·综述·

内质网应激在骨代谢及其稳态中的作用

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【摘要】 骨稳态是破骨细胞和成骨细胞共同作用的过程。骨组织中存在大量的细胞外基质蛋白。在蛋白合成过程中,未折叠及错误折叠蛋白增多导致内质网应激,诱发肌醇必需酶1α(IRE1α)、内质网膜蛋白激酶(PERK)和活化转录因子6(ATF6)家族介导的非折叠蛋白应答。当过度应激时将造成软骨发育不良、骨关节炎和牙周炎骨吸收等疾病。本文就近年内质网应激在骨代谢中作用的研究进展做一综述,有助于进一步了解内质网应激在骨代谢及治疗相关疾病中的作用及意义。

【关键词】 内质网应激; 非折叠蛋白应答; 细胞凋亡; 骨代谢

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Endoplasmic reticulum stress in skeletal development and bone homostasis

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【**Abstract**】 Bone homeostasis is a process of interaction between osteoclasts and osteoblasts, with abundant extracellular matrix proteins existing in bone tissue. During protein synthesis, the increase of unfolded and misfolded proteins lead to endoplasmic reticulum stress, which induce the unfolded protein responses mediated by IRE1α, PERK and ATF6 family. Excessive stress leads to chondrodysplasia, osteoarthritis and periodontitis bone resorption. This review focuses on the role of endoplasmic reticulum stress in bone metabolism and it is of great significance for our further understanding of bone metabolism and treatment of related diseases.

【**Key words**】 Endoplasmic reticulum stress; Unfolded protein response; Apoptosis; Bone metabolism

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内质网是真核生物中蛋白合成、修饰和加工的重要场所。未折叠的蛋白进入内质网中经蛋白折叠、组装、加工和包装,形成具有三级或四级结构的蛋白质向高尔基体转运,此过程称为细胞分泌通路[1]。当细胞蛋白合成负荷过重,或细胞受到各种外界压力时,未折叠及错误折叠的蛋白在内质网内腔积聚,形成内质网应激[2]。内质网应激能诱发非折叠蛋白应答,通过肌醇必需酶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)家族跨膜蛋白感受内质网中蛋白折叠异常,诱发一系列信号通路调节基因表达、减少内质网蛋白负荷和增加内质网容量,从而达到缓解内质网应激的目的[3-4]。研究表明,非折叠蛋白应答与全身疾病密切相关,对骨骼代谢具有影响作用[5-7]。

骨重建是骨骼持续形成、塑形和修复的过程,由破骨细胞介导骨吸收和成骨细胞诱导骨形成共同完成,以维持骨稳态[8]。正常情况下,成骨细胞、软骨细胞和破骨细胞需持续分泌大量细胞外基质蛋白和蛋白酶等,这些细胞蛋白合成负荷较重,容易发生内质网应激。当内质网应激不可避免地持续存在时,非折叠蛋白应答会诱发细胞凋亡,导致牙周炎骨吸收、软骨发育不良和骨关节炎等疾病的发生[5,9-10]。内质网应激在骨代谢中的调节作用是近年研究热点,本文就内质网应激在破骨、成骨分化及软骨发育中的调节作用的研究进展做一综述。

一、非折叠蛋白应答通路

1. IRE1α轴:IRE1α是内质网Ⅰ型跨膜蛋白。当内质网应激发生时,IRE1α脱离与免疫球蛋白结合蛋白质(binding protein for immunoglobulins, BIP)/78 000调节蛋白(glucose-regulated protein of 78 000, GRP78)复合体的结合后,IRE1α聚合并自磷酸化,发生结构域的改变激活核酸内切酶的活性[11]。X盒-结合蛋白1(X box-binding protein 1, XBP1)的mRNA能够与IRE1α的核酸内切酶活性结合,其中一个26 nt的内含子被剪切后产生一个新的mRNA,翻译成具有活性的转录因子XBP1s(X box-binding protein 1 splicing)。XBP1s能够进入细胞核与内质网应激反应元件(ER stress response

element,ERSE)的基因启动子结合,启动内质网蛋白转位、折叠、分泌,以及降解错误折叠蛋白的相关基因的表达[12]。另一方面,研究发现IRE1α在内质网应激中同时具有核酸外切酶(regulated IRE1-dependent decay,RIDD)活性,能够剪切一小组mRNA及microRNA前体并将其降解。RIDD的剪切位点均含有5′-CUGCAG-3′序列,位于二级或三级结构的"发夹"环状结构上。RIDD活性能够通过降解特定mRNA减少内质网蛋白合成压力,发挥缓解内质网应激的作用[7]。

2. PERK轴:PERK激活机制与IRE1α相类似。磷酸化后的PERK与真核生物起始因子2的α亚基(eukaryotic initiation factor 2α,eIF2α)结合,促使其N端第51位丝氨酸磷酸化。此外,磷酸化eIF2α能够暂时性抑制蛋白翻译合成[13],限制新合成的蛋白流入内质网,从而缓解内质网应激。磷酸化eIF2α能促进转录激活因子4(activating transcription factor 4,ATF4)的表达,进而促进与氨基酸代谢、凋亡自噬以及蛋白合成相关的基因表达[14]。ATF4同时参与eIF2α去磷酸化的反馈调节,与蛋白磷酸酶1(protein phosphatase 1,PP1)及其亚单位生长停滞与DNA损害可诱导蛋白34(growth arrest and DNA damage inducible protein 34,GADD34)组成的复合体结合,能够促使eIF2α去磷酸化[15],对内质网应激恢复后蛋白合成具有重要作用。当内质网应激持续存在时,ATF4能激活CCAAT增强子结合蛋白同源蛋白(CCAAT/enhancer-binding protein homologous protein,CHOP)。CHOP通过激活GADD34使eIF2α去磷酸化,促使蛋白合成增加,加剧内质网应激。同时,CHOP可激活内质网氧化还原酶-1α(endoplasmic reticulum oxidoreductin 1α,ERO1),改变内质网中的氧化还原状态,进一步促使细胞凋亡[16]。

3. ATF6轴与ATF6家族因子CREBH和OASIS:跨膜蛋白ATF6胞质侧由转录激活结构域和含bZIP的结构域组成,其内质网腔内的感受器具有多个Bip结合位点和两个高尔基定位信号[17]。当内质网应激发生时,ATF6通过高尔基定位信号转移到高尔基体中,被S1P蛋白酶(site-1 protease,S1P)和S2P蛋白酶(site-2 protease,S2P)剪切,释放N端转录激活结构域,进入细胞核中与ERSE的基因启动子结合,发挥与IRE1α-XBP1相同的作用,缓解内质网应激[18-19]。老星形胶质细胞特异性诱导物质(old astrocyte specifically induced substance,OASIS)和cAMP应答元件结合蛋白H(cAMP response element-binding protein H,CREBH)与ATP6属于同一家族,与ATP6发挥相同的作用。然而,CREBH与OASIS具有一定细胞特异性,倾向于在成骨细胞中表达,通过调控核因子κB(nuclear factor-κB,NF-κB)受体激活蛋白配体(receptor activator of NF-κB ligand,RANKL)生成在骨骼生理性发育及病理状态中发挥重要作用[20]。

二、内质网应激在成骨分化和软骨发育中的作用

成骨细胞起源于多能的骨髓基质干细胞(marrow stromal stem cell,MSC),MSC在不同环境及细胞因子的诱导下能够分化为骨、软骨、肌肉和脂肪等组织[21]。以下主要从内质网应激诱导的非折叠蛋白应答包括PERK和ATF6家族介导的通路,阐述其在成骨分化及软骨发育中发挥的作用。

1. PERK-eIF2α-ATF4通路促进成骨分化:ATF4位于多数调节成骨分化通路的下游,是调控成骨分化的关键因子。ATF4能够进入细胞核并结合成骨细胞特异性元件1,诱导骨钙素合成,促进骨质矿化。有研究显示,ATF4基因敲除小鼠的骨骼血管及微血管密度严重受损[22]。缺氧情况下,ATF4能够提高成骨细胞中低氧诱导因子1(hypoxia-inducible factor 1,HIF-1)及血管内皮生长因子(vascular endothelial growth factor,VEGF)表达,在骨基质血管生成和骨重塑中发挥重要作用。在循环机械力作用下,牙周韧带细胞发生内质网应激,并通过PERK-eIF2α-ATF4通路促进成骨细胞分化,造成韧带骨化[23-24]。慢性牙周炎常导致牙槽骨吸收,炎症能通过影响PERK通路延长内质网应激和影响成骨分化,在慢性牙周炎进展中起到重要作用[25]。研究证实,使ATF4激活的CHOP能降低原始成骨细胞中钙化骨结节形成,对成骨细胞的分化具有抑制作用[26]。然而亦有研究则指出,CHOP缺乏会损伤成骨细胞功能,小鼠骨形成比例下降[27],进一步研究分析CHOP缺乏小鼠骨微结构改变认为内质网应激相关的CHOP通路在骨形成中有重要作用,CHOP缺乏导致的骨量减少具有性别差异[28]。上述研究表明,PERK通路下游分子ATF4在成骨调控中发挥重要作用,且被认为是过度内质网应激时调控细胞凋亡的关键分子CHOP,对成骨细胞功能发挥同样具有重要作用,关于其对成骨细胞作用存在一定争议。

2. ATF6、CREBH和OASIS在成骨代谢中的作用:ATF6是内质网膜上的应激感受器,ATF6的大量表达可增加骨钙素表达,在成骨细胞分化中起到重要作用[29]。炎症因子抑制骨形成蛋白2(bone morphogenetic protein 2,BMP-2)诱导的成骨分化,在慢性牙周炎炎症反应骨缺失中起到重要作用。研究表明,肿瘤坏死因子α(tumor necrosis factor α,TNF-α)通过上调NF-κB通路增加CREBH表达,抑制成骨细胞分化[30]。OASIS则通过非折叠蛋白应答激活*Col1a1*基因转录,合成Ⅰ型胶原。OASIS缺失小鼠表现出严重的骨质减少,包括骨基质中Ⅰ型胶原减少和成骨细胞活性降低[31]。

3. 内质网应激在软骨发育中的作用:在软骨发育中,软骨细胞形成软骨原基,原基内的软骨细胞有序分化、增殖和排列形成生长板结构。软骨生长盘不同区域产生不同的非折叠蛋白应答[32]。软骨细胞处于缺氧状态以及受到较大的机械压力时,细胞产生内质网应激,软骨细胞凋亡,导致下颌软骨变薄[33-34]。PERK-ATF4通路上调,反式激活*Sox9*[SRY(sex-determining region Y)-box9],抑制软骨细胞分化导致软骨发育不良[35]。而ATF4能通过调节印度刺猬因子(Indian hedgehog,IHH)表达介导长骨形成[36]。上述研究表明,软骨细胞可通过上调PERK-ATF4通路并转录激活不同的因子来发挥不同的软骨调节作用。XBP1失活小鼠Schmid型干骺端软骨发育不良(Schmid metaphyseal chondrodysplasia,MCD)的症状没有明显变化,提示IRE1α-XBP1通路在MCD中没有明显作用[37]。然而,另一研究提出在XBP1失活小鼠中,软骨

细胞增殖下调,生长盘肥大区缩短,胚胎中XBP1失活导致长骨骨化延迟,提示XBP1对软骨内成骨过程中软骨细胞增殖以及骨化时间有重要作用[38]。因此,IRE1α-XBP1通路对软骨发育的影响尚存在争议,XBP1在软骨发育中的具体机制仍有待进一步研究。

三、内质网应激在破骨细胞生成中的作用

破骨细胞由造血干细胞分化而来,在调节机体生理功能如骨代谢及造血中起到重要作用[39]。在破骨细胞生成中,有两个关键调控因子分别是RANKL和巨噬细胞集落刺激因子(macrophage colony-stimulating factor, M-CSF)[40]。成骨细胞等表达的RANKL与受体RANK结合,能够激活一系列下游通路促进破骨前体细胞及单核细胞融合、活化及分化为破骨细胞。RANK激活下游通路同时介导细胞内钙离子的波动,进而导致与破骨细胞生成密切相关的因子包括c-Fos蛋白和活化T细胞核因子1蛋白(the nuclear factor of activated T cells cytoplasmic 1, NFATc1)的激活[41]。许多研究指出,内质网应激与破骨生成存在密切关系[42-43]。

1. IRE1α-XBP1通路诱导RANKL以及直接结合NFATc1促进破骨生成:IRE1α-XBP1通路是非折叠蛋白应答中进化最保守的通路。研究指出,IRE1α-XBP1轴在破骨生成中具有重要作用。抑制IRE1α-XBP1通路能显著抑制破骨细胞形成及成纤维细胞中RANKL的表达。在小鼠颅骨模型中,破骨生成以及骨溶解也受到抑制,提示XBP1s能介导RANKL表达调节破骨细胞分化[44]。肌醇1,4,5-三磷酸受体2(inositol 1,4,5-trisphosphate receptors 2, ITPR2)和ITPR3能调节内质网中钙离子流,在一定程度上激活非折叠蛋白应答IRE1α-XBP1通路。激活的XBP1s可直接结合NFATc1的基因启动子区,激活NFATc1的转录,调控破骨细胞生成[45]。

2. RANKL经CREBH调节NFATc1表达,促进破骨细胞生成:如前所述,CREBH是位于内质网膜上的转录因子,介导内质网应激的非折叠蛋白应答。研究表明,CREBH在RANKL诱导的破骨细胞生成有重要作用。RANKL通过诱导内质网应激,激活内质网膜上CREBH,其胞质结构域释放进入细胞核中,调控与破骨生成密切相关的调节因子NFACT1表达,从而促进破骨细胞生成[4]。在炎症骨吸收中,前炎症因子TNF-α通过NF-κB通路上调CREBH,抑制BMP-2介导的骨生成,同时又能通过提高NFACT1的表达促进破骨分化,提示CREBH在炎症反应中调节骨代谢的重要作用。

3. 非折叠蛋白应答促进RANKL表达:非折叠蛋白应答持续过度激活时,将诱导一系列细胞因子包括RANKL产生甚至导致细胞死亡。使用衣霉素药物诱导非折叠蛋白应答能够促进培养的初代成骨细胞RANKL的表达,而药物阻断非折叠蛋白应答则RANKL表达减少。沉默降解未折叠蛋白的酶则会诱导非折叠蛋白应答加剧,同时促进RANKL的mRNA表达[20]。上述研究表明,过度的非折叠蛋白应答能够促进成骨细胞及骨细胞中RANKL的表达,导致骨吸收丧失。内质网应激诱导的非折叠蛋白应答可作为RANKL的上游通路,影响破骨细胞生成。

四、总结和展望

细胞中内质网应激能够引发非折叠蛋白应答,通过内质网膜上的信号感受器,介导一系列信号通路传递到胞核中诱导相关基因表达,缓解内质网应激。在骨代谢中,非折叠蛋白应答能调节软骨细胞、成骨细胞、破骨细胞的分化以及骨形成,而过度的非折叠蛋白应答能诱导细胞凋亡,产生软骨发育不良、骨关节炎和牙周炎骨吸收等疾病。然而,内质网应激在骨代谢中调节的具体作用机制尚未完全阐明,部分调节机制的研究亦存在争议。过度的内质网应激能通过非折叠蛋白应答诱导细胞凋亡,导致相应组织进入病理状态。何种程度的应激作为临界点调控细胞凋亡以及具体的阈值调控机制仍有待进一步研究。因此,阐明内质网应激诱导的非折叠蛋白应答在破骨细胞、成骨细胞分化和软骨发育中的作用,对于进一步理解骨代谢及治疗相关疾病有重要意义。

利益冲突 所有作者均声明不存在利益冲突

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