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内质网应激介导的牙周炎骨改建失衡的研究进展

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【摘要】 牙周炎是以牙周组织破坏为特征的慢性感染性疾病,宿主的免疫反应是导致附着丧失、牙槽骨吸收的重要原因。蛋白合成负荷过重时,易产生未折叠或错误折叠蛋白,其在内质网内腔积聚后产生内质网应激(ERS)。虽然细胞可以通过相关通路诱发非折叠蛋白应答反应(UPR)缓解ERS,但在牙周炎病理环境下,ERS不可避免地持续存在,而与之互作的UPR会介导促炎转录程序并诱发细胞凋亡,导致骨改建失衡、牙槽骨质丢失。本文就ERS介导的牙周炎骨改建失衡及其潜在治疗靶点相关研究进行回顾,以进一步了解ERS在牙周炎骨代谢及治疗中的作用和意义。

【关键词】 牙周炎; 内质网应激; 非折叠蛋白应答; 细胞凋亡; 牙槽骨质丢失

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Advances in endoplasmic reticulum stress-mediated bone remodeling imbalance in periodontitis

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【Abstract】 Periodontitis is a chronic infectious disease characterized by the destruction of periodontal tissue. The host's immune response is an important cause of attachment loss and alveolar bone resorption. When protein synthesis is overloaded, it is easy to produce unfolded or misfolded proteins which accumulate in the endoplasmic reticulum lumen and cause endoplasmic reticulum stress (ERS). Although the cells can induce an unfolded protein response (UPR) to mitigate ERS through related pathways, ERS inevitably persists in the pathological environment of periodontitis, and the interacting UPR can mediate pro-inflammatory transcriptional procedures and induce apoptosis, leading to the imbalance of bone remodeling and alveolar bone loss. This article reviewed the studies on ERS mediated bone remodeling imbalance in periodontitis and its potential therapeutic targets in order to further understand the role and significance of ERS in bone metabolism and treatment of periodontitis.

【Key words】 Periodontitis; Endoplasmic reticulum stress; Unfolded protein response; Apoptosis; Alveolar bone loss

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牙周炎是一种以牙周组织破坏为特征的慢性感染性疾病,通常引起牙周组织炎症、附着丧失和牙槽骨吸收,是成人牙齿脱落的重要原因[1]。牙周组织微生物感染是牙周炎的启动因子,但对牙周组织的不可逆破坏主要是由宿主免疫反应引起的[2]。目前,牙周炎的治疗策略主要是利用牙周刮治器和抗菌药物来减少细菌负荷[3],而对于由宿主免疫反应引起的牙周组织破坏目前尚缺乏有效治疗方法[4]。

内质网质量控制(endoplasmic reticulum quality control,ERQC)识别并消除错误折叠的蛋白质以维持细胞稳态[5]。环境或遗传因素对ERQC的抑制会导致蛋白质错误折叠增加[6],从而导致内质网中错误折叠或未折叠蛋白质的蓄积,进而发生内质网应

激(endoplasmic reticulum stress, ERS)[7]。在ERS时,非折叠蛋白应答反应(unfolded protein response, UPR)通过3个信号通路分支被激活,各分支都涉及内质网膜上的蛋白质传感器:肌醇必需酶1α(inositol-requiring enzyme 1α, IRE1α)、内质网膜蛋白激酶(PRK-like ER kinase, PERK)和活化转录因子6(activating transcription factor 6, ATF6),上述传感器将错误折叠信息传递到细胞核和细胞质中,诱发一系列信号通路调节相关基因表达,减少蛋白负荷,增加容量,以恢复内质网稳态,缓解ERS[8]。而在牙周炎病理情况下,ERS不可避免地持续存在时,UPR会诱发细胞凋亡,导致牙槽骨改建失衡而发生牙槽骨吸收[9]。本文就ERS介导的牙周炎骨改建失衡及其可能存在治疗靶点的相关研究进展进行综述。

一、内质网应激介导的牙周炎骨改建失衡

骨改建平衡是由成骨细胞、破骨细胞共同维持,若由破骨细胞介导的骨吸收水平高于成骨细胞诱导的骨形成水平,将导致骨改建失衡,牙槽骨质丢失。

诸多证据表明,在慢性牙周炎患者的牙龈和牙周组织中,PERK、葡萄糖调节蛋78(glucose regulated protein 78, GRP78)和CCAAT增强子结合蛋白同源蛋白(CCAAT/enhancer-binding protein homologous protein, CHOP)等多种ERS相关基因上调,提示ERS参与了牙周炎的病理生理过程[10-12]。研究还表明,牙周炎中ERS基因的表达变化参与了局部免疫反应过程[13],如PERK可通过ERS介导细胞死亡介质CHOP来诱发炎症反应,进一步的研究证明,UPR也参与了实验性牙周炎小鼠牙槽骨的破坏[14-15]。UPR的3个主要通路IRE1a-X盒结合蛋白1(X-box binding protein 1, XBP1)、PERK-真核生物起始因子2的α亚基(eukaryotic initiation factor 2α, eIF2α)和ATF6都被证明介导促炎转录程序[14]。以上研究结果肯定了ERS-UPR互作与牙周炎骨改建之间的相关性。

炎症微环境下,组织细胞发生ERS后,首先通过激活ERS下游UPR通路缓解ERS,如在IRE1α-XBP1通路中,IRE1α从内质网结合蛋白伴侣-免疫球蛋白重链结合蛋白(binding protein for immunoglobulins, BIP)/GRP78复合体中脱离,发生同源寡聚化并自磷酸化,激活核酸内切酶的活性,将XBP1的mRNA剪切生成X盒结合蛋白1剪接体(X box-binding protein 1 splicing, XBP1s),进而激活UPR,详见图1。XBP1s是许多UPR基因的关键转录激活因子,通过产生蛋白和伴侣蛋白来调节内质网蛋白折叠和运输、磷脂生物合成、内质网膜扩张和内质网相关蛋白降解,从而缓解ERS[16]。

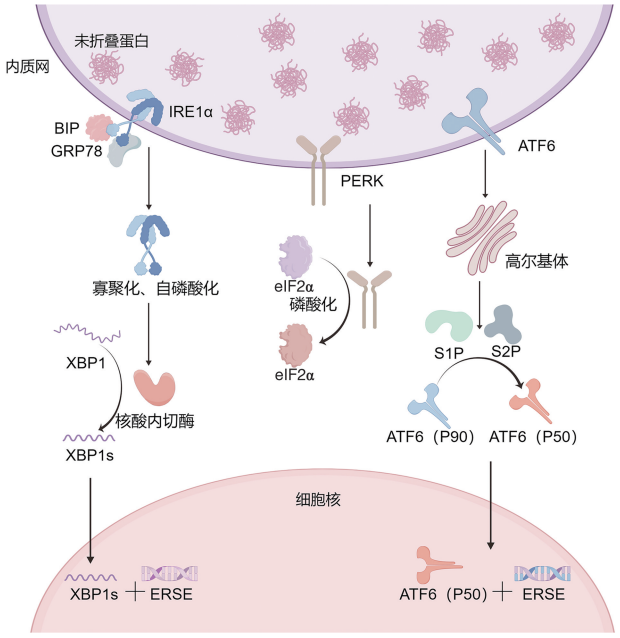

图1 内质网应激(ERS)通过非折叠蛋白应答反应(UPR)的代偿途径 肌醇必需酶1α(IRE1α)-X盒结合蛋白1(XBP1)通路:XBP1的mRNA被IRE1α激活的核酸内切酶剪切为X盒结合蛋白1剪接体(XBP1s)后,进入细胞核,与内质网应激反应元件(ERSE)结合,启动UPR;内质网膜蛋白激酶(PERK)-真核生物起始因子2的α亚基(eIF2α)通路:磷酸化的PERK促进eIF2α磷酸化,磷酸化eIF2α能够暂时抑制蛋白合成和新合成蛋白流入内质网,以缓解ERS[13];活化转录因子6(ATF6)通路:ATF6通过高尔基体定位信号转移至高尔基体中,被位点1蛋白酶(S1P)和位点2蛋白酶(S2P)剪切,剪切成的片段进入胞核结合ERSE,启动UPR靶基因的转录[17],本图由Figdraw绘制。

严重或长时间的ERS将导致UPR无法代偿,而UPR将介导促炎反应和细胞凋亡,如:长期ERS不仅可能通过IRE1α降低XBP1s的有益性,还可能激活IRE1α的负面特性,促进炎症和细胞凋亡[18];此外,持续的ERS还可激活PERK信号通路,降低牙周膜干细胞(periodontal ligament stem cell, PDLSC)的成骨分化能力[19],当UPR启动的适应性机制无法补偿过度的ERS时,UPR将介导促炎反应诱导细胞凋亡[20];Bhattarai等[21]还发现,ERS还可通过激活CHOP转录途径参与牙周炎对血管钙化的影响,最终诱导细胞凋亡。

此外,ERS亦介导破骨细胞(osteoclasts, OC)的分化。研究表明,单核细胞趋化蛋白1(monocyte chemoattractant protein-1, MCP-1)诱导单核细胞分化为OC前体细胞是由ERS介导的[22],且抑制ERS水

平可阻断OC标志物的表达[23]。巨噬细胞极化失衡也是慢性牙周炎症持续发展、成骨和(或)破骨细胞稳态破坏,以及骨缺损的关键因素[24]。牙周炎中,促炎性的M1型巨噬细胞占主导地位,能分泌多种炎症因子如白细胞介素1(IL-1)和肿瘤坏死因子α(TNF-α)等,导致牙周组织破坏、牙槽骨吸收[25-27]。研究表明,巨噬细胞向促炎性M1型极化的过程中,其典型特征如Toll样受体(TLR)信号的激活、炎性小体的组装与激活,以及促炎细胞因子的表达,均受到UPR的3条主要通路的调控增强。这一发现强调了巨噬细胞极化与ERS下游通路之间的密切联系[28]。

综上所述,炎症引起长时间或严重的ERS将加重炎症,引起牙周组织细胞凋亡,PDLSC等成骨分化能力下降,破骨细胞分化增强,骨改建失衡,牙槽骨质丢失。

二、内质网应激介导的牙周炎骨改建失衡的机制

1. ERS激发UPR的3个通路介导了骨改建失衡

(1)IRE1α-XBP1通路:IRE1α调控XBP1的活性,XBP1的表达反映了IRE1α-XBP1通路的变化趋势[29]。发生持续而严重的ERS时,IRE-1α通过系列反应激活c-Jun氨基末端蛋白激酶(c-Jun N-terminal kinase,JNK)信号通路,上调CHOP、*Bcl-2*家族中的促凋亡因子PUMA、BID和BIM,同时下调抗凋亡基因*Bcl-2*、*Bcl-XL*,引发线粒体途径介导的细胞凋亡[30]。*Bcl-2*通过抑制Caspase激活、调节代谢、抗氧化、调节DNA损伤和修复反应来维持细胞稳态[31]。过表达XBP1s时,PDLSC中Bcl-2表达上调,Caspase-3表达显著降低,提示XBP1s的表达水平与PDLSC的增殖、凋亡息息相关[32]。

(2)PERK-eIF2α通路:当ERS持续存在时,持续活化的PERK可通过上调CHOP基因,形成PERK通路的负反馈调节,诱导细胞凋亡;Shirakawa等[33]发现,过表达的CHOP可下调抗凋亡基因*Bcl-2*的表达,加速细胞凋亡,且CHOP还能通过损伤成骨细胞功能抑制其分化,并降低钙化结节的形成。

(3)ATF6通路:cAMP应答元件结合蛋白H(cAMP response element binding protein H,CREBH)与ATF6结构相似,能发挥相同作用。活化T细胞核因子1蛋白(the nuclear factor of activated T cells cytoplasmic 1,NFACT1)是一种与破骨细胞分化密切相关的调节因子。研究表明,CREBH在NF-κB受体激活蛋白配体(receptor activator of NF-κB ligand,RANKL)诱导的破骨细胞生成中有重要作用[34],见图2。在炎症骨吸收中,TNF-α可通过NF-κB通路上调CREBH抑制成骨细胞分化[35]。此外,NF-κB能在NFACT1启动子中结合NF-κB结合元件,诱导NFACT1表达,最后NFATc1可通过结合自身启动子形成自我调节反馈系统,高度诱导自身表达。

2. ERS水平上调将介导巨噬细胞的极化失衡,加重组织炎性反应,导致骨改建失衡:研究表明,炎症

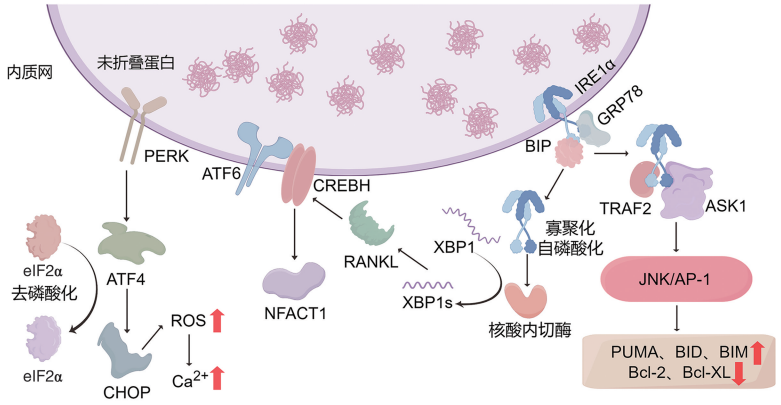

图2 持续的内质网应激(ERS)经非折叠蛋白应答反应(UPR)通路介导的骨改建失衡 肌醇必需酶1α(IRE1α)-X盒结合蛋白1(XBP1)通路:活化IRE-1α与TNF受体相关因子2(TRAF2)结合后激活细胞凋亡信号调节激酶1(ASK1),三者形成复合物后激活c-Jun氨基末端蛋白激酶(JNK)信号通路,介导细胞凋亡[29];内质网膜蛋白激酶(PERK)-真核生物起始因子2的α亚基(eIF2α)通路中:持续活化的PERK通过促进转录激活因子4(ATF4) mRNA的表达,上调CCAAT增强子结合蛋白同源蛋白(CHOP)基因,表达关键凋亡因子CHOP,其使eIF2α去磷酸化,致该通路代偿失效,加剧内质网应激(ERS),形成恶性循环,进而诱导细胞凋亡。CHOP可通过激活内质网氧化还原酶-1α改变内质网氧化还原状态,上调活性氧水平(ROS),触发Ca^{2+}释放,诱导细胞凋亡[15];活化转录因子6(ATF6)通路:持续表达的X盒结合蛋白1剪接体(XBP1s)将促进NF-κB受体激活蛋白配体(RANKL)的表达,RANKL激活内质网膜上cAMP应答元件结合蛋白H(CREBH),使其进入胞核,促进活化T细胞核因子1蛋白(NFACT1)的表达,进而促进破骨细胞的分化[36-37],本图由Figdraw绘制。

微环境下,巨噬细胞中ERS激活后,下游的IRE1α、PERK通路被活化,导致巨噬细胞向促炎性M1型极化,而抑制IRE1α和PERK后可抑制M1型极化过程;此外,研究还证实了IRE1α和PERK可通过STAT1和STAT6信号通路调控巨噬细胞M1-M2表型转化[38-39]。同时,巨噬细胞ERS水平增高还可促进其炎症因子分泌。在巨噬细胞中,生理状态下IRE1、PERK和ATF6分别与GRP78结合形成稳定的复合物,当发生ERS时,GRP78与3种感受态蛋白解离,激活下游3个通路:(1)IRE1能与TNF受体相关因子2组成复合体,激活κB抑制分子(inhibitors of κB,IκB)激酶复合物,引起IκB降解,从而活化NF-κB;(2)PERK活化后抑制IκB翻译,增大NF-κB与IκB的比值,促进NF-κB向核内转移;(3)ATF6可将蛋白激酶B磷酸化,进而激活下游的NF-κB[40]。3个经典通路均可激活NF-κB通路,NF-κB易位到细胞核中,将促进IL-1β等炎症因子的表达,最终加剧局部的炎症进程[41]。

三、以控制ERS水平为治疗方向的研究现状

1. ERS介导牙周炎骨改建失衡的潜在治疗靶点(表1):瞬时受体电位锚蛋白1(transient receptor potential A1,TRPA1)是一种非选择性渗透性的Ca^{2+}通道,研究发现抑制TRPA1能通过下调PERK、eIF2α、ATF-4、CHOP通路来抑制ERS,显著降低牙周炎微环境中PDLSC的氧化应激和细胞凋亡水平,从而改善牙周炎的发展[11]。*SERPINH1*是ERS的靶基因,产物为热休克蛋白47(heat shock protein 47,HSP47),其表达提高了IRE1a的激活水平并增强其下游信号传导,能有效缓解ERS[42],而高血糖牙周炎中*SERPINH1*的下调可导致人牙龈上皮细胞(human gingival epithelial cell,HGEC)长期或严重的ERS[43]。一项研究发现,过表达XBP1s可调节自噬,对PDLSC的增殖起到积极作用,可抑制其凋亡的发生,且XBP1s还能增加Runt相关转录因子2、碱性磷酸酶、骨唾液酸蛋白和骨钙素等成骨相关因子的mRNA表达,促进PDLSC的成骨能力[31]。细胞周期蛋白依赖激酶8(cyclin-dependent kinase 8,CDK8)是一种参与细胞自噬调控的环状RNA。研究发现,ERS与CircCDK8的表达存在潜在联系,CircCDK8可通过在低微环境中触发自噬活来抑制PDLSC的成骨分化[44]。此外,有研究证实了ERS激活的JNK、PERK通路可介导TNF-α诱导的骨髓间充质干细胞(bone marrow mesenchymal stem cell,BMSC)炎症,抑制其成骨分化[45-46]。一项动物研究表明,降低ERS水平有利于细胞分化增殖,可促进成骨[47]。

表1 抑制间充质干细胞内质网应激(ERS)水平的调控靶点

靶点	涉及通路	上调/下调	机制
TRPA1	PERK	下调	抑制炎性PDLSC的氧化应激和凋亡[11]
HSP47	IRE1α	下调	导致HGEC发生持续或严重的ERS[41]
METTL3	-	下调	诱导OC凋亡[45]
CircCDK8	-	上调	抑制PDLSC成骨分化[47]
XBP1	IRE1α	上调	促进PDLSC成骨能力[31]
TNF-α	JNK、PERK	上调	抑制BMSC和PDLSC的成骨分化[48-49]

注:"-"为不涉及非折叠蛋白应答反应通路;TRPA1为瞬时受体电位锚蛋白1;HSP47为热休克蛋白47;METTL3为甲基转移样酶-3;CircCDK8为位于细胞周期蛋白依赖激酶8基因上的环状RNA;XBP1为X盒结合蛋白1;TNF-α为肿瘤坏死因子α;PERK为内质网膜蛋白激酶通路;IPE1α为肌醇必需酶1α通路,JNK为c-Jun氨基末端蛋白激酶信号通路;PDLSC为牙周膜干细胞;HGEC为人牙龈上皮细胞;OC为破骨细胞;BMSC为骨髓间充质干细胞。

此外,UPR的表达水平与炎症条件下PDLSC的成骨作用密切相关[12]。甲基转移样酶3(methyltransferase-like 3,METTL3)是一种关键的甲基转移酶,催化mRNA的N^6-甲基腺苷(m^6A)修饰,METTL3诱导的m^6A甲基化能通过靶向促进Runt相关转录因子2的表达来促进BMSC的成骨分化[48]。研究表明,METTL3在成骨细胞分化过程中上调[49],敲低METT3后会导致UPR靶基因GRP78的表达增强,激活过度的ERS,促进成骨细胞凋亡,抑制炎症条件下成骨细胞的增殖和分化,阻碍成骨[50-51],同时增强了促炎细胞因子的表达,增加了NF-κB信号通路中JNK的磷酸化[49]。

综上所述,抑制ERS可有效降低PDLSC的炎症反应和细胞凋亡,增强其成骨分化能力,因此寻找特定调控靶点抑制间充质干细胞的ERS水平对促进牙周炎成骨具有积极意义。

2. 调整ERS水平的相关治疗方法及药物

(1)不同细胞来源的外泌体(exosomes):外泌体作为天然的纳米材料,可携带和传递生物信号到邻近和远处的细胞,调节受体细胞的生理和病理状态[52],由于携带生物信号浓度可控和内源性、异质性的优势使其比合成载体更具优势[53]。Cui等[54]和Ku等[55]分离了M2型巨噬细胞外泌体M2-exos,并发现M2-exos具有炎症靶向作用,能通过减少过度ERS来加速炎

性PDLSC的成骨和骨质分化,并促进巨噬细胞从M1表型到M2表型的极化。褪黑素能在不同病理生理情况下调节炎症和细胞凋亡[56],M2-exos加入适量褪黑素后能有效提高成骨、牙骨质和成牙活性,降低破骨细胞活性,具有很大的体外牙周再生价值和潜力[54];另外,巨噬细胞外泌体可通过miRNA如miR-99a/146b/378a调节牙周炎微环境中M2型巨噬细胞的极化并减轻炎症[57]。Nakao等[58]发现,TNF-α预处理牙龈组织源性间充质干细胞(gingival tissue-derived mesenchymal stem cell, GMSC)后,可以增加其外泌体的数量和外泌体CD73的表达,局部注射可显著减少小鼠牙周破骨细胞数量和骨吸收,且外泌体CD73可诱导M2型巨噬细胞极化。来自脂肪来源干细胞的外泌体(exosomes from adipose-derived stem cell, ADSC-Exos)也被证实可通过抑制M1标志物的表达,促进M2标志物的表达调节M1/M2巨噬细胞表型的极化促进骨的愈合[59]。上述研究提示,利用不同细胞外泌体携带生物信号降低靶细胞ERS水平、调节M1/M2巨噬细胞表型极化可能是牙周炎治疗的潜在方法。

(2)可溶性环氧化物水解酶制剂[1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea, TTPU]:环氧二碳三烯酸(epoxyeicosatrienoic acid, EET)是花生四烯酸的代谢物,主要由可溶性环氧化物水解酶(soluble epoxide hydrolase, sEH)代谢成相应的二醇。EET具有抗炎特性,抑制sEH可对炎症性骨质流失具有保护作用。Trindade-da-Silva等[60]发现,TTPU能在很大程度上消除了牙周炎引起的骨质流失,可能是基于抑制sEH减少了破骨细胞关键分子,降低炎症引发的ERS和牙龈组织中相关细胞的凋亡作用。

(3)合成化合物Salubrinal(C21H17Cl3N4OS, 480Da):Salubrinal能选择性抑制eIF2α的去磷酸化。研究表明,Salubrinal能通过减轻ERS,降低CHOP表达而减少细胞凋亡,同时,Salubrinal还可减少破骨细胞数量、抑制骨吸收,增加成骨细胞数量、促进骨形成,并抑制牙周组织中TNF-α的表达水平[61]。上述研究提示,Salubrinal可能是牙周炎的潜在治疗药物。

(4)花青素-3-O-葡萄糖苷(cyanidin-3-O-glucoside, C3G):C3G在体外和体内研究中,均能阻止ERS和UPR标志物的异常升高[62]。C3G可通过降低牙周组织细胞的ERS水平,下调NF-κB、CHOP等表达,降低细胞凋亡水平来减少牙周炎导致的牙槽骨丢失[63],以上结果均提示C3G可能成为牙周炎的治疗药物。

四、总结与展望

牙周组织细胞发生ERS时,通过一系列信号通路传递到胞核中诱导相关基因表达,引发UPR以缓解ERS,形成正反馈机制。但是,当UPR无法缓解持续而严重的ERS时,会介导促炎转录程序并诱发细胞凋亡,导致牙槽骨质丢失,加重牙周组织炎症。本文总结了目前已发现的在ERS激发UPR通路上可能存在的治疗靶点、调控ERS水平相关的治疗方法和治疗药物,希望为牙周相关免疫治疗提供参考依据。目前,ERS导致牙周炎骨改建失衡的具体机制尚未完全阐明,何种阈值的ERS水平作为调控临界点及其具体调控机制仍有待研究。因此,阐明以ERS介导的牙周炎骨改建失衡的具体机制、涉及的信号通路,并以此为依据寻找治疗精准靶点、治疗方法,对于进一步理解牙周炎骨改建失衡及治疗牙周炎有重要意义。

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