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· 综述 ·

昼夜节律紊乱对牙周炎的影响及机制研究进展

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【摘要】 牙周炎是最常见的口腔疾病之一,是由菌斑微生物与宿主免疫系统间复杂的相互作用所致的慢性炎症性疾病,严重影响身心健康和生活质量。近 30 年来,我国牙周炎的负担呈上升趋势,且预计在未来 25 年牙周炎的发病率也可能呈不断上升趋势。吸烟、糖尿病、免疫水平、遗传因素、压力和年龄等多种因素都会影响牙周炎的发病率,增加患病风险。昼夜节律与牙周组织稳态密切相关,调节牙周组织对外界损伤的敏感性及其修复能力。在正常的昼夜节律下,牙周组织可以有效抵御外界引起的损伤,并促进受损细胞的修复。然而,当昼夜节律紊乱时,牙周组织的自我保护和修复机制受损,就会导致损伤不断积累。昼夜节律紊乱对牙周组织的影响是多因素的,可以通过调节炎症反应、氧化应激和 DNA 损伤修复影响牙周组织的自我保护和修复机制。目前,昼夜节律紊乱加重牙周炎的发病机制尚未明确。本文就昼夜节律紊乱对牙周炎的影响及可能机制进行综述,为进一步阐明两者的关系提供证据。

【关键词】 昼夜节律; 生物钟; 昼夜节律紊乱; 转录翻译反馈环路; 牙周组织; 牙周炎; 氧化应激; 免疫反应; DNA 损伤修复

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Research progress on the impact and mechanisms of circadian rhythm disorders on periodontitis ZHANG Yuxin, JIN Luyuan. Department of General Dentistry and Integrated Emergency Dental Care, Beijing Stomatological Hospital, Capital Medical University, Beijing 100050, China

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【Abstract】 Periodontitis is one of the most common oral diseases and is characterised by a chronic inflammatory disorder caused by the complex interaction between microbial plaque and the host immune system. It significantly affects both physical and mental health as well as quality of life. Over the past 30 years, the burden of periodontitis in China has been rising, and it is expected that the incidence of periodontal disease will continue to increase over the next 25 years. Various factors, such as smoking, diabetes, immune levels, genetic predisposition, stress, and age, can influence the incidence of periodontitis and increase the risk of periodontitis. Circadian rhythms are closely related to the homeostasis of periodontal tissues, regulating their sensitivity to external injuries and their ability to repair. Under normal circadian rhythms, periodontal tissues can effectively resist external damage and promote the repair of damaged cells. However, when circadian rhythm disorders occur, the self-protection and repair mechanisms of periodontal tissues are impaired, leading the accumulation of continuous damage. The impact of circadian rhythm disorders on periodontal tissues is multifactorial, influencing the self-protection and repair mechanisms through regulation of inflammatory response, oxidative stress, and DNA damage repair, thereby promoting the onset and progression of periodontitis. Currently, the exact mechanisms by which circadian rhythm disorders exacerbate periodontitis remain unclear. This article reviews the effects of circadian rhythm disorders on periodontitis and possible mechanisms, providing evidence to fur-



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ther clarify their relationship.

【Key words】 circadian rhythm; circadian clock; circadian rhythm disorder; transcriptional-translational feedback loop; periodontal tissue; periodontitis; oxidative stress; immune response; DNA damage repair

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牙周炎作为全球最常见的慢性炎症性疾病之一,以牙周支持组织进行性破坏为特征,其发病机制与宿主免疫失调、病原微生物侵袭及局部氧化应激等多因素有关^[1]。牙周炎还与心脑血管疾病、糖尿病、慢性肾病、呼吸系统疾病、阿尔茨海默病等全身疾病密切相关^[2]。2019 年,全球约有 11 亿例重度牙周炎患者,患病率达到 17%^[3]。近 30 年来,我国牙周炎发病率呈上升趋势,且预计在未来 25 年牙周炎的发病率也可能呈不断上升趋势^[4]。牙周病的发生发展及其所致影响需要得到更多的重视。

近年研究发现,轮班工作、睡眠障碍等导致的昼夜节律紊乱与牙周炎等慢性炎症性疾病风险升高显著相关^[5]。昼夜节律紊乱对牙周炎的影响机制涉及多层面交互作用,包括时钟基因对宿主免疫的调控^[6-7]、微生物组的昼夜波动^[8]及骨重塑失衡^[9]等。尽管相关研究逐渐增多,昼夜节律调控牙周炎的具体分子机制仍未完全阐明,且昼夜节律干预在牙周治疗中的应用潜力尚待探索。笔者对昼夜节律紊乱影响牙周炎的流行病学证据及其潜在作用机制进行了阐述,旨在为基于昼夜节律的个性化口腔疾病防治提供参考。

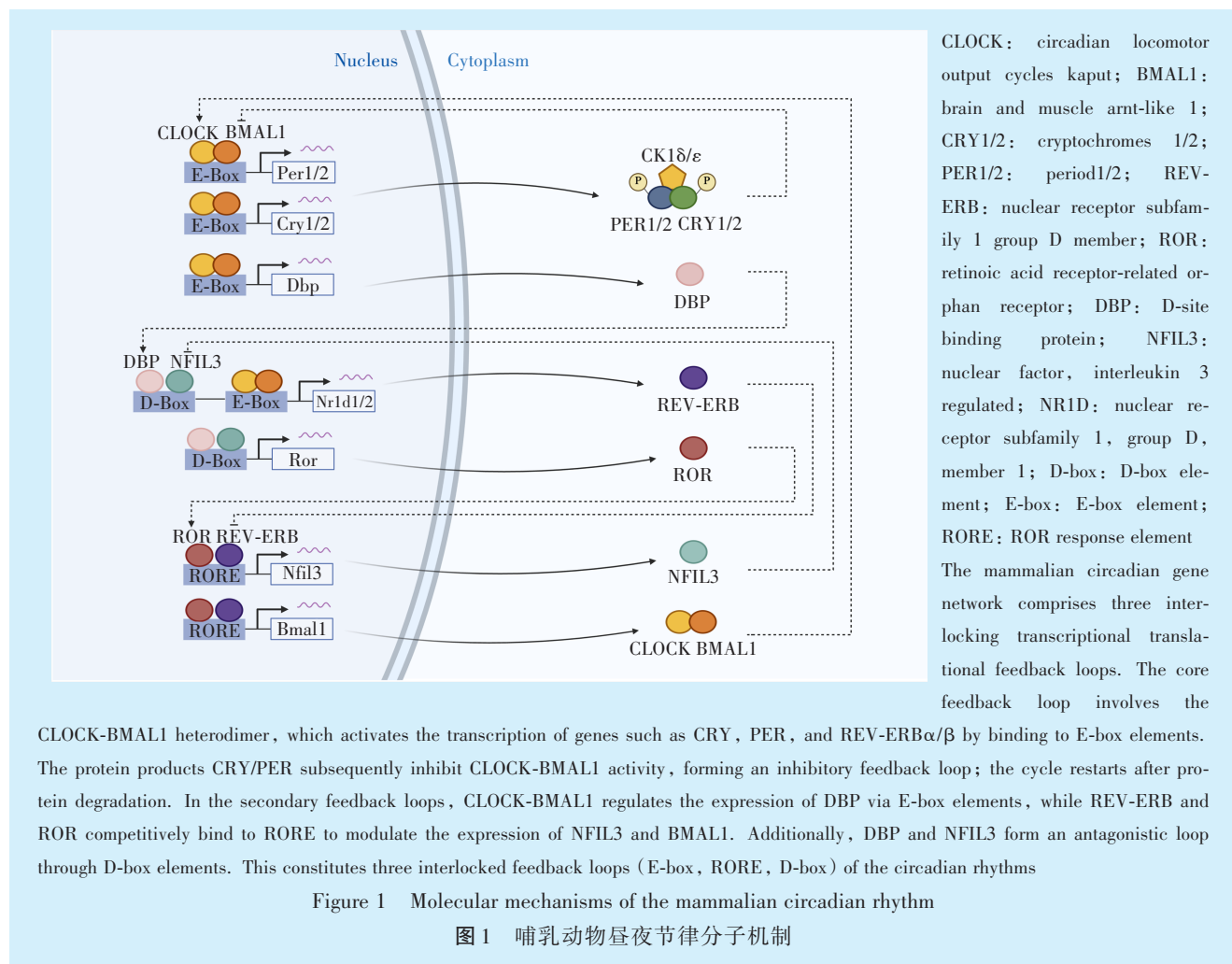
1 昼夜节律

由于地球自转会产生昼夜交替,为了适应相关环境、温度等周期性变化,哺乳动物衍生出一种内在自主计时机制称为昼夜节律(circadian rhythm),又称为生物钟(circadian clock),其周期约为 24 h。正常的生物节律是保障各项生理功能的必要因素,当遗传因素和/或环境因素改变时,例如不适当的光照、睡眠限制、时差、轮班工作、不规则的食物摄入,就可以打破这种平衡,从而引起多种疾病的发生,包括癌症、糖尿病、心血管疾病、内分泌疾病、炎症、精神障碍、免疫系统改变和生殖障碍等^[10-11]。昼夜节律调控人体各种生理活动的过程,包括输入和输出,主要是视网膜接收光信号

后,通过视神经将环境信号传递给调控中枢,随即将节律信号转换成神经信号或内分泌信号传递到外周器官或组织,由此参与机体的各项生理活动。调控昼夜节律的核心时钟位于下丘脑视交叉上核(suprachiasmatic nucleus, SCN)的中枢系统,周围时钟存在于外周器官组织内^[12]。调控这一过程分子机制依赖于自身的转录翻译反馈环路(transcriptional-translational feedback loop, TTFL)^[13]。核心基因由昼夜节律输出周期终止基因(circadian locomotor output cycles kaput, Clock)、脑和肌肉 ARNT 样蛋白 1(brain and muscle arnt-like 1, Bmal1)、隐花色素(cryptochromes, Cry)(包括 Cry1/2),周期基因(period, Per)(包括 Per1/2/3),核受体家族 1 组 D 成员(nuclear receptor subfamily 1, group D member, Rev-erb)(包括 Rev-erb α/β),维甲酸相关孤儿受体(retinoic acid receptor-related orphan receptor, Ror)(包括 Ror $\alpha/\beta/\gamma$)等组成。它们共同发挥作用,产生大约每 24 h 重复 1 次的基因表达节律。哺乳动物的昼夜节律基因网络由 3 个互锁的转录反馈环路组成。E-box 元件(E-box element)介导的核心反馈环路位于两个次级互锁反馈环路的上游。具体而言,CLOCK 和 BMAL1 蛋白形成异源二聚体,与 DNA 上的 E-box 元件结合,激活含 E-box 元件的基因转录,其中包含 Cry、Per、Rev-erb α/β 等昼夜节律基因^[14]。Cry、Per 翻译后的蛋白质抑制 BMAL1 复合物的转录活性,形成抑制性反馈回路。之后 CRY 和 PER 蛋白被降解,抑制作用减弱,重新开始转录激活。除了核心反馈环路之外,CLOCK-BMAL1 复合物还与核激素受体 REV-ERB α/β 和 ROR $\alpha/\beta/\gamma$ 以及 DNA 结合蛋白(D-site binding protein, DBP)和白细胞介素 3 调控的核因子(nuclear factor, interleukin 3 regulated, Nfil3)一起参与另外两个次级反馈环路,形成三个互锁反馈环路的转录网络。CLOCK 和 BMAL1 调节核受体亚家族 1, 组 D, 成员 1(nuclear receptor subfamily 1, group D, member 1, Nr1d1)(包括

Nr1d1/2) 基因的表达, 这些基因分别编码核受体 REV-ERB α/β 。在第一个次级互锁环中, REV-ERB α/β 和激活物 RAR 相关孤儿受体 (relational operator replacement, ROR) 由 CLOCK-BMAL1 通过 E-box 元件转录激活, 然后通过其启动子中的 RORE 元件 (ROR response element, RORE) 反馈调控 Clock 和 Bmal1 的转录。在第二个互锁环中, CLOCK-BMAL1 通过 E-box 元件直接激活转录激活因子 DBP 的表达, 然后 DBP 通过 D-box 元件

(D-box element) 促进 ROR 的表达。通过 RORE 元件, REV-ERB 和 ROR 控制 Nfil3 的转录, 其编码的蛋白质产物 NFIL3 通过 D-box 元件与 ROR α/β 形成负反馈环^[15] (图 1)。总体而言, CLOCK-BMAL1 通过 E-box 元件介导节律性转录激活, REV-ERB 和 ROR 在 RORE 元件处的竞争性结合、DBP 和 NFIL3 在 D-box 元件处的竞争性结合, 这三个连锁的转录反馈环调节大多数基因, 影响包括睡眠、代谢和衰老等多个方面。



CLOCK-BMAL1 heterodimer, which activates the transcription of genes such as CRY, PER, and REV-ERB α/β by binding to E-box elements. The protein products CRY/PER subsequently inhibit CLOCK-BMAL1 activity, forming an inhibitory feedback loop; the cycle restarts after protein degradation. In the secondary feedback loops, CLOCK-BMAL1 regulates the expression of DBP via E-box elements, while REV-ERB and ROR competitively bind to RORE to modulate the expression of NFIL3 and BMAL1. Additionally, DBP and NFIL3 form an antagonistic loop through D-box elements. This constitutes three interlocking feedback loops (E-box, RORE, D-box) of the circadian rhythms

2 昼夜节律与牙周组织

牙周组织由牙龈、牙周膜、牙槽骨、牙骨质组成。牙周组织的生理状态活动呈现出明显的昼夜节律。一方面, 牙周组织中可发现昼夜节律相关基因 Bmal1、Crys 和 Pers 等的节律性表达^[9], 此外, 牙周组织骨形成相关基因如骨钙素、骨桥蛋白、骨膜素、Runt 相关转录因子 2 (runt-related transcription factor 2, RUNX2) 的表达也具有昼夜节律^[16]。牙周膜成纤维细胞中骨保护素 (osteoprotegerin,

OPG)/细胞核因子 κ B 受体活化因子配基 (receptor activator of nuclear factor- κ B ligand, RANKL) 系统受 BMAL1 相关昼夜节律影响^[17]。肿瘤增殖抗原 (Ki67) 的表达受昼夜节律调控, Ki67 表达的失调可能导致过度增殖和肿瘤发展^[18]。另外, 受缺氧诱导因子 (hypoxia inducible factor, HIF) 调控的血管内皮生长因子 (vascular endothelial growth factor, VEGF) 的表达也体现出昼夜节律性^[19]。同时还发现, 节律基因表达改变也会引起牙周组织的变化。

如Bmal1基因敲除小鼠的牙槽间隔骨密度降低,牙槽间隔骨吸收速度增加^[9]。

唾液和龈沟液是牙周微生态的一部分,起着分泌、消化、营养、缓冲等作用。唾液流速以及钠、钾、镁、氯化物和无机磷酸盐的浓度也存在昼夜节律变化^[20]。人唾液中的白细胞介素1 β (interleukin-1 β , IL-1 β)和肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)作为炎症标志物,也受到昼夜节律基因的调节^[6],唾液中最重要消化酶之一唾液淀粉酶(salivary alpha-amylase, SAA)也存在昼夜波动^[21],免疫球蛋白A(immunoglobulin A, IgA)的分泌也表现出昼夜节律依赖性。皮质醇作为牙周破坏相关的标志物,在唾液中的水平也表现出昼夜变化,皮质醇的分泌在早晨达到峰值,而在夜晚水平较低^[22]。褪黑素是松果体和其他器官合成和分泌的一种内源性昼夜节律控制激素,24%~33%的血浆褪黑激素通过唾液分泌进入口腔^[23]。在健康个体中,褪黑素主要在凌晨12点~2点分泌,在白天降至最低^[24]。褪黑素已被证实具有抗氧化和抗炎作用,在骨形成和减少骨吸收中起着重要作用^[25]。唾液、血浆和龈沟液中的褪黑素水平与牙周组织的健康程度密切相关。

3 昼夜节律与牙周炎

3.1 昼夜节律紊乱与牙周炎

昼夜节律与牙周组织稳态密切相关,调节牙周组织对外界损伤的敏感性及其修复能力。在正常的昼夜节律下,牙周组织可以有效抵御外界引起的损伤,并促进受损细胞的修复。当昼夜节律被打乱时,牙周组织的自我保护和修复机制受损,就会导致损伤不断积累^[26]。现代生活改变了人们农耕时代以来建立起来的作息时间表,一些现代文明社会所独有的药物、酒精、人工照明、夜班、旅行时差等生活因素,都可以导致昼夜节律紊乱。研究表明,轮班工作引起的睡眠模式改变会增加牙周炎的患病风险^[27],也有研究表明睡眠时间过短(≤ 5 h)或过度也会显著增加牙周炎的风险^[28],压力和睡眠质量差会对牙周炎的患病率及严重程度产生成倍的影响^[29-30]。儿童的睡眠方式也与其牙周状态有关^[31]。然而,昼夜节律紊乱加重牙周炎的确切发病机制仍尚未明确。

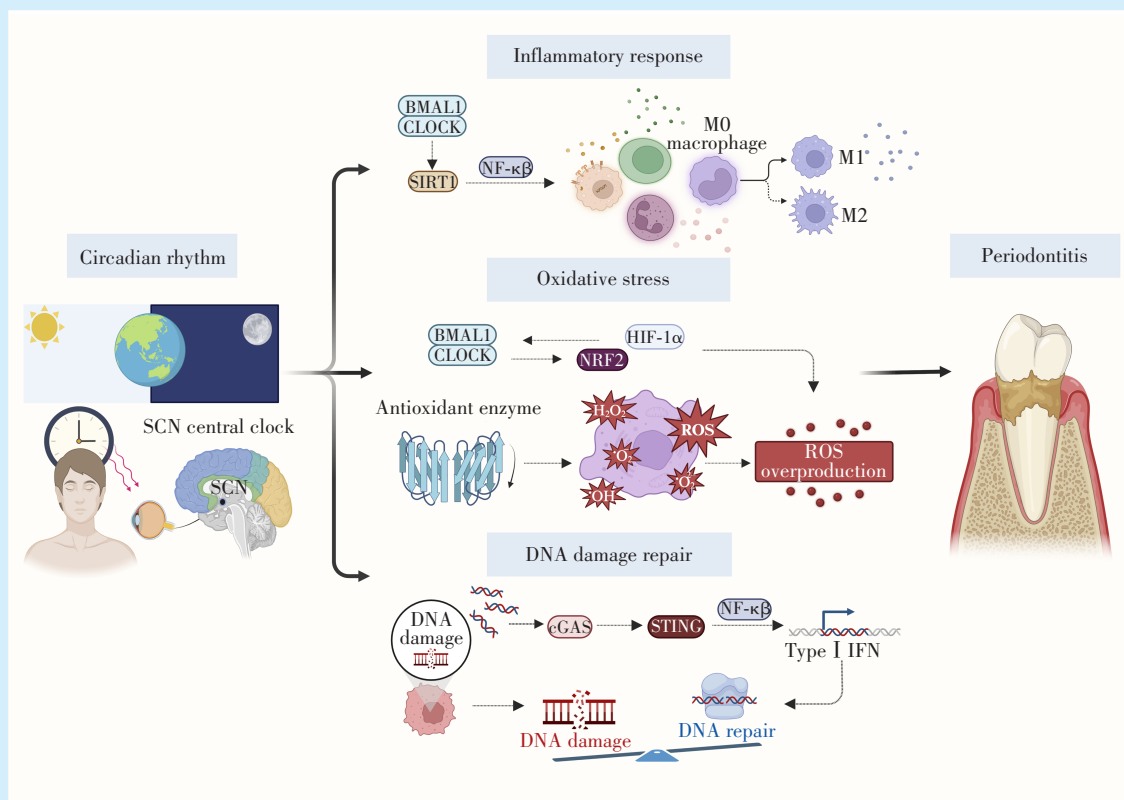
3.2 昼夜节律紊乱影响牙周炎进展的机制

牙槽骨代谢的稳态与昼夜节律息息相关。当熬夜、倒时差、轮班工作所致的昼夜节律紊乱时,

会导致机体激素分泌的节律和水平发生显著改变。牙槽骨的改建受局部炎症情况和全身激素水平共同影响。光信号作为内源性时钟最主要的刺激因素,可以调控SCN时钟基因的表达,并使SCN节律信息通过各种类型的输出(包括神经元连接,内分泌信号和体温节奏)传输到其他周围组织。褪黑素作为光周期的信使,由褪黑素受体(melatonin receptor, MT)介导对靶组织的反应。这些受体分布在大脑以及包括牙周组织在内的周围组织中。牙周炎患者的褪黑素水平降低,且与牙周炎的严重程度密切相关^[24,32]。褪黑素可以抑制促炎因子IL-1 β 和TNF- α 的释放,还可以通过减少RANKL的合成、增加OPG的合成来促进成骨细胞的形成,减少骨吸收^[33],对维持牙周组织牙槽骨代谢稳态有着重要作用。提前给予牙周炎大鼠褪黑素,其炎症因子水平、骨吸收的程度、骨强度均会恢复到接近正常的水平^[34]。糖皮质激素在SCN向外周破骨细胞传递昼夜节律信号的过程中起着关键作用,控制骨吸收的昼夜节律。唾液皮质醇的昼夜节律可能与侵袭性牙周疾病相关^[35]。

昼夜节律的破坏通常会导致睡眠周期、激素和体温的变化。当激素水平失衡,其对代谢、生长及免疫反应的调节也受到影响。褪黑素、皮质醇、糖皮质激素都会影响机体免疫水平,这进一步导致炎症反应加重,而炎症又会加剧氧化应激和DNA损伤。活性氧(reactive oxygen species, ROS)可以与DNA反应,并损害嘌呤和嘧啶碱或脱氧核糖主链^[36]。总体而言,昼夜节律紊乱对牙周炎的影响是多因素的,通过调节炎症反应、氧化应激和DNA损伤修复促进了牙周炎的发生和发展(图2)。

3.2.1 昼夜节律紊乱加重牙周组织炎症反应水平 昼夜节律紊乱会改变唾液、龈沟液的成分。夜间睡眠时间减少会改变炎症因子如白细胞介素6(interleukin-6, IL-6)分泌的昼夜节律,导致夜间IL-6水平降低,白天IL-6水平升高^[37]。IL-6可以激活下丘脑-垂体-肾上腺(hypothalamus-pituitary-adrenal, HPA)轴,调节促肾上腺皮质激素释放激素的分泌,影响皮质醇的分泌节律^[38]。节律紊乱的工人唾液和龈沟液中的炎症因子TNF- α 、IL-6水平较高^[39],IL-6、TNF- α 水平升高加速牙龈附着丧失和牙周袋的形成。其分子机制的关键靶点可能是BMAL1与核转录因子(nuclear transcription factor- κ B, NF- κ B)之间的相互作用。Bmal1和Clock基因通过调控沉默调节蛋白1(recombinant sirtuin 1,



The impact of circadian rhythm disruption on periodontitis is multifactorial, promoting the onset and progression of the disease through three primary mechanisms: exacerbating inflammatory response levels in periodontal tissues, aggravating oxidative stress levels in periodontal tissues, and disrupting the balance of DNA damage repair in periodontal tissues. SCN: suprachiasmatic nucleus; CLOCK: circadian locomotor output cycles kaput; BMAL1: brain and muscle arnt-like 1; HIF-1 α : hypoxia inducible factor- 1 α ; NRF2: nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; IFN-I: type I interferons; NF- κ B, nuclear transcription factor- κ B

Figure 2 The mechanisms by which circadian rhythm disruption affects periodontitis progression

图2 昼夜节律紊乱影响牙周炎进展的机制

SIRT1)参与先天免疫系统的调节过程,当生物体出现昼夜节律紊乱时,会引发SIRT1与烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD)之间的解离作用^[40-41],进而增强NF- κ B转录因子的转录活性,介导牙周病发病相关的促炎细胞因子释放,同时,激活的NF- κ B途径会抑制BMAL1的表达,进一步加剧牙周炎症^[6,42]。

昼夜节律参与细胞周期调控,影响细胞的成熟,几乎所有免疫细胞中都存在昼夜节律。巨噬细胞是关键的先天免疫细胞之一,通过细胞表面的Toll样受体(Toll-like receptors, TLR),诱导一系列信号级联反应,使细胞转入免疫活性状态^[43-44],它与牙周炎的进展息息相关。巨噬细胞表面TLR及其下游信号通路受昼夜节律调控^[45]。昼夜节律基因Bmal1、Per1、Per2的缺失可以影响巨噬细胞的极化,使其表现为M1促炎表型^[46]。昼夜节律紊乱

可以促进巨噬细胞中的关键因子赖氨酸特异性去甲基酶6A(lysine-specific demethylase 6A, Kdm6a)的表达加重牙周炎^[47]。BMAL1通过调控NR1D1抑制NLR家族Pyrin域蛋白3(NLR Family, pyrin domain containing protein 3, NLRP3)炎症小体信号通路,同时直接结合焦孔素D(gasdermin D, GSDMD)启动子的E-box元件抑制其转录,从而调控GSDMD介导的细胞焦亡。GSDMD介导的焦亡加速了牙周炎进展,而昼夜节律紊乱下BMAL1的进一步下调通过增强GSDMD活性加剧了牙周组织破坏^[48]。

3.2.2 昼夜节律紊乱加剧牙周组织氧化应激水平 氧化应激(oxidative stress, OS)是由于内源性或外源性刺激使机体ROS产生过多和/或清除较少,引起组织细胞氧化损伤的反应^[49]。氧化应激状态是指机体内部的促氧化系统与抗氧化系统功

能之间的动态失衡,其特征是ROS的积累。ROS在牙周炎的发生发展中具有重要作用,牙周炎患者的血清、唾液和龈沟液中ROS及氧化应激水平较健康组增高^[50],且患者的探诊深度、附着水平及出血指数等与龈沟液中活性氧代谢物水平相关^[51-52]。唾液具有强大的抗氧化活性,健康人唾液存在氧化还原水平的平衡。牙周炎患者唾液的抗氧化水平低于健康人,因此无法完全清除一天可能增加的自由基^[53]。在正常的条件下,氧化应激酶包括超氧化物歧化酶(superoxide dismutase, SOD),谷胱甘肽过氧化物酶(glutathione peroxidase, GPX),过氧化氢酶(catalase, CAT),谷胱甘肽还原酶(glutathione reductase, R-GSSG)的活性以及谷胱甘肽(glutathione, GSH)的浓度在凌晨2点达到峰值。说明睡眠期间是维持氧化还原平衡的重要时段,睡眠限制过度氧化应激的形成^[54]。

牙周组织中存在活跃的外周时钟基因, BMAL1、CLOCK以及PER1、PER2被证明可以在牙周膜成纤维细胞及牙龈上皮细胞及颌骨组织中表达。核心时钟基因Clock和Bmal1能通过启动子上的E-BOX元件调控核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, NRF2)及其下游抗氧化应激蛋白的节律性表达,使其发挥抗氧化应激作用;也有研究证实NRF2通过调节BMAL1下游靶点REV-ERB α 的转录间接抑制BMAL1和CLOCK的表达^[55-56]。因此,NRF2和时钟基因组成了一个连锁反应环,将细胞氧化还原信号整合到生物钟节律性变化中。昼夜节律基因通过调节抗氧化应激通路控制ROS表达,当昼夜节律紊乱时,Bmal1表达下调,血清丙二醛(malondialdehyde, MDA)水平和牙周组织中ROS含量升高^[57]。而ROS也可以通过调控增强子Zeste同源物2(enhancer of zeste homolog 2, EZH2)的功能,影响其与昼夜节律核心蛋白CLOCK、BMAL1和PER的相互作用,降低昼夜节律基因的表达进而调控昼夜节律^[58]。昼夜节律基因与缺氧诱导因子-1 α (hypoxia inducible factor-1 α , HIF-1 α)的关联呈现动态变化,HIF-1 α 作为核心缺氧调控因子,在健康状态时与昼夜节律基因表现为负相关,而在牙周炎或疾病状态时部分转为正相关^[59],这也说明牙周炎时正常的调控网络被打乱,局部的缺氧适应受到破坏,两者关系由拮抗转化为异常协同,从而加剧了炎症和骨破坏。

3.2.3 昼夜节律紊乱打破牙周组织DNA损伤修复

的平衡 DNA损伤是指核基因组和线粒体基因组在受到外源性和内源性因素刺激时发生的包括单链断裂、双链断裂、碱基损伤和DNA交联等在内的损伤。DNA损伤在细胞中不断发生,细胞因此进化出DNA损伤修复(DNA damage response, DDR)。DDR从DNA损伤的识别开始,需要多种DNA修复途径的参与,根据DNA损伤的类型和程度,细胞会启动一系列信号通路改变染色质,激活或阻滞细胞检查点,改变转录和翻译来修复DNA损伤^[60]。有临床研究显示,夜班会导致细胞昼夜节律和DNA损伤修复基因之间的失调,改变人类DNA损伤修复的正确时间^[61]。模拟轮班作息显著扰乱了癌症特征相关信号通路基因的昼夜节律表达模式,经模拟夜班条件干预后,机体对内源性及外源性DNA损伤的易感性均呈现显著增强趋势。

DNA损伤的敏感性受到昼夜节律基因的影响。Clock、Bmal1、Cry1/2等昼夜节律基因突变或异常表达可以通过调控损伤识别位点的活性,影响细胞对DNA损伤的敏感性。Clock基因突变小鼠和Bmal1基因敲除小鼠表现为对DNA交联剂环磷酰胺敏感性增加,原因可能是由于检查点过度激活导致损伤积累增加;Cry1/2缺失的小鼠对相同药物则表现出耐药性,这可能与DNA损伤耐受性增强或DNA修复抑制有关^[62]。

DNA修复活动具有昼夜节律性,DNA修复过程在白天更活跃,夜间效率较低^[61]。8-羟基脱氧鸟苷(8-hydroxy-2'-deoxyguanosine, 8-OHdG)是最常使用氧化应激诱导的DNA损伤的生物标志物,人淋巴细胞中的DNA修复酶8-氧鸟嘌呤DNA糖基化酶(8-oxoguanine DNA glycosylase, OGG1)的活性在夜间达到最低,在清晨达到最高,这与DNA损伤标志物8-氧鸟嘌呤(8-oxo-7, 8-dihydroguanine, 8-OXOG)水平的变化相对应^[63]。昼夜节律紊乱小鼠牙周组织中8-OHdG表达水平显著增加^[57]。生物钟协调DNA修复活动以减少氧化损伤对修复酶活性的影响,降低突变风险^[64]。一些昼夜节律蛋白直接参与DNA损伤修复相关通路。时钟周期蛋白2(clock cycle protein 2, CLK-2)通过与ATR-Chk1信号通路中的成分相互作用,影响S期检查点的激活和Chk1的稳定性,当昼夜节律紊乱时会导致Chk1降解加速,引发基因组不稳定性,促进癌症发生^[65];而Per1则与ATM-Chk2通路相关,通过调节Chk2的稳定性和G2/M检查点来调控DNA双链断裂修复效率^[66-67]。这表明,昼夜节律系统不仅调控

日常生理节律,还在维持基因组稳定性和应对DNA损伤中发挥重要作用。

DNA损伤会诱导I型干扰素(type I interferons, IFN-I)和其他炎症因子的表达^[68],通过激活环鸟苷酸-腺苷酸合成酶(cyclic GMP-AMP synthase, cGAS)-干扰素基因刺激因子(stimulator of interferon genes, STING)信号通路,即cGAS-STING通路,造成牙周膜细胞的DNA损伤,cGAS可以调节牙周炎症中的NF- κ B信号通路活化^[69],促进牙周炎的发生。长期非消散性炎症会诱发氧化还原反应,导致线粒体功能紊乱和DNA氧化^[70],进一步导致DNA损伤加重。DNA损伤修复的失调也会影响昼夜节律,沉默信息调节因子1(sirtuin 1, SIRT1)参与昼夜节律调节的转录激活和转录抑制,DNA损伤使多聚ADP核糖聚合酶1[poly(ADP-ribose) polymerase 1, PARP1]通过竞争NAD供应来降低SIRT1活性从而触发SIRT1引起的昼夜节律相位的改变^[71]。

3.3 昼夜节律紊乱与牙周炎相关的全身疾病

昼夜节律与牙周炎相关的全身疾病也存在一定关系。糖尿病是牙周炎的危险因素之一,昼夜节律紊乱会导致胰岛素抵抗^[72]并与2型糖尿病和心血管疾病的发展有关^[73]。昼夜节律紊乱也是骨质疏松症的促进因素,流行病学调查显示,相较于常规日间工作者,轮班制人群表现出更显著的骨密度值下降且骨折风险较高^[74],而骨质疏松者下颌骨密度也较低,但节律紊乱是否会导致牙槽骨骨质疏松还缺乏相关研究。牙周致病菌牙龈卟啉单胞菌可通过激活NF- κ B信号通路,增加氧化反应,加速动脉粥样硬化的形成^[75]。Virto等^[76]研究表明,患有牙周炎的肥胖大鼠褪黑素浓度明显低于单纯肥胖和牙周炎大鼠,说明昼夜节律的关键调控因素褪黑素的缺乏可能是解释肥胖合并牙周炎的关键机制之一。

4 小结

随着现代生活方式的改变,饮食、睡眠不规律、压力、夜间光照等因素都可以使人的生物节律紊乱,增加口腔乃至全身系统性疾病的患病风险。目前,已有不少研究表明昼夜节律与牙周炎之间存在联系。昼夜节律紊乱可以通过调节免疫反应、加重氧化应激、干扰DNA损伤修复等多方面加重牙周炎症状况。也有研究表明睡眠时间与牙周炎两者之间没有显著关系。Zhou等^[77]研究发现短

睡眠与牙齿脱落和牙周炎的风险均无关。Han等^[78]研究显示,女性群体中,牙周炎患病风险随睡眠时间延长而增加,睡眠 ≥ 9 h的女性牙周炎患病率更高。Park等^[27]研究表明睡眠持续时间 ≤ 5 h或 ≥ 9 h的轮班工作人员患牙周炎风险较高,但在睡眠时间 ≤ 5 h或 ≥ 9 h的白班工人中没有观察到。Han等^[79]报告的显示,白天睡觉的人会增加牙周炎的风险。这提示或许睡眠节律对牙周炎的影响比睡眠时间更大,但尚未有相关的文献论证。在数据分析过程中,也需要考虑多种因素对研究结果的影响,包括关于对睡眠时长的定义,研究对象的选择,不同年龄、种族、生活习惯等因素是否对结果有不同的影响。

综上所述,目前昼夜节律对牙周炎的影响及其机制还有待研究,昼夜节律在临床前和临床治疗中的功能转化还需要进一步探索,由于研究中疾病模型通常是夜行性的啮齿类动物,与昼行性的人类存在差别,加上生物节律系统反馈调节分子网络的复杂性,使临床转化受到一定的阻碍。小鼠是研究哺乳动物昼夜节律的有价值的模型动物,但有研究表明夜间急性光照能够促进小鼠的快速眼动睡眠和非快速眼动睡眠^[80]。目前常用的昼夜节律紊乱动物模型构建方式主要包括核心昼夜节律基因敲除的干预模型、光照位移诱导昼夜节律紊乱模型、改变食物种类诱导昼夜节律紊乱模型以及改变进食行为影响昼夜节律紊乱模型等造模方式^[69]。因此,未来在动物实验模型构建过程中需要不断优化,同时,也需要更多基础实验和临床试验相结合来推动其发展。当对生物节律的研究不断深入,未来临床上或许可以通过纠正饮食、睡眠不规律等不良生活习惯来预防牙周炎,利用小分子药物或基因治疗等措施有效改善牙周炎、促进骨发育。同时,可以通过选择适宜的给药时间和药物类型,来有效增加药物的治疗效果。

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参考文献

- [1] Kwon T, Lamster IB, Levin L. Current concepts in the management of periodontitis[J]. *Int Dent J*, 2021, 71(6): 462-476. doi: 10.1111/ijdj.12630.
- [2] Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities[J]. *Nat Rev Immunol*, 2021, 21(7): 426-440. doi: 10.1038/s41577-020-00488-6.

- [3] Cui Y, Tian G, Li R, et al. Epidemiological and sociodemographic transitions of severe periodontitis incidence, prevalence, and disability-adjusted life years for 21 world regions and globally from 1990 to 2019: an age-period-cohort analysis[J]. *J Periodontol*, 2023, 94(2): 193-203. doi: 10.1002/JPER.22-0241.
- [4] 余一鸣, 吴玉莹, 吴雨焯, 等. 我国1990—2019年成人牙周病疾病负担现状分析及牙周病发病趋势预测[J]. *中华口腔医学杂志*, 2023, 58(12): 1265-1272. doi: 10.3760/cma.j.cn112144-20230815-00077.
Yu YM, Wu YY, Wu YX, et al. Situational analysis of periodontal disease burden for adults in China from 1990 to 2019 and its incidence trend prediction[J]. *Chin J Stomatol*, 2023, 58(12): 1265-1272. doi: 10.3760/cma.j.cn112144-20230815-00077.
- [5] Alqaderi H, Goodson JM, Agaku I. Association between sleep and severe periodontitis in a nationally representative adult US population[J]. *J Periodontol*, 2020, 91(6): 767-774. doi: 10.1002/JPER.19-0105.
- [6] Sehirli AO, Chukwunyere U, Aksoy U, et al. The circadian clock gene Bmal1: role in COVID-19 and periodontitis[J]. *Chronobiol Int*, 2021, 38(6): 779-784. doi: 10.1080/07420528.2021.1895198.
- [7] Fortin BM, Pfeiffer SM, Insua-Rodríguez J, et al. Circadian control of tumor immunosuppression affects efficacy of immune checkpoint blockade[J]. *Nat Immunol*, 2024, 25(7): 1257-1269. doi: 10.1038/s41590-024-01859-0.
- [8] Chellappa SL, Engen PA, Naqib A, et al. Proof-of-principle demonstration of endogenous circadian system and circadian misalignment effects on human oral microbiota[J]. *FASEB J*, 2022, 36(1): e22043. doi: 10.1096/fj.202101153R.
- [9] Koshi R, Matsumoto K, Imanishi Y, et al. Morphological characteristics of interalveolar septum and mandible in BMAL1 gene knockout mice[J]. *J Oral Sci*, 2020, 63(1): 83-86. doi: 10.2334/josnusd.20-0403.
- [10] Zhang Z, Li W, Han X, et al. Circadian rhythm disruption-mediated downregulation of Bmal1 exacerbates DSS-induced colitis by impairing intestinal barrier[J]. *Front Immunol*, 2024, 15: 1402395. doi: 10.3389/fimmu.2024.1402395.
- [11] Sinturel F, Gos P, Petrenko V, et al. Circadian hepatocyte clocks keep synchrony in the absence of a master pacemaker in the suprachiasmatic nucleus or other extrahepatic clocks[J]. *Genes Dev*, 2021, 35(5/6): 329-334. doi: 10.1101/gad.346460.120.
- [12] Sato T, Sato S. Circadian regulation of metabolism: commitment to health and diseases[J]. *Endocrinology*, 2023, 164(7): bqad086. doi: 10.1210/endo/bqad086.
- [13] Moeller JS, Bever SR, Finn SL, et al. Circadian regulation of hormonal timing and the pathophysiology of circadian dysregulation[J]. *Compr Physiol*, 2022, 12(4): 4185-4214. doi: 10.1002/cphy.c220018.
- [14] Patke A, Young MW, Axelrod S. Molecular mechanisms and physiological importance of circadian rhythms[J]. *Nat Rev Mol Cell Biol*, 2020, 21(2): 67-84. doi: 10.1038/s41580-019-0179-2.
- [15] Wood SH, Hindle MM, Mizoro Y, et al. Circadian clock mechanism driving mammalian photoperiodism[J]. *Nat Commun*, 2020, 11(1): 4291. doi: 10.1038/s41467-020-18061-z.
- [16] Ye L, Mei G, Liu H, et al. Circadian rhythm disruption aggravates alveolar bone loss in rat apical periodontitis[J]. *Int Endod J*, 2025, 58(5): 744-756. doi: 10.1111/iej.14201.
- [17] Balsalobre A, Marcacci L, Schibler U. Multiple signaling pathways elicit circadian gene expression in cultured Rat-1 fibroblasts[J]. *Curr Biol*, 2000, 10(20): 1291-1294. doi: 10.1016/s0960-9822(00)00758-2.
- [18] He QY, Jin F, Li YY, et al. Prognostic significance of downregulated BMAL1 and upregulated Ki-67 proteins in nasopharyngeal carcinoma[J]. *Chronobiol Int*, 2018, 35(3): 348-357. doi: 10.1080/07420528.2017.1406494.
- [19] Sato F, Sato H, Jin D, et al. Smad3 and Snail show circadian expression in human gingival fibroblasts, human mesenchymal stem cell, and in mouse liver[J]. *Biochem Biophys Res Commun*, 2012, 419(2): 441-446. doi: 10.1016/j.bbrc.2012.02.076.
- [20] Uchida H, Ovitt CE. Novel impacts of saliva with regard to oral health[J]. *J Prosthet Dent*, 2022, 127(3): 383-391. doi: 10.1016/j.prosdent.2021.05.009.
- [21] Thieux M, Guyon A, Seugnet L, et al. Salivary α -amylase as a marker of sleep disorders: a theoretical review[J]. *Sleep Med Rev*, 2024, 74: 101894. doi: 10.1016/j.smrv.2023.101894.
- [22] O'Byrne NA, Yuen F, Butt WZ, et al. Sleep and circadian regulation of cortisol: a short review[J]. *Curr Opin Endocr Metab Res*, 2021, 18: 178-186. doi: 10.1016/j.coemr.2021.03.011.
- [23] Vasey C, McBride J, Penta K. Circadian rhythm dysregulation and restoration: the role of melatonin[J]. *Nutrients*, 2021, 13(10): 3480. doi: 10.3390/nu13103480.
- [24] Ye L, Mei G, Liu H, et al. Circadian rhythm disruption aggravates alveolar bone loss in rat apical periodontitis[J]. *Int Endod J*, 2025, 58(5): 744-756. doi: 10.1111/iej.14201.
- [25] Sold VM, Aguilar JJ, Farias A, et al. Melatonin protects gingival mesenchymal stem cells and promotes differentiation into osteoblasts[J]. *Cell Biochem Funct*, 2022, 40(6): 636-646. doi: 10.1002/cbf.3733.
- [26] Wang C, Barnoud C, Cenerenti M, et al. Dendritic cells direct circadian anti-tumour immune responses[J]. *Nature*, 2023, 614(7946): 136-143. doi: 10.1038/s41586-022-05605-0.
- [27] Park JS, Jeong Y, Jung J, et al. Shift work sleep disorder is closely associated with an increased risk for periodontal disease[J]. *J Clin Periodontol*, 2021, 48(8): 1066-1075. doi: 10.1111/jcpe.13508.
- [28] Zhou Q, Ye F, Zhang S. Sleep duration and risk of periodontitis: a systematic review and meta-analysis[J]. *Int Dent J*, 2024, 74(3): 418-425. doi: 10.1016/j.identj.2024.02.016.
- [29] Iwasaki M, Usui M, Ariyoshi W, et al. Sleep duration and severe periodontitis in middle-aged Japanese workers[J]. *J Clin Periodontol*, 2022, 49(1): 59-66. doi: 10.1111/jcpe.13561.
- [30] Marruganti C, Luthra S, Hussain SB, et al. Healthy lifestyles and better periodontal health: results from two large population-based surveys[J]. *J Periodontol Res*, 2025, 60(2): 144-153. doi: 10.1111/jre.13320.
- [31] Mehdipour A, Abbasi R, Keykha E, et al. The association between dental caries, periodontal status, and sleep patterns in children[J]. *Int J Clin Pediatr Dent*, 2024, 17(8): 925-932. doi: 10.5005/jp-

- journals-10005-2901.
- [32] Wang C, Wang L, Wang X, et al. Beneficial effects of melatonin on periodontitis management: far more than oral cavity[J]. *Int J Mol Sci*, 2022, 23(23): 14541. doi: 10.3390/ijms232314541.
- [33] 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. doi: 10.1002/JPER.18-0748.
- [34] Renn TY, Huang YK, Feng SW, et al. Prophylactic supplement with melatonin successfully suppresses the pathogenesis of periodontitis through normalizing RANKL/OPG ratio and depressing the TLR4/MyD88 signaling pathway[J]. *J Pineal Res*, 2018, 64(3): e12464. doi: 10.1111/jpi.12464.
- [35] Mathew A, Mn P, Menon PK, et al. A clinical study on the circadian rhythm of salivary cortisol on aggressive periodontitis and its correlation with clinical parameters using electrochemiluminescence immunoassay method[J]. *J Contemp Dent Pract*, 2019, 20(4): 482-488.
- [36] Halliwell B, Whiteman M. Measuring reactive species and oxidative damage *in vivo* and in cell culture: how should you do it and what do the results mean?[J]. *Br J Pharmacol*, 2004, 142(2): 231-255. doi: 10.1038/sj.bjp.0705776.
- [37] Zielinski MR, Gibbons AJ. Neuroinflammation, sleep, and circadian rhythms[J]. *Front Cell Infect Microbiol*, 2022, 12: 853096. doi: 10.3389/fcimb.2022.853096.
- [38] Li Y, Androulakis IP. The SCN-HPA-periphery circadian timing system: mathematical modeling of clock synchronization and the effects of photoperiod on jetlag adaptation[J]. *J Biol Rhythms*, 2023, 38(6): 601-616. doi: 10.1177/07487304231188541.
- [39] Roestamadjji RI, Nastiti NI, Surboyo MDC, et al. The risk of night shift workers to the glucose blood levels, saliva, and dental caries [J]. *Eur J Dent*, 2019, 13(3): 323-329. doi: 10.1055/s-0039-1697211.
- [40] Dierickx P, Zhu K, Carpenter BJ, et al. Circadian REV-ERBs repress E4bp4 to activate NAMPT-dependent NAD⁺ biosynthesis and sustain cardiac function[J]. *Nat Cardiovasc Res*, 2022, 1(1): 45-58. doi: 10.1038/s44161-021-00001-9.
- [41] Liu L, Cao Q, Gao W, et al. Melatonin ameliorates cerebral ischemia-reperfusion injury in diabetic mice by enhancing autophagy *via* the SIRT1-BMAL1 pathway[J]. *FASEB J*, 2021, 35(12): e22040. doi: 10.1096/fj.202002718RR.
- [42] Shen Y, Endale M, Wang W, et al. NF- κ B modifies the mammalian circadian clock through interaction with the core clock protein BMAL1[J]. *PLoS Genet*, 2021, 17(11): e1009933. doi: 10.1371/journal.pgen.1009933.
- [43] Owen AM, Luan L, Burelbach KR, et al. MyD88-dependent signaling drives toll-like receptor-induced trained immunity in macrophages[J]. *Front Immunol*, 2022, 13: 1044662. doi: 10.3389/fimmu.2022.1044662.
- [44] Yue Y, Liu X, Li Y, et al. The role of TLR4/MyD88/NF- κ B pathway in periodontitis-induced liver inflammation of rats[J]. *Oral Dis*, 2021, 27(4): 1012-1021. doi: 10.1111/odi.13616.
- [45] Brooks JF 2nd, Behrendt CL, Ruhn KA, et al. The microbiota coordinates diurnal rhythms in innate immunity with the circadian clock[J]. *Cell*, 2021, 184(16): 4154-4167. e12. doi: 10.1016/j.cell.2021.07.001.
- [46] Xu H, Li H, Woo SL, et al. Myeloid cell-specific disruption of Period1 and Period2 exacerbates diet-induced inflammation and insulin resistance[J]. *J Biol Chem*, 2014, 289(23): 16374-16388. doi: 10.1074/jbc.M113.539601.
- [47] Ma X, Chen X, Duan Z, et al. Circadian rhythm disruption exacerbates the progression of macrophage dysfunction and alveolar bone loss in periodontitis[J]. *Int Immunopharmacol*, 2023, 116: 109796. doi: 10.1016/j.intimp.2023.109796.
- [48] Wang Y, Li R, Ye Q, et al. Circadian disruption by simulated shift work aggravates periodontitis *via* orchestrating BMAL1 and GSDMD-mediated pyroptosis[J]. *Int J Oral Sci*, 2025, 17(1): 14. doi: 10.1038/s41368-024-00331-x.
- [49] Jaganjac M, Milkovic L, Zarkovic N, et al. Oxidative stress and regeneration[J]. *Free Radic Biol Med*, 2022, 181: 154-165. doi: 10.1016/j.freeradbiomed.2022.02.004.
- [50] Baltacıoğlu E, Kehribar MA, Yuva P, et al. Total oxidant status and bone resorption biomarkers in serum and gingival crevicular fluid of patients with periodontitis[J]. *J Periodontol*, 2014, 85(2): 317-326. doi: 10.1902/jop.2013.130012.
- [51] Sun X, Ping Y, Li X, et al. Activation of PGC-1 α -dependent mitochondrial biogenesis supports therapeutic effects of silibinin against type I diabetic periodontitis[J]. *J Clin Periodontol*, 2023, 50(7): 964-979. doi: 10.1111/jcpe.13811.
- [52] Martínez-Herrera M, Abad-Jiménez Z, Silvestre FJ, et al. Effect of non-surgical periodontal treatment on oxidative stress markers in leukocytes and their interaction with the endothelium in obese subjects with periodontitis: a pilot study[J]. *J Clin Med*, 2020, 9(7): 2117. doi: 10.3390/jcm9072117.
- [53] Diab R, Choufani A, Dagher J, et al. The influence of circadian rhythm on the antioxidant capacity of saliva in periodontal diseases [J]. *Cureus*, 2024, 16(3): e56174. doi: 10.7759/cureus.56174.
- [54] Budkowska M, Cecerska-Heryć E, Marciniowska Z, et al. The influence of circadian rhythm on the activity of oxidative stress enzymes [J]. *Int J Mol Sci*, 2022, 23(22): 14275. doi: 10.3390/ijms232214275.
- [55] Wang J, Bai Y, Yin S, et al. Circadian clock gene BMAL1 reduces urinary calcium oxalate stones formation by regulating NRF2/HO-1 pathway[J]. *Life Sci*, 2021, 265: 118853. doi: 10.1016/j.lfs.2020.118853.
- [56] Wible RS, Ramanathan C, Sutter CH, et al. NRF2 regulates core and stabilizing circadian clock loops, coupling redox and time-keeping in *mus musculus*[J]. *Elife*, 2018, 7: e31656. doi: 10.7554/eLife.31656.
- [57] Liu X, Cao N, Liu X, et al. Circadian rhythm disorders aggravate periodontitis by modulating BMAL1[J]. *Int J Mol Sci*, 2022, 24(1): 374. doi: 10.3390/ijms24010374.
- [58] Zhang HY, Li KY, Wang YL, et al. ROS regulates circadian rhythms by modulating Ezh2 interactions with clock proteins[J]. *Redox Biol*, 2025, 81: 103526. doi: 10.1016/j.redox.2025.103526.

- [59] Ebersole JL, Gonzalez OA. Mucosal circadian rhythm pathway genes altered by aging and periodontitis[J]. PLoS One, 2022, 17(12): e0275199. doi: 10.1371/journal.pone.0275199.
- [60] Shokrollahi M, Stanic M, Hundal A, et al. DNA double-strand break-capturing nuclear envelope tubules drive DNA repair[J]. Nat Struct Mol Biol, 2024, 31(9): 1319-1330. doi: 10.1038/s41594-024-01286-7.
- [61] Koritala BSC, Porter KI, Arshad OA, et al. Night shift schedule causes circadian dysregulation of DNA repair genes and elevated DNA damage in humans[J]. J Pineal Res, 2021, 70(3): e12726. doi: 10.1111/jpi.12726.
- [62] Gorbacheva VY, Kondratov RV, Zhang R, et al. Circadian sensitivity to the chemotherapeutic agent cyclophosphamide depends on the functional status of the CLOCK/BMAL1 transactivation complex[J]. Proc Natl Acad Sci USA, 2005, 102(9): 3407-3412. doi: 10.1073/pnas.0409897102.
- [63] Manzella N, Bracci M, Strafella E, et al. Circadian modulation of 8-oxoguanine DNA damage repair[J]. Sci Rep, 2015, 5: 13752. doi: 10.1038/srep13752.
- [64] Marri D, Filipovic D, Kana O, et al. Prediction of mammalian tissue-specific CLOCK-BMAL1 binding to E-box DNA motifs[J]. Sci Rep, 2023, 13(1): 7742. doi: 10.1038/s41598-023-34115-w.
- [65] Choi SH, Cho K, Kim ES, et al. Proline-serine-threonine-repeat region of MDC1 mediates Chk1 phosphorylation and the DNA double-strand break repair[J]. Int J Biochem Cell Biol, 2022, 143: 106152. doi: 10.1016/j.biocel.2021.106152.
- [66] Bellet MM, Stincardini C, Costantini C, et al. The circadian protein PER1 modulates the cellular response to anticancer treatments[J]. Int J Mol Sci, 2021, 22(6): 2974. doi: 10.3390/ijms22062974.
- [67] Jeon J, Lee S, Park JM, et al. Circadian control of cisplatin-DNA adduct repair and apoptosis in culture cells[J]. Int J Biochem Cell Biol, 2023, 162: 106454. doi: 10.1016/j.biocel.2023.106454.
- [68] Du Y, Hu P, Ding X, et al. Deficiency of ATF3 facilitates both angiotensin II-induced and spontaneously formed aortic aneurysm and dissection development by activating cGAS-STING pathway [J]. Clin Transl Med, 2025, 15(1): e70147. doi: 10.1002/ctm2.70147.
- [69] Ma C, Shen B, Chen L, et al. Impacts of circadian disruptions on behavioral rhythms in mice[J]. FASEB J, 2024, 38(22): e70183. doi: 10.1096/fj.202401536R.
- [70] Hamsanathan S, Anthonymuthu T, Han S, et al. Integrated-omics approach reveals persistent DNA damage rewires lipid metabolism and histone hyperacetylation *via* MYS-1/Tip60[J]. Sci Adv, 2022, 8(7): eabl6083. doi: 10.1126/sciadv.abl6083.
- [71] Levine DC, Hong H, Weidemann BJ, et al. NAD⁺ controls circadian reprogramming through PER2 nuclear translocation to counter aging[J]. Mol Cell, 2020, 78(5): 835-849.e7. doi: 10.1016/j.molcel.2020.04.010.
- [72] Jouffe C, Weger BD, Martin E, et al. Disruption of the circadian clock component BMAL1 elicits an endocrine adaption impacting on insulin sensitivity and liver disease[J]. Proc Natl Acad Sci USA, 2022, 119(10): e2200083119. doi: 10.1073/pnas.2200083119.
- [73] Gao Y, Gan T, Jiang L, et al. Association between shift work and risk of type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of observational studies[J]. Chronobiol Int, 2020, 37(1): 29-46. doi: 10.1080/07420528.2019.1683570.
- [74] Bukowska-Damska A, Skowronska-Jozwiak E, Kaluzny P, et al. Night shift work and osteoporosis among female blue-collar workers in Poland - a pilot study[J]. Chronobiol Int, 2020, 37(6): 910-920. doi: 10.1080/07420528.2020.1763381.
- [75] Xie M, Tang Q, Nie J, et al. BMAL1-downregulation aggravates *Porphyromonas gingivalis*-induced atherosclerosis by encouraging oxidative stress[J]. Circ Res, 2020, 126(6): e15-e29. doi: 10.1161/CIRCRESAHA.119.315502.
- [76] Virto L, Haugen HJ, Fernández-Mateos P, et al. Melatonin expression in periodontitis and obesity: an experimental *in-vivo* investigation[J]. J Periodontal Res, 2018, 53(5): 825-831. doi: 10.1111/jre.12571.
- [77] Zhou F, Liu Z, Guo Y, et al. Association of short sleep with risk of periodontal disease: a meta-analysis and Mendelian randomization study[J]. J Clin Periodontol, 2021, 48(8): 1076-1084. doi: 10.1111/jcpe.13483.
- [78] Han K, Park YM, Park JB. Evaluation of an association between long sleep duration and periodontal disease among men and women using nationally representative data[J]. Gac Sanit, 2018, 32(2): 143-150. doi: 10.1016/j.gaceta.2017.01.013.
- [79] Han DH, Kim MS, Kim S, et al. Sleep time and duration are associated with periodontitis in a representative sample of Koreans[J]. J Periodontol, 2022, 93(2): 208-217. doi: 10.1002/JPER.20-0252.
- [80] Zhang Z, Beier C, Weil T, et al. The retinal ipRGC-preoptic circuit mediates the acute effect of light on sleep[J]. Nat Commun, 2021, 12(1): 5115. doi: 10.1038/s41467-021-25378-w.

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