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巨噬细胞极化在种植体周病中表达、分子机制 及与软硬组织修复的关系研究

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[摘 要] 种植体周病是一种常见且严重影响植入物效果的并发症,其特征是种植体周围的炎症,可能导致骨丧失,最终影响种植体的稳定性。种植体周病发生机制复杂,涉及细菌因素与宿主免疫反应之间的多面交互,长期以来备受关注。巨噬细胞是一类在吞噬和清除异物中发挥重要作用的免疫细胞,研究表明其在种植体周围组织中的表达和激活差异可能决定炎症环境,影响炎症的消退与种植体周病的发展。基于此,本文对巨噬细胞极化在种植体周病的表达研究、分子机制以及在软硬组织缺损修复中的应用进行综述。

[关键词] 种植体周病;巨噬细胞;信号通路;炎症因子;调控机制

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Study on the Expression and Molecular Mechanism of Macrophage Polarization in Peri-implant Disease and its Relationship with the Repair of Hard and Soft Tissues

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[Abstract] Peri-implant disease is a prevalent and serious complication that seriously affects the implant effect. It is characterized by inflammation around the implant, which may lead to bone loss and ultimately affect the stability of the implant. The pathogenesis of peri-implant disease is complex, involving multiple interactions between bacterial factors and the host immune response, which has attracted much attention for a long time. Macrophage is a type of immune cells that play an important role in phagocytosis and foreign substances removal. Studies have shown that differences in their expression and activation in peri-implant tissues may determine the inflammatory environment and affect the regression of inflammation and the progression of peri-implant disease. Based on this, this article reviews the research on the expression of macrophage polarization in peri-implant disease, molecular mechanism and its application in the repair of hard and soft tissue defects.

[Key words] Peri-implant disease; Macrophage; Signaling pathway; Inflammatory factor; Regulatory mechanism

口腔种植修复已成为缺牙修复的首选方式。然而由于患者基数大,口腔种植手术并发症的影响显著。种植体周病(perio-implant diseases, PID)

是口腔种植修复主要的并发症,严重影响口腔种植手术的成功率^[1]。当种植体周围发生病原体感染时,局部牙龈组织中巨噬细胞广泛浸润^[2, 3]。根

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据表面标志和分泌的细胞因子,巨噬细胞可分为M1型巨噬细胞和M2型巨噬细胞。M1型巨噬细胞分泌TNF- α 、IL-1 β 、IL-6等因子,在局部组织损伤感染免疫中发挥重要作用^[4, 5];M2型巨噬细胞分泌TGF- β 、IL-4、IL-10等抗炎因子,促进组织修复^[6, 7],两者间的动态平衡在感染免疫及损伤修复中至关重要^[8]。因此,本文对巨噬细胞极化在PID中的研究进行综述。

1 巨噬细胞极化在PID中的表达

PID是种植手术的主要并发症,也是导致种植手术失败的关键原因之一。因此,如何预防和治疗PID已经成为口腔种植领域的研究热点。目前,有学者认为^[9],M1型巨噬细胞的过度激活可能导致过度炎症反应,从而诱发PID的发生,而M2型巨噬细胞则在修复和再生种植体周围组织时发挥关键作用,促进种植体周围组织的修复。M1型巨噬细胞在多项研究中被报道具有促炎作用和溶骨作用。Zhou LN等^[10]比较了炎性牙龈组织和健康牙龈组织中巨噬细胞表型,发现炎性牙龈组织中M1细胞数较多,并且与临床探诊深度呈正相关。另一项研究表明^[11],M1型巨噬细胞的表达水平与疾病的严重程度有关,M1型巨噬细胞表达越高,疾病越严重。因此,M1型巨噬细胞可能是PID发病的一个重要因素。然而有研究表明^[12],巨噬细胞的可塑性和极化是实现有效创伤修复的关键,其中M2型巨噬细胞能触发血管生成反应和促进内皮生长因子表达,加速炎症病变的消退和组织修复。Azevedo MCS等^[13]研究发现,血管活性肠肽和腺苷酸环化酶激活多肽表现出显著的免疫调节作用,使M2型巨噬细胞显著增加,从而引起成骨细胞活性增加。

总之,M1型巨噬细胞引起种植体周围组织炎症和骨吸收,M2型巨噬细胞促进种植体周围组织修复和骨生成,因此调控巨噬细胞的极化方向,抑制M1型巨噬细胞极化、促进M2型巨噬细胞极化是PID防治的关键。

2 巨噬细胞极化在PID中的调控机制

研究表明^[14, 15],巨噬细胞极化受多种信号通路的调控,包括核因子- κ B(nuclear factor kappa B, NF- κ B)信号通路、Toll样受体(Toll-

like receptor, TLR)、NLRP3炎症小体信号通路、Wnt/ β -catenin信号通路。其中,NF- κ B信号通路是主要的调控机制。NF- κ B信号通路在炎症反应中具有经典特征,并在种植体周围的骨结合中起关键作用^[16, 17]。当种植体周围组织受到外界刺激时,NF- κ B信号通路一方面触发免疫反应以避免组织损伤,另一方面可被细菌生物膜与代谢产物激活,促使巨噬细胞向M1型极化。在M1型极化状态下,巨噬细胞会释放促炎细胞因子,例如IL-1 β 、TNF- α 、IL-6,进而引起骨吸收^[18]。因此,通过抑制NF- κ B信号通路,影响巨噬细胞向M1型极化。研究显示^[19],锂钙硅酸盐可通过抑制NF- κ B信号通路从而抑制巨噬细胞极化和破骨细胞生成。抗菌肽KN-7、KR-1、KR-2可以降低I kappa B α 和p65的磷酸化水平,抑制I kappa B α 的降解和p65的核转位,从而抑制NF- κ B信号通路的激活,并提升M2型巨噬细胞的表达水平^[20]。这不仅抑制了脂多糖(lipopolysaccharide, LPS)诱导的炎症反应,还增强了成骨细胞的成骨活性,从而维持种植体周围的骨结合。

TLR是先天免疫系统中识别病原体的主要受体之一。其中,Toll样受体4(TLR4)通过识别革兰氏阴性菌的LPS,促进了IL-1 β 、IL-17和TNF- α 的产生以及破骨细胞的生成,加速了骨吸收^[21, 22]。在种植体周炎的动物模型中,通过抑制TLR4/NF- κ B的表达水平,可以减少LPS诱导的M1型巨噬细胞生成,减轻LPS诱导的炎症反应,从而缓解种植体周围骨吸收^[23]。有研究发现^[24],褪黑素能够降低TLR4蛋白和NF- κ B的表达,并下调促炎细胞因子TNF、IL-1 β 和IL-6的水平,从而抑制PID发生。

NLRP3炎症小体信号通路在抑制骨生成和促进骨吸收的过程中发挥了关键作用^[25]。研究发现^[26],牙龈卟啉单胞菌的LPS能够被TLR识别,并通过NF- κ B信号通路增加NLRP3的表达。此外,牙龈卟啉单胞菌脂多糖在缺氧状态下能够诱导牙龈成纤维细胞NLRP3炎症小体表达增加,从而发生炎症反应^[27]。

Wnt/ β -catenin信号通路是经典的Wnt信号途径之一,可调控骨组织代谢和巨噬细胞功能,在种植体周围骨再吸收和再生过程中可能产生直接或间接的影响^[28, 29]。研究表明^[30],PID患者的牙龈

组织中Wnt5a的表达水平升高,并且在牙龈卟啉单胞菌感染的巨噬细胞中Wnt5a的表达也增加,但是敲除Wnt5a后,促炎因子IL-1 β 的表达显著降低。因此,Wnt/ β -catenin信号通路可能通过调节巨噬细胞功能影响种植体周围骨吸收和骨生成。

3 巨噬细胞极化与种植体周围软硬组织修复的关系

M1型巨噬细胞和M2型巨噬细胞共同参与了种植体周围软硬组织的修复,在软组织修复过程中,由于炎症反应,巨噬细胞向M1型极化并吞噬微生物或碎片,引发种植体表面的炎症和伤口愈合反应。M2型巨噬细胞则通过分泌TGF- β 等抗炎因子,诱导激活成纤维细胞,分泌相关因子以调节纤维化,阻止瘢痕组织形成。在骨组织修复过程中,M1型巨噬细胞通过分泌炎性因子来促进破骨细胞分化,直接调控破骨细胞生成。M2型巨噬细胞可产生TGF- β 和成骨因子,促进新骨形成^[31, 32]。

为了减少种植体周围组织中的M1型巨噬细胞促炎作用,并增强M2型巨噬细胞的修复作用,多项研究致力于通过对种植体材料改性来调控巨噬细胞极化的过程。Guo X等^[33]合成了一种仿贻贝儿茶酚肽,通过干扰整合素- $\alpha 2 \beta 1$ 和整合素- $\alpha v \beta 3$,促进M1型巨噬细胞向M2型巨噬细胞极化。Wang Y等^[34]研究发现,通过改良的SLA亲水表面能够促使巨噬细胞向M2型极化,从而有助于成纤维细胞胶原合成。Yang C等^[35]通过在种植体表面负载含丁酸钠的3D多孔磺化聚醚醚酮,提高了巨噬细胞吞噬能力,并诱导巨噬细胞向M2型极化,促进骨再生。因此,通过种植体表面改性可以诱导巨噬细胞向M2型抗炎方向极化,从而促进种植体周围组织炎症消退以及软硬组织的修复。

4 总结

深入理解巨噬细胞极化的调控机制有助于揭示PID的发生与发展机制。随着生物技术和免疫学的进步,精准调控巨噬细胞极化状态的方法可能成为预防和治疗PID的新策略。通过靶向调节巨噬细胞功能,促进M2型极化或抑制M1型极化,以平衡免疫反应和组织修复,将为PID的治疗提供有效方案。此外,鉴于该领域的研究尚处于起步阶

段,未来研究需要集中于更全面的体内和体外模型探索,以便将这些基础研究成果转化为临床应用,从而改善患者预后,并提高口腔种植修复的长期成功率。

[参考文献]

- [1] Araujo MG, Lindhe J. Peri-implant health[J]. J Clin Periodontol, 2018, 45 Suppl 20: S230-S236.
- [2] Fretwurst T, Garaicoa-Pazmino C, Nelson K, et al. Characterization of macrophages infiltrating peri-implantitis lesions[J]. Clin Oral Implants Res, 2020, 31(3): 274-281.
- [3] Li Y, Li X, Guo D, et al. Immune dysregulation and macrophage polarization in peri-implantitis[J]. Front Bioeng Biotechnol, 2024, 12: 1291880.
- [4] Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm[J]. Nat Immunol, 2010, 11(10): 889-896.
- [5] Locati M, Mantovani A, Sica A. Macrophage activation and polarization as an adaptive component of innate immunity[J]. Adv Immunol, 2013, 120: 163-184.
- [6] Tang L, Zhang H, Wang C, et al. M2A and M2C Macrophage Subsets Ameliorate Inflammation and Fibroproliferation in Acute Lung Injury Through Interleukin 10 Pathway[J]. Shock, 2017, 48(1): 119-129.
- [7] Locati M, Curtale G, Mantovani A. Diversity, Mechanisms, and Significance of Macrophage Plasticity[J]. Annu Rev Pathol, 2020, 15: 123-147.
- [8] Chen X, Zhao Y. Genetic Involvement in Dental Implant Failure: Association With Polymorphisms of Genes Modulating Inflammatory Responses and Bone Metabolism[J]. J Oral Implantol, 2019, 45(4): 318-326.
- [9] 张艺, 张晓梦, 史俊宇, 等. 巨噬细胞极化在种植体周围组织愈合的作用及研究进展[J]. 口腔医学, 2020, 40(7): 644-647.
- [10] Zhou LN, Bi CS, Gao LN, et al. Macrophage polarization in human gingival tissue in response to periodontal disease[J]. Oral Dis, 2019, 25(1): 265-273.
- [11] Galarraga-Vinueza ME, Obreja K, Ramanauskaite A, et al. Macrophage polarization in peri-implantitis lesions[J]. Clin Oral Investig, 2021, 25(4): 2335-2344.
- [12] de Seny D, Cobraiville G, Leprince P, et al. Biomarkers of

- inflammation and innate immunity in atrophic nonunion fracture[J]. *J Transl Med*, 2016, 14(1):258.
- [13] Azevedo MCS, Fonseca AC, Colavite PM, et al. Macrophage Polarization and Alveolar Bone Healing Outcome: Despite a Significant M2 Polarizing Effect, VIP and PACAP Treatments Present a Minor Impact in Alveolar Bone Healing in Homeostatic Conditions[J]. *Front Immunol*, 2021, 12:782566.
- [14] 霍花, 宋斌, 廖健. 种植体周病的相关信号通路机制及其交互调控作用[J]. *临床口腔医学杂志*, 2024, 40(5):310-314.
- [15] Lawrence T. Coordinated regulation of signaling pathways during macrophage activation[J]. *Microbiol Spectr*, 2016, 4(5):MCHD-0025-2015.
- [16] Tobeiha M, Moghadasian MH, Amin N, et al. RANKL/RANK/OPG Pathway: A Mechanism Involved in Exercise-Induced Bone Remodeling[J]. *Biomed Res Int*, 2020, 2020:6910312.
- [17] Zhao Z, Du Y, Yan K, et al. Exercise and osteoimmunology in bone remodeling[J]. *FASEB J*, 2024, 38(7):e23554.
- [18] Lasserre JF, Brex MC, Toma S. Oral Microbes, Biofilms and Their Role in Periodontal and Peri-Implant Diseases[J]. *Materials (Basel)*, 2018, 11(10):1802.
- [19] Pan C, Chen L, Wu R, et al. Lithium-containing biomaterials inhibit osteoclastogenesis of macrophages in vitro and osteolysis in vivo[J]. *J Mater Chem B*, 2019, 7(15):2566.
- [20] Zhang Q, Yu S, Hu M, et al. Antibacterial and Anti-Inflammatory Properties of Peptide KN-17[J]. *Microorganisms*, 2022, 10(11):2114.
- [21] Deng S, Hu Y, Zhou J, et al. TLR4 mediates alveolar bone resorption in experimental peri-implantitis through regulation of CD45⁺ cell infiltration, RANKL/OPG ratio, and inflammatory cytokine production[J]. *J Periodontol*, 2020, 91(5):671-682.
- [22] Pan K, Hu Y, Wang Y, et al. RANKL blockade alleviates peri-implant bone loss and is enhanced by anti-inflammatory microRNA-146a through TLR2/4 signaling[J]. *Int J Implant Dent*, 2020, 6(1):15.
- [23] He CY, Jiang LP, Wang CY, et al. Inhibition of NF- κ B by Pyrrolidine Dithiocarbamate Prevents the Inflammatory Response in a Ligature-Induced Peri-Implantitis Model: A Canine Study[J]. *Cell Physiol Biochem*, 2018, 49(2):610-625.
- [24] Wu X, Qiao S, Wang W, et al. Melatonin prevents peri-implantitis via suppression of TLR4/NF- κ B[J]. *Acta Biomater*, 2021, 134:325-336.
- [25] Briot K, Geusens P, Em Bultink I, et al. Inflammatory diseases and bone fragility[J]. *Osteoporos Int*, 2017, 28(12):3301-3314.
- [26] Ding PH, Yang MX, Wang NN, et al. Porphyromonas gingivalis-Induced NLRP3 Inflammasome Activation and Its Downstream Interleukin-1 β Release Depend on Caspase-4[J]. *Front Microbiol*, 2020, 11:1881.
- [27] Yang K, Xu S, Zhao H, et al. Hypoxia and Porphyromonas gingivalis-lipopolysaccharide synergistically induce NLRP3 inflammasome activation in human gingival fibroblasts[J]. *Int Immunopharmacol*, 2021, 94:107456.
- [28] Houshyar KS, Tapping C, Bottrelli MR, et al. Wnt Pathway in Bone Repair and Regeneration - What Do We Know So Far[J]. *Front Cell Dev Biol*, 2019, 6:170.
- [29] Adami G. Regulation of bone mass in inflammatory diseases[J]. *Best Pract Res Clin Endocrinol Metab*, 2022, 36(2):101611.
- [30] Zhang Q, Liu J, Ma L, et al. Wnt5a is involved in LOX-1 and TLR4 induced host inflammatory response in peri-implantitis[J]. *J Periodontal Res*, 2020, 55(2):199-208.
- [31] Lee JWY, Bance ML. Physiology of Osseointegration[J]. *Otolaryngol Clin North Am*, 2019, 52(2):231-242.
- [32] Muñoz J, Akhavan NS, Mullins AP, et al. Macrophage Polarization and Osteoporosis: A Review[J]. *Nutrients*, 2020, 12(10):2999.
- [33] Guo X, Bai J, Ge G, et al. Bioinspired peptide adhesion on Ti implants alleviates wear particle-induced inflammation and improves interfacial osteogenesis[J]. *J Colloid Interface Sci*, 2022, 605:410-424.
- [34] Wang Y, Zhang Y, Sculean A, et al. Macrophage behavior and interplay with gingival fibroblasts cultured on six commercially available titanium, zirconium, and titanium-zirconium dental implants[J]. *Clin Oral Investig*, 2019, 23(8):3219-3227.
- [35] Yang C, Ouyang L, Wang W, et al. Sodium butyrate-modified sulfonated polyetheretherketone modulates macrophage behavior and shows enhanced antibacterial and osteogenic functions during implant-associated infections[J]. *J Mater Chem B*, 2019, 7(36):5541-5553.