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训练免疫：糖尿病与牙周炎的潜在机制联系

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摘　要

糖尿病高血糖可诱导髓系细胞发生持久的代谢与表观遗传重编程，形成促炎记忆状态，使免疫细胞在后续刺激中反应增强。即使血糖得到控制，此类免疫记忆仍持续存在，导致牙周炎症加剧、组织破坏加重。靶向训练免疫机制，为防治糖尿病相关牙周炎提供了新的潜在策略。

关键词

训练免疫，糖尿病，牙周炎，代谢重编程，表观遗传重编程，骨髓造血系统

Trained Immunity: Underlying Mechanistic Links between Diabetes and Periodontitis

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Abstract

Hyperglycemia induces persistent metabolic and epigenetic reprogramming in myeloid cells, establishing a pro-inflammatory memory state that enhances immune cell responses to subsequent stimuli. Even after glycemic control is achieved, this immune memory persists, leading to exacerbated

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periodontal inflammation and increased tissue destruction. Targeting the mechanisms of trained immunity offers new potential strategies for the prevention and treatment of diabetes-associated periodontitis.

Keywords

Trained Immunity, Diabetes, Periodontitis, Metabolic Reprogramming, Epigenetic Reprogramming, Bone Marrow Hematopoietic System

1. 引言

牙周炎是一种慢性、多因素性、炎症性疾病，由牙齿表面积聚的牙菌斑生物膜激活宿主免疫炎症反应，是牙齿脱落的主要原因[1]。据估算，全球范围内轻度牙周炎的患病率约为 62%，其中重度牙周炎患者约占 23.6%，这使得牙周炎成为人类第七大常见疾病[2] [3]。大量流行病学研究揭示牙周炎与糖尿病、肥胖[4]、心血管疾病[5] [6]、类风湿性关节炎[7]等系统性疾病密切相关。

糖尿病是一种持续性代谢性疾病，已成为全球最广泛的代谢性疾病之一。糖尿病以血糖升高为主要特征，这些症状源于胰岛素分泌不足、胰岛素抵抗或上述机制的组合[8]。糖尿病的临床影响并不限于高血糖本身，对心血管[9]、神经系统[10]、免疫系统[11] [12]等也产生继发性影响。1993 年，Loe 首次指出糖尿病患者牙周炎风险升高，指出其为糖尿病第六大并发症[13]。糖尿病患者在牙周炎疾病管理中残留风险较高，使得传统治疗方法常常不足以全面控制牙周炎。研究表明，既往疾病如血脂异常、高血糖或肥胖等可能导致持久的“遗留效应”，即尽管血糖得到了控制，但代谢变化可能持续存在，表现出“代谢记忆”，这增加了糖尿病共病的风险[14] [15]，包括牙周组织破坏[16] [17]。研究表明，这现象可能与在糖尿病患者中观察到的“训练免疫”有关。

长久以来，人们认为抗原特异性和对病原体的长期记忆是获得性免疫的特征，然而，最近研究指出先天性免疫细胞也能“记住”特定刺激，如病原相关分子模式(PAMPs)、损伤相关分子模式(DAMPs) [18] [19]或高血糖[20]。先天免疫记忆，也被称为训练免疫，其特征是先天免疫细胞及其祖细胞在面对初次刺激时，发生持久性代谢重编码与表观遗传重编码，导致对随后的、甚至是异源性刺激的持久性增强的反应[18] [19]。最近有研究表明，牙周炎中高血糖诱导的先天免疫反应的激活及代谢重编码，证实训练免疫可能是糖尿病与牙周炎相关联的机制[21]。因此，深入探讨训练免疫背后的机制或能为预防和管理糖尿病相关牙周炎的提供新视角与方法。

2. 训练免疫

传统上，脊椎动物的免疫系统被划分为两大分支：适应性免疫系统与先天免疫系统。依据这一分类，先天免疫系统构成第一道防线，引发针对病原体的非特异性快速保护性反应[22]；适应性免疫系统则形成特异性的长效记忆，保护机体免受同一病原体的再次侵袭[23]。

然而，近年来的发现对这一固有观念提出了挑战：免疫细胞在病原体挑战后也能获得“记忆”能力[24]。髓系细胞在经历相同或不同刺激的再次作用时，会表现出增强的反应性。这种现象被称为先天免疫记忆或“训练免疫”，在抗感染防护、疫苗非特异性保护效应的诱导以及多种炎症疾病的发病机制中起

关键作用[25]。

训练免疫的建立主要基于两大支柱：表观遗传重编程与代谢重编程。当受到某些微生物来源配体(如真菌细胞壁成分 β-葡聚糖或结核病疫苗卡介苗)刺激后，这些免疫细胞经历显著的功能重编程变化，从而在后续刺激中产生更强反应能力[26]。

2.1. 代谢重编码与训练免疫

先天免疫细胞的训练过程涉及糖酵解、氧化磷酸化、三羧酸循环和脂质代谢等多条代谢通路的协同作用[27]，这些代谢变化与表观遗传重编程紧密耦联，共同决定免疫记忆的持久性。糖酵解上调是巨噬细胞活化的关键[28]，在 β-葡聚糖[29]、卡介苗[30]等多种诱导模型中均得到证实。其代谢物如葡萄糖-6-磷酸可作为表观遗传修饰酶的辅因子，己糖激酶和丙酮酸激酶等糖酵解相关基因也呈现激活型组蛋白修饰，实现代谢与表观遗传的联动[29] [31]。三羧酸循环代谢重编程是训练免疫的核心特征。β-葡聚糖可诱导细胞转向糖酵解(Warburg 效应) [29]。谷氨酰胺代谢积累的延胡索酸能抑制组蛋白去甲基化酶 KDM5，促进染色质开放，增强促炎因子表达[31]。其他中间产物如琥珀酸可稳定 HIF-1α 促进炎症[32]，乙酰辅酶 A 可作为组蛋白乙酰化底物，参与炎症调控[33]。胆固醇合成通路同样不可或缺。他汀类药物能抑制训练免疫，其抑制的甲羟戊酸可通过 IGF1R-Akt-mTOR 通路增强免疫记忆[34]。脂代谢中，脂肪酸合成可促进训练免疫，相关基因伴随 H3K4me3 修饰增加[35]。总之，训练免疫依赖于特定代谢网络与表观遗传修饰(如 H3K4me1、H3K4me3、H3K27ac 等)的深度耦联，不同刺激下各通路的平衡状态决定了免疫训练的强度与特性。

2.2. 表观遗传重编码与训练免疫

训练免疫中先天免疫细胞在二次刺激时产生更强、更快的转录反应，其核心机制在于持久的“表观遗传重编程”。在静息的先天免疫细胞(如单核细胞、巨噬细胞)中，大多数编码促炎基因和效应基因由于被抑制性组蛋白(如 H3K27me3)标记处于转录抑制状态。初次训练刺激(如 β-葡聚糖、卡介苗 BCG，或内源性信号如氧化低密度脂蛋白)通过模式识别受体招募 NF-κB、AP-1 等转录因子，它们与谱系决定因子(如 PU.1)协同，招募组蛋白修饰酶(如 HATs、KMTs)和染色质重塑复合物。这导致抑制性标记被移除，并在基因调控区域沉积激活性组蛋白标记：启动子区出现 H3K4me3，增强子区则出现 H3K4me1 和 H3K27ac，同时染色质可及性全局增加[19] [36] (见表 1)。

Table 1. Changes in epigenetic modifications caused by different stimuli
表 1. 不同刺激导致的表观遗传修饰变化

物种	诱导剂	表观遗传修饰变化	主要表型
植物	病原感染(如 SAR)	H3K4me3、H3K9ac 等	系统性获得抗性(SAR)，增强对再次感染的抵抗力[37] [38]
小鼠	β-葡聚糖	H3K4me1、H3K4me3、H3K27me3	增强对金黄色葡萄球菌等感染的抵抗，单核/巨噬细胞功能增强[39]-[41]
小鼠	脂多糖	H3K4me1、H3K9me2 下调	诱导耐受或训练，促炎基因下调，部分抗菌基因上调[42] [43]
小鼠	BCG(卡介苗)	H3K4me3、H3K27ac	诱导单核细胞训练，增强对白色念珠菌等异源病原的抵抗[44] [45]
小鼠	白色念珠菌(减毒株)	H3K4me3、H3K9me3	单核细胞功能重编程，增强对再次感染的保护[39] [46]
小鼠	高糖环境	H3K4me1 增加、H3K9me3 减少	长期促炎状态，增强 NF-κB 活性，参与“高血糖记忆”[47]

续表

小鼠/人类	巨细胞病毒	DNA 甲基化变化、PLZF 表达下调	NK 细胞记忆形成，抗原特异性或非特异性保护，增强细胞因子分泌[48]-[51]
人类	氧化低密度脂蛋白	H3K4me3、H3K27ac	单核细胞长期促炎表型，促进泡沫细胞形成，参与动脉粥样硬化[52]
人类	BCG 接种	H3K4me3、H3K27ac	单核细胞训练，增强对异源感染的抵抗力，持续数月甚至一年[45] [53] [54]
人类	西式饮食/代谢失调	H3K4me1、H3K9me3 变化	长期促炎表型，与 2 型糖尿病、阿尔茨海默病等慢性炎症疾病相关[47] [52] [55]

注：该表格包含了研究中不同诱导条件引起的表观遗传修饰变化。

训练免疫的关键特征在于，初次刺激移除后，上述表观遗传改变并非完全消退，而是在特定基因组位点上选择性保留，形成所谓的“表观遗传疤痕”。这使得相关基因处于一种“预激活”或“待命”状态。研究表明，由组蛋白甲基转移酶 Set7 催化沉积在增强子区的 H3K4me1 标记，在刺激消失后仍能长期存在。缺乏 Set7 的小鼠无法建立有效的训练免疫应答，凸显了该标记的核心作用[56]。

然而，表观遗传重编程并非孤立发生，它与其他调控层次紧密交织，共同塑造训练免疫表型。训练信号可导致转录因子网络的持续改变，如 STAT1 等转录因子的持续活化或敏感化，这些转录因子在二次应答时能更高效地启动转录程序[43] [57]。另一方面，某些 micro RNA (如 miR-155)在训练后被诱导并长期存在[58]。miR-155 通过抑制负向调控信号通路的磷酸酶，使细胞维持在一种“活化”状态，从而放大二次应答[59]。

最终，这些表观遗传变化的诱导与维持，与细胞代谢重编程(如糖酵解和三羧酸循环的改变)密切相关。代谢产物可作为表观修饰酶的底物或辅因子，从而将代谢变化与基因表达的持久重塑直接联系起来。因此，训练免疫是代谢、表观遗传和转录调控网络协同作用的结果，使先天免疫细胞获得类记忆的功能增强。

2.3. 训练免疫中的骨髓生成

由于外周成熟髓系细胞寿命短暂，其持续数月的“高反应性”表型必须由长寿命的造血干细胞与祖细胞所支持，这构成了先天免疫记忆的系统基础。β-葡聚糖和 BCG 疫苗的分别依赖 IL-1β 和 IFN-γ 信号通过诱导 HSPCs 发生持续代谢重编码和表观遗传重编码。骨髓移植实验提供了最直接的证据。研究发现，将经过 BCG 训练的供体小鼠骨髓移植给未受训的受体，发现后者也能获得对结核杆菌感染的增强抵抗力。在人体研究中，BCG 疫苗接种后 90 天，仍能检测到捐献者骨髓 HSPCs 的转录组向髓系偏倚及表现遗传改变[60]-[62]。代谢性刺激同样在骨髓层面发挥作用，对 $Ldlr^{-/-}$小鼠进行为期四周的高脂饮食，可激活 NLRP3 炎性小体及 IL-1β 信号，诱导骨髓产生持久的转录与表观遗传重编程，且在恢复正常饮食后，其髓系细胞仍保持高反应性[63]。

3. 糖尿病中的训练免疫

高血糖不仅是糖尿病的一大标志，更是一种持续性内源性刺激，驱动训练免疫。研究指出即使血糖控制后，糖尿病引起的代谢紊乱仍然可能通过“代谢记忆”加剧牙周炎时的牙槽骨破坏[21]。

胰岛素抵抗的发展最初会导致较高的血浆胰岛素水平来克服抵抗状态。免疫细胞经胰岛素处理后，激活单核细胞内 PI3K/Akt/mTOR 通路，导致细胞代谢的改变[64]。J. van Diepen [65]等人发现，经高葡萄糖条件预处理的人类单核细胞，即使在正常葡萄糖条件下培养 5 天，后续 LPS 再刺激后，其 IL-6 和 TNF-α 分泌增加，且糖酵解也增强。该过程可能涉及由赖氨酸甲基转移酶家族(MLL)家族带来的表观遗传变化

H3K4me3。临床证据显示，糖尿病患者单核细胞中促炎基因位点的 H3K4me3 和 H3K9ac 修饰异常丰富，证实代谢记忆通过表观遗传修饰在较长时间内维持促炎表型[66]。同样，中性粒细胞也受高血糖影响，代谢重编程导致辅酶 A 积累，触发组蛋白乙酰化，促进中性粒细胞外陷阱(NET)的过度形成。这一现象不仅加剧了炎症反应，还延缓了糖尿病患者的伤口愈合[67]。

糖尿病背景下先天免疫细胞的长期功能性重编码可归因于高血糖环境激活骨髓造血干细胞和祖细胞，导致髓系细胞分化偏斜，尤其是单核细胞与中性粒细胞的增殖与释放。在链脲佐菌素诱导的糖尿病小鼠模型中，高血糖通过上调 S100A8/A9 蛋白表达，促进骨髓造血，增加循环中的中性粒细胞和 $Ly6C^{+}$单核细胞，进而加速动脉粥样硬化进程[68]。高血糖还被证明可诱导骨髓来源巨噬细胞(BMDM)及其前体祖细胞持续的功能变化。Bailey 等人[20]用正常血糖小鼠或链脲佐菌素诱导的糖尿病小鼠的供体细胞产生骨髓嵌合体，并将它们转移到喂饲西方饮食的 $Ldlr^{-/-}$早期小鼠体内。接受糖尿病小鼠造血祖细胞移植的受体小鼠表现出更严重的血管硬化斑块形成，这表明高血糖促使供体小鼠 HSCs 的长期改变。进一步研究表明，高血糖介导的先天免疫细胞及其祖细胞表观遗传修饰变化，是使其在后续分化中持续表现出促炎特征的原因。高血糖暴露会导致 HSPCs 中 NF-κB-p65 启动子区域的 H3K4me1 标记积累，由其分化而来的单核细胞仍表现出增强的 IL-6 和 TNF-α 分泌能力[69]。这些研究证实了高血糖可通过介导先天免疫细胞及其祖细胞内持续的表观遗传学修饰传递“代谢记忆”。

在代谢紊乱，如糖尿病中，脂质代谢异常不仅是葡萄糖代谢异常的副产物，也是其导致慢性炎症的原因。氧化低密度脂蛋白、脂蛋白、甲羟戊酸及游离脂肪酸等代谢物通过代谢重编程与表观遗传重塑，诱导单核/巨噬细胞及其骨髓祖细胞形成持续促炎表型，构成糖尿病“代谢记忆”的免疫基础[36] [70]。氧化低密度脂蛋白激活糖酵解及氧化磷酸化，上调甲羟戊酸通路，促进 H3K4me3 富集于促炎基因启动子，同时下调胆固醇外排转运体 ABCA1/ABCG1，驱动泡沫细胞形成[52] [71] [72]。脂蛋白通过其携带的氧化磷脂介导单核细胞训练，增强细胞向内皮黏附及动脉壁归巢[73]。游离脂肪酸(如棕榈酸)经 TLR4/mTOR 通路诱导 H3K4me3 修饰[74]。临床研究证实，家族性高胆固醇血症及冠心病患者循环单核细胞呈现 H3K4me3 富集、糖酵解增强及炎症因子分泌上调，且他汀治疗无法逆转[75] [76]。

4. 牙周炎与训练免疫

训练免疫作为一种先天免疫记忆形式，不仅参与感染防御，更在慢性炎症性疾病中发挥关键作用。在牙周炎中，训练免疫通过诱导髓系细胞及祖细胞的持久性功能重编程成为牙周炎与多种全身性疾病(如类风湿关节炎[77])共病关联的核心机制。

作为牙周炎进展中的髓系细胞—单核细胞/巨噬细胞，在牙周炎训练后产生持续性功能重编码，表现为促炎表型。体外培养的慢性牙周炎患者外周血单核细胞，面对 LPS 再次刺激，呈现更高水平的促炎细胞因子(如 TNF-α、IL-6)分泌，这种高反应性可持续存在[78]。牙周炎对髓系细胞的长期性作用，除了导致持续的促炎表型，还影响其后代细胞的功能状态。小鼠皮下[79]和颅骨[80] [81]持续的牙龈卟啉单胞菌感染不仅增加了破骨细胞前体池和增强了破骨细胞的活性，加重骨破坏，而且还降低了宿主的免疫反应，从而促进了牙周炎特有的慢性形式的维持。

除单核细胞/巨噬细胞外，其他髓系细胞，如中性粒细胞，也被认为与牙周炎相关先天免疫记忆有关。研究发现，牙周炎患者及小鼠中的中性粒细胞均表现出超活化状态，包括活性氧(ROS)产生增加、脱颗粒增强以及中性粒细胞外陷阱(NETs)形成增多[82]。重要的是，Yu 等人证明细胞外陷阱在先天免疫记忆中发挥了重要作用[83]。中性粒细胞中的组蛋白去乙酰化酶抑制剂可以促进 NETs 的形成，这表明表观遗传学修饰在中性粒细胞介导的训练免疫中的潜在作用机制[84]。

牙周炎相关的先天免疫记忆的持续性取决于骨髓前体细胞的代谢与表观遗传重编码。一项使用 ^{18}F-

FDG-PET/CT 成像测量牙周炎和造血组织活性的研究显示两者之间存在正相关，提示牙周炎可能影响骨髓的造血反应，这是牙周炎诱导的训练免疫能够长期维持的核心[85]。另外，动物实验证实，将经历牙周炎小鼠的骨髓移植给健康小鼠，受体在受到关节炎二次刺激时，病情显著恶化。这直接证明了牙周炎可在骨髓层面建立的、可遗传的炎症记忆作用[77]。

总之，在牙周炎中，训练免疫作用是由局部感染触发，在骨髓造血系统中通过代谢与表观遗传重编码，并通过外周循环髓系细胞系统性播散。这种牙周炎对骨髓造血细胞的不良训练，不仅是导致牙周炎慢性化及骨质破坏加剧的内在机制，更是牙周炎与全身共病，如心血管疾病、类风湿性关节炎、糖尿病等双向恶化的途径。

5. 高血糖背景下的训练免疫作用加剧牙周炎

最新研究显示，糖尿病诱导的表观遗传重编程在骨髓造血干细胞通过训练免疫将骨髓细胞诱导为持续促炎状态，即使代谢异常被纠正后，牙周炎仍持续加重，为“代谢记忆”提供了关键的分子解释[21]。

为了探讨高血糖、训练免疫与牙周炎之间的联系，一项使用链氨酰唑胺诱导小鼠糖尿病的研究进行了全面调查。研究结果显示，经高浓度葡萄糖处理的巨噬细胞转换回正常葡萄糖处理后，细胞的吞噬作用、趋化性、衰老表型和抗原提呈能力仍有持续的变化。当糖尿病小鼠的骨髓移植到正常血糖水平小鼠，并进行结扎诱导牙周炎模型建立时，牙槽骨破坏显著加重，同时牙龈组织中糖酵解蛋白，如 HK2、PKM2 表达增加[21]。另有研究提出，糖尿病小鼠的骨髓细胞在正常血糖条件下分化为 BMDMs 并受到刺激后，IL-6 表达显著增加，这些结果都提示了糖尿病来源 BMDM 即使在正常糖浓度情况下，仍保留其促炎能力，这些都是潜在加重牙周炎牙槽骨破坏的机制[20]。

从细胞代谢角度层面看，糖尿病诱导的细胞代谢重编码的典型特征是髓系细胞从以氧化磷酸化为主的静息代谢，向以糖酵解为主的激活代谢转变，并伴随着 TCA 循环与脂质代谢通路重排[86]。这些代谢改变为后续促炎转录程序提供代谢驱动因素，使促炎因子产生能力更强；另一方面，代谢-表观遗传耦合使促炎基因处于“预备状态”，从而在牙周局部遭遇同等或相似刺激时，产生更强的 TNF-α、IL-6、IL-1β 等炎症输出，并延长炎症持续时间。牙周炎的临床核心后果之一是牙槽骨吸收，其本质是炎症驱动的骨免疫失衡。牙周致病刺激可促使巨噬细胞向促炎极化，并与破骨分化/骨吸收相关通路相互促进，最终推动牙槽骨破坏。在糖尿病训练免疫背景下，牙周炎刺激会引发更强的炎症因子释放，ROS/NETs 生成与组织损伤，并进一步破坏牙周组织，持续的高炎症微环境通过骨免疫网络促进 RANKL 相关破骨程序与破骨细胞分化，导致牙槽骨吸收加重[86]。

在表观遗传层面，高糖可在单核细胞等留下与既往 HbA1c 相关的组蛋白乙酰化印记，并通过糖酵解增强等代谢改变促使促炎基因位点 H3K4me3 等标记富集、染色质更开放，部分机制可能涉及 MLL 等甲基转移酶上调及代谢中间体对去甲基化酶的抑制，从而巩固促炎转录易感状态[66]。研究发现，牙周局部也存在 DNA 甲基化与 HDAC 等失衡，且 DNMT/HDAC/BET 抑制可减轻炎症与骨丢失，提示系统性训练记忆与局部表观遗传易感共同推动糖尿病患者牙周炎更重、更难消退[87]。由于外周髓系细胞寿命短，训练免疫的长期性更可能依赖骨髓“中枢训练”。研究发现，高糖重编程 HSC/HSPC 并驱动髓系偏向性造血，使后续生成的单核/中性粒细胞持续呈促炎倾向[68]。与此同时，牙周炎本身也可训练骨髓：小鼠结扎性牙周炎在表型缓解后仍可见 LSK/GMP 促炎基因染色质可及性升高，且 HSPC 内 IL-1 信号对适应不良训练关键[77]。因此，糖尿病患者即使血糖控制良好，牙周菌斑 PAMP 反复刺激使训练过的髓系细胞产生更强炎症因子、ROS 与 NETs，破坏屏障并促菌血症/低度内毒素血症，进一步强化骨髓生成；同时通过扩大破骨前体池与增强破骨生成，加速牙槽骨吸收。

6. 总结与展望

预计在不久的将来，糖尿病及其相关牙周炎的发病率将继续上升，尤其是在代谢综合征高发的地区，如中国。尽管当前临床指南强调血糖和血脂水平的管理，但大规模研究表明，即使是代谢参数控制良好的糖尿病患者，仍面临显著的增高的牙周炎患病风险。这凸显了治疗范式的转变，糖尿病驱动的“训练免疫”机制为应对这一挑战提供了新颖途径。

最新研究表明，糖尿病通过诱导训练免疫显著加速牙周炎的病理进展。这一过程表现为骨髓细胞持续的代谢重编程、表观遗传变化失调以及促炎介质的过度产生。这些发现解释了为何仅针对代谢紊乱(如高血糖)的干预措施不足以有效降低牙周炎风险，同时也强调了通过调节训练免疫力实现精准医疗的潜力。可能的治疗靶点包括抑制炎症信号通路、逆转异常表观遗传修饰，或调节关键代谢过程。这可能包括利用纳米载体向骨髓细胞进行靶向药物递送、开发针对炎症相关基因座的表观遗传编辑技术，以及在训练免疫关键启动阶段实施短期干预措施。此外，对特定分子标志物(如 IPLs)的更详细检查，可能为开发更具选择性和有效的治疗策略奠定基础。

然而，目前的研究也存在一定的局限性。现有机制研究多来自于经典训练免疫模型，如 β-葡聚糖、氧化低密度脂蛋白等，而牙周炎发生时，牙周致病菌是否能诱导骨髓 HSPCs、循环单核细胞、牙周组织局部局势细胞发生独特的表观遗传印记尚未阐明；当前研究大多是动物实验及体外模型验证，在人体临床数据中的证据有限。同时，对基于“训练免疫”治疗糖尿病牙周炎的策略，也存在巨大挑战。我们应该认识到表观修饰酶广谱抑制可能会带来的脱靶毒性、牙周组织局部靶向药物递送存在较大的技术难度、人类 HSPCs 的活性检测难以常规开展以及训练免疫标志物缺乏临床阈值判断标准。尽管当前的转化面临挑战，针对训练免疫是克服糖尿病牙周炎“代谢记忆”的新范式，可能推动牙周炎治疗从单纯聚焦代谢调控转向结合免疫重塑的战略转变。

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参考文献

[1] Isola, G., Polizzi, A., Serra, S., Boato, M. and Sculean, A. (2025) Relationship between Periodontitis and Systemic Diseases: A Bibliometric and Visual Study. *Periodontology* 2000, **98**, 228-240. https://doi.org/10.1111/prd.12621

[2] Trindade, D., Carvalho, R., Machado, V., Chambrone, L., Mendes, J.J. and Botelho, J. (2023) Prevalence of Periodontitis in Dentate People between 2011 and 2020: A Systematic Review and Meta-Analysis of Epidemiological Studies. *Journal of Clinical Periodontology*, **50**, 604-626. https://doi.org/10.1111/jcpe.13769

[3] Chen, M.X., Zhong, Y.J., Dong, Q.Q., Wong, H.M. and Wen, Y.F. (2021) Global, Regional, and National Burden of Severe Periodontitis, 1990-2019: An Analysis of the Global Burden of Disease Study 2019. *Journal of Clinical Periodontology*, **48**, 1165-1188. https://doi.org/10.1111/jcpe.13506

[4] Marruganti, C., Suvan, J.E. and D'Aiuto, F. (2023) Periodontitis and Metabolic Diseases (Diabetes and Obesity): Tackling Multimorbidity. *Periodontology 2000*, 1-16. https://doi.org/10.1111/prd.12536

[5] Orlandi, M., Graziani, F. and D'Aiuto, F. (2020) Periodontal Therapy and Cardiovascular Risk. *Periodontology* 2000, **83**, 107-124. https://doi.org/10.1111/prd.12299

[6] Polizzi, A., Nibali, L., Tartaglia, G.M. and Isola, G. (2025) Impact of Nonsurgical Periodontal Treatment on Arterial Stiffness Outcomes Related to Endothelial Dysfunction: A Systematic Review and Meta-Analysis. *Journal of Periodontology*, **96**, 330-345. https://doi.org/10.1002/jper.24-0422

[7] Möller, B., Kollert, F., Sculean, A. and Villiger, P.M. (2020) Infectious Triggers in Periodontitis and the Gut in Rheumatoid Arthritis (RA): A Complex Story about Association and Causality. *Frontiers in Immunology*, **11**, Article No. 1108. https://doi.org/10.3389/fimmu.2020.01108

[8] Antar, S.A., Ashour, N.A., Sharaky, M., Khattab, M., Ashour, N.A., Zaid, R.T., *et al*. (2023) Diabetes Mellitus: Classification, Mediators, and Complications; a Gate to Identify Potential Targets for the Development of New Effective

Treatments. *Biomedicine & Pharmacotherapy*, **168**, Article 115734. https://doi.org/10.1016/j.biopha.2023.115734

[9] Strain, W.D. and Paldánius, P.M. (2018) Diabetes, Cardiovascular Disease and the Microcirculation. *Cardiovascular Diabetology*, **17**, Article No. 57. https://doi.org/10.1186/s12933-018-0703-2

[10] Abbott, C.A., Malik, R.A., van Ross, E.R.E., Kulkarni, J. and Boulton, A.J.M. (2011) Prevalence and Characteristics of Painful Diabetic Neuropathy in a Large Community-Based Diabetic Population in the U.K. *Diabetes Care*, **34**, 2220-2224. https://doi.org/10.2337/dc11-1108

[11] Berbudi, A., Rahmadika, N., Tjahjadi, A.I. and Ruslami, R. (2020) Type 2 Diabetes and Its Impact on the Immune System. *Current Diabetes Reviews*, **16**, 442-449. https://doi.org/10.2174/1573399815666191024085838

[12] Herold, K.C., Delong, T., Perdigoto, A.L., Biru, N., Brusko, T.M. and Walker, L.S.K. (2024) The Immunology of Type 1 Diabetes. *Nature Reviews Immunology*, **24**, 435-451. https://doi.org/10.1038/s41577-023-00985-4

[13] Löe, H. (1993) Periodontal Disease: The Sixth Complication of Diabetes Mellitus. *Diabetes Care*, **16**, 329-334. https://doi.org/10.2337/diacare.16.1.329

[14] Chen, Z. and Natarajan, R. (2022) Epigenetic Modifications in Metabolic Memory: What Are the Memories, and Can We Erase Them? *American Journal of Physiology-Cell Physiology*, **323**, C570-C582. https://doi.org/10.1152/ajpcell.00201.2022

[15] Bekkering, S., Saner, C., Riksen, N.P., Netea, M.G., Sabin, M.A., Saffery, R., *et al*. (2020) Trained Immunity: Linking Obesity and Cardiovascular Disease across the Life-Course? *Trends in Endocrinology & Metabolism*, **31**, 378-389. https://doi.org/10.1016/j.tem.2020.01.008

[16] Graves, D.T., Ding, Z. and Yang, Y. (2020) The Impact of Diabetes on Periodontal Diseases. *Periodontology 2000*, **82**, 214-224. https://doi.org/10.1111/prd.12318

[17] Dong, H., Sun, Y., Nie, L., Cui, A., Zhao, P., Leung, W.K., *et al*. (2024) Metabolic Memory: Mechanisms and Diseases. *Signal Transduction and Targeted Therapy*, **9**, Article No. 38. https://doi.org/10.1038/s41392-024-01755-x

[18] Netea, M.G., Domínguez-Andrés, J., Barreiro, L.B., Chavakis, T., Divangahi, M., Fuchs, E., *et al*. (2020) Defining Trained Immunity and Its Role in Health and Disease. *Nature Reviews Immunology*, **20**, 375-388. https://doi.org/10.1038/s41577-020-0285-6

[19] Netea, M.G., Joosten, L.A.B., Latz, E., Mills, K.H.G., Natoli, G., Stunnenberg, H.G., *et al*. (2016) Trained Immunity: A Program of Innate Immune Memory in Health and Disease. *Science*, **352**, aaf1098. https://doi.org/10.1126/science.aaf1098

[20] Edgar, L., Akbar, N., Braithwaite, A.T., Krausgruber, T., Gallart-Ayala, H., Bailey, J., *et al*. (2021) Hyperglycemia Induces Trained Immunity in Macrophages and Their Precursors and Promotes Atherosclerosis. *Circulation*, **144**, 961-982. https://doi.org/10.1161/circulationaha.120.046464

[21] Nie, L., Sun, Y., Dong, H., You, M., Cui, A., Yue, Z., *et al*. (2025) DHFR-Driven Metabolic Memory Sustains Periodontal Tissue Destruction. *Journal of Dental Research*, **104**, 1495-1505. https://doi.org/10.1177/00220345251340632

[22] Turvey, S.E. and Broide, D.H. (2010) Innate Immunity. *Journal of Allergy and Clinical Immunology*, **125**, S24-S32. https://doi.org/10.1016/j.jaci.2009.07.016

[23] Chi, H., Pepper, M. and Thomas, P.G. (2024) Principles and Therapeutic Applications of Adaptive Immunity. *Cell*, **187**, 2052-2078. https://doi.org/10.1016/j.cell.2024.03.037

[24] Netea, M.G., Quintin, J. and van der Meer, J.W.M. (2011) Trained Immunity: A Memory for Innate Host Defense. *Cell Host & Microbe*, **9**, 355-361. https://doi.org/10.1016/j.chom.2011.04.006

[25] Fanucchi, S., Domínguez-Andrés, J., Joosten, L.A.B., Netea, M.G. and Mhlanga, M.M. (2021) The Intersection of Epigenetics and Metabolism in Trained Immunity. *Immunity*, **54**, 32-43. https://doi.org/10.1016/j.immuni.2020.10.011

[26] Bekkering, S., Domínguez-Andrés, J., Joosten, L.A.B., Riksen, N.P. and Netea, M.G. (2021) Trained Immunity: Reprogramming Innate Immunity in Health and Disease. *Annual Review of Immunology*, **39**, 667-693. https://doi.org/10.1146/annurev-immunol-102119-073855

[27] Domínguez-Andrés, J., Joosten, L.A. and Netea, M.G. (2019) Induction of Innate Immune Memory: The Role of Cellular Metabolism. *Current Opinion in Immunology*, **56**, 10-16. https://doi.org/10.1016/j.coi.2018.09.001

[28] Wang, T., Liu, H., Lian, G., Zhang, S., Wang, X. and Jiang, C. (2017) Hif1α-Induced Glycolysis Metabolism Is Essential to the Activation of Inflammatory Macrophages. *Mediators of Inflammation*, **2017**, Article ID: 9029327. https://doi.org/10.1155/2017/9029327

[29] Cheng, S., Quintin, J., Cramer, R.A., Shepardson, K.M., Saeed, S., Kumar, V., *et al*. (2014) mTOR- and Hif-1α-Mediated Aerobic Glycolysis as Metabolic Basis for Trained Immunity. *Science*, **345**, Article 1250684. https://doi.org/10.1126/science.1250684

[30] Arts, R.J.W., Carvalho, A., La Rocca, C., Palma, C., Rodrigues, F., Silvestre, R., *et al*. (2016) Immunometabolic

Pathways in BCG-Induced Trained Immunity. *Cell Reports*, **17**, 2562-2571. https://doi.org/10.1016/j.celrep.2016.11.011

[31] Arts, R.J.W., Novakovic, B., ter Horst, R., Carvalho, A., Bekkering, S., Lachmandas, E., *et al*. (2016) Glutaminolysis and Fumarate Accumulation Integrate Immunometabolic and Epigenetic Programs in Trained Immunity. *Cell Metabolism*, **24**, 807-819. https://doi.org/10.1016/j.cmet.2016.10.008

[32] Tannahill, G.M., Curtis, A.M., Adamik, J., Palsson-McDermott, E.M., McGettrick, A.F., Goel, G., *et al*. (2013) Succinate Is an Inflammatory Signal That Induces Il-1β through Hif-1α. *Nature*, **496**, 238-242. https://doi.org/10.1038/nature11986

[33] Wellen, K.E., Hatzivassiliou, G., Sachdeva, U.M., Bui, T.V., Cross, J.R. and Thompson, C.B. (2009) ATP-Citrate Lyase Links Cellular Metabolism to Histone Acetylation. *Science*, **324**, 1076-1080. https://doi.org/10.1126/science.1164097

[34] Bekkering, S., Arts, R.J.W., Novakovic, B., Kourtzelis, I., van der Heijden, C.D.C.C., Li, Y., *et al*. (2018) Metabolic Induction of Trained Immunity through the Mevalonate Pathway. *Cell*, **172**, 135-146.e9. https://doi.org/10.1016/j.cell.2017.11.025

[35] van der Heijden, C.D.C.C., Keating, S.T., Groh, L., Joosten, L.A.B., Netea, M.G. and Riksen, N.P. (2019) Aldosterone Induces Trained Immunity: The Role of Fatty Acid Synthesis. *Cardiovascular Research*, **116**, 317-328. https://doi.org/10.1093/cvr/cvz137

[36] Bahrar, H., Bekkering, S., Stienstra, R., Netea, M.G. and Riksen, N.P. (2023) Innate Immune Memory in Cardiometabolic Disease. *Cardiovascular Research*, **119**, 2774-2786. https://doi.org/10.1093/cvr/cvad030

[37] Luna, E. and Ton, J. (2012) The Epigenetic Machinery Controlling Transgenerational Systemic Acquired Resistance. *Plant Signaling & Behavior*, **7**, 615-618. https://doi.org/10.4161/psb.20155

[38] Kachroo, A. and Robin, G.P. (2013) Systemic Signaling during Plant Defense. *Current Opinion in Plant Biology*, **16**, 527-533. https://doi.org/10.1016/j.pbi.2013.06.019

[39] Quintin, J., Saeed, S., Martens, J.H.A., Giamarellos-Bourboulis, E.J., Ifrim, D.C., Logie, C., *et al*. (2012) Candida Albicans Infection Affords Protection against Reinfection via Functional Reprogramming of Monocytes. *Cell Host & Microbe*, **12**, 223-232. https://doi.org/10.1016/j.chom.2012.06.006

[40] Saeed, S., Quintin, J., Kerstens, H.H.D., Rao, N.A., Aghajanirefah, A., Matarese, F., *et al*. (2014) Epigenetic Programming of Monocyte-to-Macrophage Differentiation and Trained Innate Immunity. *Science*, **345**, Article 1251086. https://doi.org/10.1126/science.1251086

[41] Di Luzio, N.R. and Williams, D.L. (1978) Protective Effect of Glucan against Systemic Staphylococcus Aureus Septicemia in Normal and Leukemic Mice. *Infection and Immunity*, **20**, 804-810. https://doi.org/10.1128/iai.20.3.804-810.1978

[42] Foster, S.L., Hargreaves, D.C. and Medzhitov, R. (2007) Gene-Specific Control of Inflammation by TLR-Induced Chromatin Modifications. *Nature*, **447**, 972-978. https://doi.org/10.1038/nature05836

[43] Yoshida, K., Maekawa, T., Zhu, Y., Renard-Guillet, C., Chatton, B., Inoue, K., *et al*. (2015) The Transcription Factor ATF7 Mediates Lipopolysaccharide-Induced Epigenetic Changes in Macrophages Involved in Innate Immunological Memory. *Nature Immunology*, **16**, 1034-1043. https://doi.org/10.1038/ni.3257

[44] van't Wout, J.W., Poell, R. and van Furth, R. (1992) The Role of BCG/PPD-Activated Macrophages in Resistance against Systemic Candidiasis in Mice. *Scandinavian Journal of Immunology*, **36**, 713-720. https://doi.org/10.1111/j.1365-3083.1992.tb03132.x

[45] Kleinnijenhuis, J., Quintin, J., Preijers, F., Joosten, L.A.B., Ifrim, D.C., Saeed, S., *et al*. (2012) Bacille Calmette-Guérin Induces NOD2-Dependent Nonspecific Protection from Reinfection via Epigenetic Reprogramming of Monocytes. *Proceedings of the National Academy of Sciences*, **109**, 17537-17542. https://doi.org/10.1073/pnas.1202870109

[46] Vecchiarelli, A., Cenci, E., Puliti, M., Blasi, E., Puccetti, P., Cassone, A., *et al*. (1989) Protective Immunity Induced by Low-Virulence Candida Albicans: Cytokine Production in the Development of the Anti-Infectious State. *Cellular Immunology*, **124**, 334-344. https://doi.org/10.1016/0008-8749(89)90135-4

[47] Brasacchio, D., Okabe, J., Tikellis, C., Balcerczyk, A., George, P., Baker, E.K., *et al*. (2009) Hyperglycemia Induces a Dynamic Cooperativity of Histone Methylase and Demethylase Enzymes Associated with Gene-Activating Epigenetic Marks That Coexist on the Lysine Tail. *Diabetes*, **58**, 1229-1236. https://doi.org/10.2337/db08-1666

[48] Sun, J.C., Madera, S., Bezman, N.A., Beilke, J.N., Kaplan, M.H. and Lanier, L.L. (2012) Proinflammatory Cytokine Signaling Required for the Generation of Natural Killer Cell Memory. *Journal of Experimental Medicine*, **209**, 947-954. https://doi.org/10.1084/jem.20111760

[49] Nabekura, T., Kanaya, M., Shibuya, A., Fu, G., Gascoigne, N.R.J. and Lanier, L.L. (2014) Costimulatory Molecule DNAM-1 Is Essential for Optimal Differentiation of Memory Natural Killer Cells during Mouse Cytomegalovirus Infection. *Immunity*, **40**, 225-234. https://doi.org/10.1016/j.immuni.2013.12.011

[50] O'Sullivan, T.E., Johnson, L.R., Kang, H.H. and Sun, J.C. (2015) BNIP3- and BNIP3L-Mediated Mitophagy Promotes the Generation of Natural Killer Cell Memory. *Immunity*, **43**, 331-342. https://doi.org/10.1016/j.immuni.2015.07.012

[51] Lee, J., Zhang, T., Hwang, I., Kim, A., Nitschke, L., Kim, M., *et al*. (2015) Epigenetic Modification and Antibody-Dependent Expansion of Memory-Like NK Cells in Human Cytomegalovirus-Infected Individuals. *Immunity*, **42**, 431-442. https://doi.org/10.1016/j.immuni.2015.02.013

[52] Bekkering, S., Quintin, J., Joosten, L.A.B., van der Meer, J.W.M., Netea, M.G. and Riksen, N.P. (2014) Oxidized Low-Density Lipoprotein Induces Long-Term Proinflammatory Cytokine Production and Foam Cell Formation via Epigenetic Reprogramming of Monocytes. *Arteriosclerosis*, *Thrombosis*, *and Vascular Biology*, **34**, 1731-1738. https://doi.org/10.1161/atvbaha.114.303887

[53] Kleinnijenhuis, J., Quintin, J., Preijers, F., Benn, C.S., Joosten, L.A.B., Jacobs, C., *et al*. (2013) Long-Lasting Effects of BCG Vaccination on Both Heterologous Th1/th17 Responses and Innate Trained Immunity. *Journal of Innate Immunity*, **6**, 152-158. https://doi.org/10.1159/000355628

[54] Jensen, K.J., Larsen, N., Biering-Sørensen, S., Andersen, A., Eriksen, H.B., Monteiro, I., *et al*. (2014) Heterologous Immunological Effects of Early BCG Vaccination in Low-Birth-Weight Infants in Guinea-Bissau: A Randomized-Controlled Trial. *The Journal of Infectious Diseases*, **211**, 956-967. https://doi.org/10.1093/infdis/jiu508

[55] Bekkering, S., Joosten, L.A.B., van der Meer, J.W.M., Netea, M.G. and Riksen, N.P. (2015) The Epigenetic Memory of Monocytes and Macrophages as a Novel Drug Target in Atherosclerosis. *Clinical Therapeutics*, **37**, 914-923. https://doi.org/10.1016/j.clinthera.2015.01.008

[56] Keating, S.T., Groh, L., van der Heijden, C.D.C.C., Rodriguez, H., dos Santos, J.C., Fanucchi, S., *et al*. (2020) The Set7 Lysine Methyltransferase Regulates Plasticity in Oxidative Phosphorylation Necessary for Trained Immunity Induced by B-glucan. *Cell Reports*, **31**, 107548. https://doi.org/10.1016/j.celrep.2020.107548

[57] Ifrim, D.C., Quintin, J., Meerstein-Kessel, L., Plantinga, T.S., Joosten, L.A.B., van der Meer, J.W.M., *et al*. (2015) Defective Trained Immunity in Patients with Stat-1-Dependent Chronic Mucocutaneaous Candidiasis. *Clinical and Experimental Immunology*, **181**, 434-440. https://doi.org/10.1111/cei.12642

[58] Monticelli, S. and Natoli, G. (2013) Short-term Memory of Danger Signals and Environmental Stimuli in Immune Cells. *Nature Immunology*, **14**, 777-784. https://doi.org/10.1038/ni.2636

[59] O'Connell, R.M., Chaudhuri, A.A., Rao, D.S. and Baltimore, D. (2009) Inositol Phosphatase SHIP1 Is a Primary Target of miR-155. *Proceedings of the National Academy of Sciences*, **106**, 7113-7118. https://doi.org/10.1073/pnas.0902636106

[60] dos Santos, J.C., Barroso de Figueiredo, A.M., Teodoro Silva, M.V., Cirovic, B., de Bree, L.C.J., Damen, M.S.M.A., *et al*. (2019) β-Glucan-Induced Trained Immunity Protects against Leishmania Braziliensis Infection: A Crucial Role for Il-32. *Cell Reports*, **28**, 2659-2672.e6. https://doi.org/10.1016/j.celrep.2019.08.004

[61] Cirovic, B., de Bree, L.C.J., Groh, L., Blok, B.A., Chan, J., van der Velden, W.J.F.M., *et al*. (2020) BCG Vaccination in Humans Elicits Trained Immunity via the Hematopoietic Progenitor Compartment. *Cell Host & Microbe*, **28**, 322-334.e5. https://doi.org/10.1016/j.chom.2020.05.014

[62] Kaufmann, E., Sanz, J., Dunn, J.L., Khan, N., Mendonça, L.E., Pacis, A., *et al*. (2018) BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis. *Cell*, **172**, 176-190.e19. https://doi.org/10.1016/j.cell.2017.12.031

[63] Christ, A., Günther, P., Lauterbach, M.A.R., Duewell, P., Biswas, D., Pelka, K., *et al*. (2018) Western Diet Triggers NLRP3-Dependent Innate Immune Reprogramming. *Cell*, **172**, 162-175.e14. https://doi.org/10.1016/j.cell.2017.12.013

[64] Ratter, J.M., van Heck, J.I.P., Rooijackers, H.M.M., Jansen, H.J., van Poppel, P.C.M., Tack, C.J., *et al*. (2021) Insulin Acutely Activates Metabolism of Primary Human Monocytes and Promotes a Proinflammatory Phenotype. *Journal of Leukocyte Biology*, **110**, 885-891. https://doi.org/10.1002/jlb.3ab0120-019rr

[65] Thiem, K., Keating, S.T., Netea, M.G., Riksen, N.P., Tack, C.J., van Diepen, J., *et al*. (2021) Hyperglycemic Memory of Innate Immune Cells Promotes *in Vitro* Proinflammatory Responses of Human Monocytes and Murine Macrophages. *The Journal of Immunology*, **206**, 807-813. https://doi.org/10.4049/jimmunol.1901348

[66] Miao, F., Chen, Z., Genuth, S., Paterson, A., Zhang, L., Wu, X., *et al*. (2014) Evaluating the Role of Epigenetic Histone Modifications in the Metabolic Memory of Type 1 Diabetes. *Diabetes*, **63**, 1748-1762. https://doi.org/10.2337/db13-1251

[67] Shrestha, S., Lee, Y., Lee, H., Choi, Y., Park, B., Kim, M., *et al*. (2024) Diabetes Primes Neutrophils for Neutrophil Extracellular Trap Formation through Trained Immunity. *Research*, **7**, Article No. 0365. https://doi.org/10.34133/research.0365

[68] Nagareddy, P.R., Murphy, A.J., Stirzaker, R.A., Hu, Y., Yu, S., Miller, R.G., *et al*. (2013) Hyperglycemia Promotes Myelopoiesis and Impairs the Resolution of Atherosclerosis. *Cell Metabolism*, **17**, 695-708. https://doi.org/10.1016/j.cmet.2013.04.001

[69] Vinci, M.C., Costantino, S., Damiano, G., Rurali, E., Rinaldi, R., Vigorelli, V., *et al*. (2024) Persistent Epigenetic Signals Propel a Senescence-Associated Secretory Phenotype and Trained Innate Immunity in $CD34^+$ Hematopoietic Stem Cells

from Diabetic Patients. *Cardiovascular Diabetology*, **23**, Article No. 107. https://doi.org/10.1186/s12933-024-02195-1

[70] Bai, Y., Wu, J. and Jian, W. (2025) Trained Immunity in Diabetes: Emerging Targets for Cardiovascular Complications. *Frontiers in Endocrinology*, **16**, Article ID: 1533620. https://doi.org/10.3389/fendo.2025.1533620

[71] Keating, S.T., Groh, L., Thiem, K., Bekkering, S., Li, Y., Matzaraki, V., *et al*. (2020) Rewiring of Glucose Metabolism Defines Trained Immunity Induced by Oxidized Low-Density Lipoprotein. *Journal of Molecular Medicine*, **98**, 819-831. https://doi.org/10.1007/s00109-020-01915-w

[72] Groh, L.A., Ferreira, A.V., Helder, L., van der Heijden, C.D.C.C., Novakovic, B., van de Westerlo, E., *et al*. (2021) Oxldl-Induced Trained Immunity Is Dependent on Mitochondrial Metabolic Reprogramming. *Immunometabolism*, **3**, e210025. https://doi.org/10.20900/immunometab20210025

[73] van der Valk, F.M., Bekkering, S., Kroon, J., Yeang, C., Van den Bossche, J., van Buul, J.D., *et al*. (2016) Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. *Circulation*, **134**, 611-624. https://doi.org/10.1161/circulationaha.116.020838

[74] Caslin, H.L., Cottam, M.A., Piñon, J.M., Boney, L.Y. and Hasty, A.H. (2023) Weight Cycling Induces Innate Immune Memory in Adipose Tissue Macrophages. *Frontiers in Immunology*, **13**, Article ID: 984859. https://doi.org/10.3389/fimmu.2022.984859

[75] Bekkering, S., Stiekema, L.C.A., Bernelot Moens, S., Verweij, S.L., Novakovic, B., Prange, K., *et al*. (2019) Treatment with Statins Does Not Revert Trained Immunity in Patients with Familial Hypercholesterolemia. *Cell Metabolism*, **30**, 1-2. https://doi.org/10.1016/j.cmet.2019.05.014

[76] Stiekema, L.C.A., Willemsen, L., Kaiser, Y., Prange, K.H.M., Wareham, N.J., Boekholdt, S.M., *et al*. (2021) Impact of Cholesterol on Proinflammatory Monocyte Production by the Bone Marrow. *European Heart Journal*, **42**, 4309-4320. https://doi.org/10.1093/eurheartj/ehab465

[77] Li, X., Wang, H., Yu, X., Saha, G., Kalafati, L., Ioannidis, C., *et al*. (2022) Maladaptive Innate Immune Training of Myelopoiesis Links Inflammatory Comorbidities. *Cell*, **185**, 1709-1727.e18. https://doi.org/10.1016/j.cell.2022.03.043

[78] Noz, M.P., Plachokova, A.S., Smeets, E.M.M., Aarntzen, E.H.J.G., Bekkering, S., Vart, P., *et al*. (2021) An Explorative Study on Monocyte Reprogramming in the Context of Periodontitis *in Vitro* and *in Vivo*. *Frontiers in Immunology*, **12**, Article ID: 695227. https://doi.org/10.3389/fimmu.2021.695227

[79] Zhao, Y., Li, Z., Su, L., Ballesteros-Tato, A., Katz, J., Michalek, S.M., *et al*. (2020) Frontline Science: Characterization and Regulation of Osteoclast Precursors Following Chronic *Porphyromonas gingivalis* Infection. *Journal of Leukocyte Biology*, **108**, 1037-1050. https://doi.org/10.1002/jlb.1hi0620-230r

[80] Cai, X., Li, Z., Zhao, Y., Katz, J., Michalek, S.M., Feng, X., *et al*. (2020) Enhanced Dual Function of Osteoclast Precursors Following Calvarial *porphyromonas Gingivalis* Infection. *Journal of Periodontal Research*, **55**, 410-425. https://doi.org/10.1111/jre.12725

[81] Su, L., Xu, Q., Zhang, P., Michalek, S.M. and Katz, J. (2017) Phenotype and Function of Myeloid-Derived Suppressor Cells Induced by Porphyromonas Gingivalis Infection. *Infection and Immunity*, **85**, e00213-17. https://doi.org/10.1128/iai.00213-17

[82] Wang, J., Zhou, Y., Ren, B., Zou, L., He, B. and Li, M. (2021) The Role of Neutrophil Extracellular Traps in Periodontitis. *Frontiers in Cellular and Infection Microbiology*, **11**, Article ID: 639144. https://doi.org/10.3389/fcimb.2021.639144

[83] Gao, Y., Zhang, J., Liu, Z., Ma, K., Lin, X., Zhang, J., *et al*. (2022) Extracellular Trap Can Be Trained as a Memory Response. *Virulence*, **13**, 471-482. https://doi.org/10.1080/21505594.2022.2046950

[84] Hamam, H., Khan, M. and Palaniyar, N. (2019) Histone Acetylation Promotes Neutrophil Extracellular Trap Formation. *Biomolecules*, **9**, Article 32. https://doi.org/10.3390/biom9010032

[85] Ishai, A., Osborne, M.T., El Kholy, K., Takx, R.A.P., Ali, A., Yuan, N., *et al*. (2019) Periodontal Disease Associates with Arterial Inflammation via Potentiation of a Hematopoietic-Arterial Axis. *JACC*: *Cardiovascular Imaging*, **12**, 2271-2273. https://doi.org/10.1016/j.jcmg.2019.05.015

[86] Liu, Y., Lei, Y., Dai, Z., Luo, C., Gong, Q., Li, Y., *et al*. (2025) Trained Immunity: Novel Perspectives in Diabetes and Associated Complications. *Frontiers in Immunology*, **16**, Article ID: 1613602. https://doi.org/10.3389/fimmu.2025.1613602

[87] Jurdziński, K.T., Potempa, J. and Grabiec, A.M. (2020) Epigenetic Regulation of Inflammation in Periodontitis: Cellular Mechanisms and Therapeutic Potential. *Clinical Epigenetics*, **12**, Article No. 186. https://doi.org/10.1186/s13148-020-00982-7