globule epidermal growth factor 8，MFG-E8)可增强巨噬细胞对凋亡细胞的吞噬作用，同时在维持表皮组织和血液系统动态平衡方面也扮演了重要角色[5-6]。此外，还有研究发现MFG-E8参与了PD等骨代谢疾病的免疫反应，可直接作用于骨骼系统的细胞或通过免疫系统间接参与骨炎症性疾病及骨改建[7]。本文综述了MFG-E8介导的骨免疫在PD中的研究进展，以期为MFG-E8辅助PD的诊断和治疗提供新的理论依据。

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1 MFG-E8

1.1 MFG-E8的结构 MFG-E8又称乳黏附素，最初研究发现其在泌乳期的乳腺中大量表达，并与脂肪球一起分泌[8]。MFG-E8分子由两个重复的表皮生长因子(epidermal growth factor，EGF)样结构域、一个黏蛋白样结构域和两个重复的盘状蛋白样结构域(C结构域)共同组成，它的两个重复结构域中各含有一个精氨酸-甘氨酸-天冬氨酸(arginine-glycine-aspartic acid sequence，RGD)序列，可与$\alpha_v\beta_3$或$\alpha_v\beta_5$整合素以异源二聚体的形式结合，促进细胞黏附并诱导整合素介导的信号转导，可被吞噬细胞识别。此外，又因其在乳脂球中含量丰富，氨基酸序列与EGF、凝血因子Ⅷ的盘状结构域相似，因此被命名为乳脂肪球表皮生长因子8[9]。Aziz等[10]发现人类和小鼠MFG-E8蛋白的肽链长度不同，因此将其分为不同的亚型。人类MFG-E8的全长型含有387个氨基酸，可产生一个约43 ku的蛋白质，而另一种亚型(约37 ku的蛋白质)则缺少氨基酸291-342片段。由于糖基化、唾液酸化等翻译后修饰，MFG-E8的大小在不同的研究中也有所不同。在小鼠中，MFG-E8全长型含有463个氨基酸(51 ku蛋白质)，而较短的亚型缺少氨基酸110-147片段，产生47 ku的蛋白质。尽管人类和小鼠中较短的MFG-E8亚型缺少原始转录本的外显子，但均保留了相同的结合域，因此具有相似的功能[11]。

1.2 MFG-E8的表达 MFG-E8作为一种外周分泌型糖蛋白可介导巨噬细胞的吞噬作用。它是由包括骨髓来源的未成熟树突细胞、生发中心的滤泡树突细胞和皮肤中的朗格汉斯细胞分泌产生的；也可由骨髓来源的巨噬细胞及激活后的腹腔巨噬细胞表达和分泌[12]。免疫组化染色显示MFG-E8在不同类型的组织中均有表达和定位[13]。

人和动物模型中MFG-E8的表达量在不同情况下会发生改变，到目前为止，已有大量的体内外研究揭示了调节MFG-E8表达的潜在信号通路。在骨髓中粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor，GM-CSF)的刺激下，未成熟树突细胞分泌的MFG-E8较巨噬细胞多30倍[14]，同时巨噬细胞中被趋化因子CX3CL1刺激的GM-CSF也可促进MFG-E8的分泌[14-15]。Aziz等[16]的体外研究表明，催乳素可上调乳腺上皮细胞和巨噬细胞MFG-E8的表达。过氧化物酶体增殖物激活受体δ(peroxisome proliferators-activated receptors-delta，PPAR-δ)基因缺陷小鼠由于凋亡细胞在体内的积聚而发生自身免疫性疾病，PPAR-δ可诱导调理素基因及MFG-E8的表达，以清除凋亡细胞并维持巨噬细胞的自我耐受状态[17]。脂多糖(lipopolysaccharide，LPS)是革兰阴性菌细胞壁的一种成分，可诱导巨噬细胞等产生炎症反应。研究发现，注射LPS的小鼠血清、脾和其他器官中MFG-E8的表达水平明显降低[18]。此外，LPS可通过Toll样受体4(Toll-like receptors-4，TLR4)/CD14信号通路使小鼠腹腔巨噬细胞样细胞系Raw264.7细胞中的MFG-E8表达下调[19-20]。缝隙连接蛋白43(connexin 43，Cx43)是MFG-E8表达的负调控因子，可通过降低MFG-E8的表达来抑制胶质瘤细胞的生长[21]。有研究证实，MFG-E8在肺纤维化[22]、黑色素瘤[23-24]、乳腺癌[25-26]、系统性红斑狼疮[27-28]等疾病中表达上调，在PD[29]、风湿性关节炎[30]、脓毒血症[31]、急性结肠炎[32]、动脉粥样硬化[33]、缺血再灌注损伤[34-35]等炎症性疾病中表达下降。MFG-E8在不同疾病中的表达变化可能作为这些疾病的诊断标志物，从而辅助对疾病的诊断和治疗。

2 MFG-E8与骨免疫

2.1 骨免疫 骨髓是造血的主要场所，含有造血干细胞、髓系和淋巴系祖细胞，以及成熟的免疫细胞(B细胞、中性粒细胞、巨噬细胞和T细胞)。骨细胞和免疫细胞具有相同的微环境，并相互作用，共同完成“骨免疫系统”的功能，因此骨免疫学领域的发展是为了研究与炎症性疾病相关的骨破坏的分子机制[36]。1972年，Horton等[37]报道了PD中免疫细胞与骨细胞之间的相互作用，指出在PD的发病过程中，细菌抗原刺激的免疫细胞会产生破骨细胞激活因子。2000年Arron与Choi[38]提出了“骨免疫学”一词，以强调T细胞介导破骨细胞产生的调节作用。

2.2 MFG-E8介导的骨免疫 早在2002年，MFG-E8已在人成骨细胞中被检测出来[39]。随后的研究发现，人单核细胞来源的破骨细胞也可表达MFG-E8[40]，由破骨细胞表达的MFG-E8可负向调节破骨细胞的形成，提示MFG-E8缺乏与PD中牙槽骨的吸收有关。结扎丝诱导的PD小鼠模型中MFG-E8的表达减少，从术后24 h到结扎完成后的第8天，MFG-E8水平逐渐升高，与导致PD相关性骨丢失的破骨细胞数量呈负相关，同一模型中MFG-E8基因缺陷小鼠在体外表现出核因子κB受体活化因子配体(receptor activator of nuclear factor-κB ligand，RANKL)诱导的破骨细胞生成增加，而在注射重组MFG-E8(recombinant protein MFG-E8，rMFG-E8)后，破骨细胞的活性被抑制[41]。近期研究进一步证实，与野生型小鼠相比，MFG-E8基因

缺陷小鼠出现骨形成障碍、矿化程度低、破骨细胞数量增多及骨吸收活性增强等现象，去除卵巢后MFG-E8基因缺陷小鼠破骨细胞生成进一步增加[7]。因此，与MFG-E8缺乏相关的骨丢失不仅限于炎症条件下，在健康小鼠去除卵巢的骨质疏松症模型中骨丢失同样与MFG-E8缺乏密切相关。Albus等[30]、Yoshimi等[42]发现，在MFG-E8基因缺陷小鼠的爪部组织中RANKL表达增加，成骨细胞数量减少，同时检测到MFG-E8在小鼠存在炎症的爪部组织中低表达，且在关节炎模型小鼠及RA患者的血清中也同样存在MFG-E8表达，经地塞米松治疗的关节炎小鼠，炎症缓解后其血清MFG-E8水平可逆转并恢复至健康水平。此外，MFG-E8不仅可直接影响破骨细胞的分化，还间接地通过成骨细胞和骨细胞中RANKL的产生来影响破骨细胞的分化。近期Chen等[43]在临床研究中发现膝骨关节炎患者血浆中的MFG-E8水平明显低于健康者，膝关节滑液中MFG-E8水平明显低于血浆，且滑液和血浆中的MFG-E8水平与膝骨关节炎的放射学严重程度呈负相关。还有研究发现，糖尿病患者骨质疏松程度与MFG-E8水平呈负相关[44]，再次证明MFG-E8在骨免疫中起重要作用，对其进行监测可能具有预测或诊断价值。

2.3 MFG-E8骨免疫在PD中的研究

2.3.1 MFG-E8在PD中的作用机制 PD作为人类最常见的感染性疾病之一，是典型的骨免疫疾病。口腔微生物菌群失调可使牙周组织发生慢性炎症，继而导致牙槽骨破坏[36]。辅助性T17(T helper 17，Th17)细胞由$CD4^+$ T细胞前体发育而来，巨噬细胞通过GM-CSF诱导抗原呈递细胞上的MFG-E8表达，吞噬凋亡细胞并抑制IL-23、IL-6的分泌，从而导致自身反应性Th17细胞受到抑制[45]。但在牙周炎症状态下，口腔细菌及其组分(如LPS)可刺激巨噬细胞、树突细胞和牙周膜细胞等抑制MFG-E8的表达[18]，使IL-23、IL-6表达增加，刺激Th17细胞在口腔黏膜中聚集并产生IL-17，而IL-17可诱导成骨细胞和牙周膜细胞中RANKL的表达，刺激破骨细胞而发生骨吸收。骨保护素(osteoprotegerin，OPG)主要由骨髓基质细胞表达，RANKL/OPG比值是决定骨量的主要因素，上调RANKL或降低OPG的诱导率，可使RANKL/OPG比值发生变化，从而有利于破骨细胞生成[46]。

2.3.2 MFG-E8在PD中的功能 Yavuz等[47]证实MFG-E8在人类龈沟液(gingival crevicular fluid，GCF)中表达，且健康人及牙龈炎患者GCF中的MFG-E8水平明显高于PD患者，并与牙周袋深度呈负相关。在接受牙周非手术与手术治疗的重度PD患者复诊期间，GCF的MFG-E8水平逐渐升高，而促炎因子IL-6、IL-17及RANKL则与MFG-E8相反，其表达水平呈进行性下降，但OPG未见明显降低。MFG-E8可降低RANKL的表达但又不影响OPG的产生，表明MFG-E8可能是炎症消退的评估指标。

研究发现，小鼠牙龈内微量注射rMFG-E8可抑制PD引起的骨丢失，并可减少TNF、IL-1等炎性介质的表达[30]。Abe等[48]将野生型小鼠牙周组织中分离出的细菌进行培养，发现rMFG-E8治疗组细菌含量较空白组明显降低。Kajikawa等[29]构建了猕猴PD模型，一侧用MFG-E8与IgG Fc受体合成的融合蛋白(MFG-E8-Fc-fusion protein，MFG-E8-Fc)治疗，另一侧用单纯IgG Fc受体治疗(对照组)。结果发现，MFG-E8-Fc治疗位点的骨丢失明显少于对照组，提示牙周组织分泌的MFG-E8不仅与牙周情况密切相关，且有助于维护牙周健康。因此，MFG-E8可作为一种新的宿主调节疗法应用于PD的治疗，也可作为PD的潜在诊断指标。

MFG-E8由先天性免疫细胞和上皮细胞产生，可参与骨免疫反应，且具有抗炎和促胞葬作用[49]，可在牙周组织与其他屏障部位的动态平衡中发挥重要作用[50]。与其他黏膜部位(如胃肠道、呼吸道)相比，牙周组织的独特之处在于它是由黏膜和骨组织共同组成的，MFG-E8调节免疫和骨细胞功能的能力表明其可能是PD宿主调控的一个潜在的重要靶点。MFG-E8是一种内源性分子，在PD时其表达下降，治疗时应使该因子恢复至正常水平，从而抑制炎症并恢复组织稳态。近年来，应用内源性活性物质治疗疾病的研究逐渐增多，与生物制剂或小分子药物相比，蛋白质替代疗法获得监管批准的可能性更高[51]。研究显示，内源性分子替代疗法如消化酶替代疗法或α_1-抗胰蛋白酶缺乏症患者的α_1-抗胰蛋白酶替代疗法等的耐受性良好[52]。

PD发病率极高，几乎影响到50%的成年人口腔健康[53]，又因其与患者全身健康密切相关[54]，且牙周治疗费用较为昂贵[55]，尤其是患者对传统牙周治疗反应不佳[56]等，探索新的牙周辅助治疗方法具有重要意义。因此，作为调节上游炎症反应和下游骨代谢过程的多功能分子，MFG-E8可能是PD的潜在替代疗法。除PD外，MFG-E8还可用于治疗其他骨炎症性疾病，如类风湿关节炎[30]等，但目前多为体外及动物实验研究，未来仍需大量临床试验来验证MFG-E8的治疗作用。

3 总结与展望

MFG-E8在骨免疫中的作用及其机制仍在深入探讨中，这对于完全阐明其在PD发生发展中的作

用，牙周疾病的辅助诊断、预后判断以及制定合理治疗方案等均具有十分重要的意义。未来应进一步研究MFG-E8调控骨免疫的机制，确定其作为PD生物标志物或治疗剂的实用性，为PD的早期诊断、治疗提供可靠的依据，这也可能成为未来研究和关注的热点。

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