



骨在能量代谢中的作用

罗湘杭^{*}, 郭乔月, 熊津铭

中南大学湘雅医院内分泌科/内分泌研究中心, 长沙 410008

^{*} 联系人, E-mail: xianghangluo@hotmail.com

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摘要 骨是机体的主要支撑框架, 兼具钙磷储存库及造血作用. 此外, 作为最大的内分泌器官, 骨在机体能量代谢中也发挥着重要作用. 骨组织内各种细胞可分泌多种骨源性分泌因子调节局部代谢功能, 并通过血循环作用于远处靶器官, 调节糖脂代谢状态和机体能量平衡. 骨的内分泌功能揭示了多种代谢性疾病的潜在病理机制, 对骨质疏松症、肥胖症和糖尿病等代谢性疾病的诊断、治疗和预防具有重要作用. 本文综述了骨和骨源性分泌因子在调控机体能量代谢中的作用, 并探讨了未来的研究方向.

关键词 骨, 能量代谢, 骨源性分泌因子, 骨代谢, 代谢性疾病

骨骼约占人体总重量的15%, 主要由骨基质、间充质干细胞系和造血干细胞系组成^[1]. 骨基质由有机物和无机物两部分组成, 其中有机物主要包括成骨细胞分泌的I型胶原和多种非胶原蛋白, 而无机物主要由钙、磷、镁等组成, 是体内重要的钙和磷储存库^[2]. 骨髓间充质干细胞(bone mesenchymal stem cells, BMSC)可分化为成骨细胞、脂肪细胞和软骨细胞. 成骨细胞通过合成类骨质和分泌基质囊泡来促进骨的矿化和形成. 成骨细胞还可转化为骨细胞, 骨细胞是骨组织中数量最多的细胞, 在骨基质的再生和维持中起着关键作用. 软骨细胞则是软骨的主要组成部分, 参与软骨内骨化这一重要过程. 造血干细胞有两种分化方向, 髓系分化为粒细胞、单核细胞、红细胞等, 而淋巴系分化为T淋巴细胞、B淋巴细胞及自然杀伤细胞. 其中单核细胞融合形成破骨细胞, 后者通过分泌有机酸和蛋白酶来溶解并吸收骨基质. 尽管目前已有诸多针对骨

组织成骨和造血功能的研究, 但关于骨在机体代谢中的作用却少有报道.

内分泌器官是指一类通过分泌肽或类固醇激素来调节远处组织功能的器官. 研究发现骨细胞产生激素如成纤维细胞生长因子(fibroblast growth factor, FGF) 23和骨钙素(osteocalcin, OCN)可以内分泌的方式调节能量平衡和矿物质稳态. 同时代谢组学研究揭示了骨质疏松症病理过程中代谢途径的变化, 进一步强调了骨作为内分泌器官的重要作用. 骨组织的代谢不仅受到其他循环激素的影响, 还会通过骨源性激素调节全身能量代谢^[3,4]. 能量代谢指机体通过生物化学反应将摄入的食物转化为能量以维持生命活动的过程, 是维持机体正常生理功能的核心过程, 此外它在生长发育和组织修复中也起着关键作用, 正常的能量代谢途径对预防肥胖、糖尿病等代谢性疾病至关重要. 骨重塑是一个耗能极高的生理过程, 包括骨吸收和骨形成.

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它在儿童时期促进骨骼的纵向生长, 在成年后则通过修复损伤来维持骨骼的健康与稳定。因为成骨细胞在形成新骨时需要大量的能量来合成和分泌蛋白质构建细胞外基质, 当能量摄入不足时骨重塑过程会受到显著影响: 如在神经性厌食症患者中, 由于长期的低热量摄入, 骨骼生长可能停止, 骨量会大幅减少, 最终导致骨质疏松症^[5]。而骨作为极大的耗能器官, 对全身的能量代谢也发挥着重要作用。骨组织内包括成骨细胞、骨细胞、BMSC、破骨细胞和脂肪细胞在内的多种细胞可以合成和分泌多种生物活性物质: 如蛋白质、多肽、细胞因子、脂肪因子和外泌体, 这些生物活性物质通过自分泌和旁分泌的方式调节骨组织局部能量代谢(图1)。此外它们还可以通过血液循环作用于远处的靶器官从而影响全身能量代谢^[6,7]。由成骨细胞分泌的OCN是首个被发现具有调节能量代谢功能的骨蛋白。最初的研究表明OCN可促进胰腺 β 细胞的增殖和胰岛素分泌^[8], 后来研究发现它还影响肠上皮细胞、脂肪细胞和肝细胞的功能^[9,10]。本文综述了近年来骨代谢在机体整体代谢中作用的研究进展, 深入探讨了骨组织内不同细胞所分泌因子在骨代谢与能量代谢相互作用中的机制。同时本文还指出了当前研究的可能发展方向及面临的挑战。

1 BMSC

BMSC是多能干细胞, 具有分化成多种不同类型细胞的潜力。此外BMSC还是调节骨髓造血微环境的重要组成部分。肥胖和糖尿病等代谢紊乱容易诱发BMSC的成脂而非成骨分化, 导致骨质疏松和骨折^[11]。BMSC已被用于细胞移植以治疗代谢疾病。动物实验和临床试验均表明BMSC移植能促进胰岛细胞的增殖, 并减轻胰岛素抵抗^[12]。

骨桥蛋白(osteopontin, OPN)是一种分泌型基质细胞蛋白。OPN在BMSC、成骨细胞、破骨细胞和软骨细胞等多种细胞中表达^[13]。BMSC分泌的OPN可作为自分泌因子调节骨的重吸收^[14,15]。现有研究已证明OPN与代谢疾病间存在相关性^[16,17]。Marciano等人发现OPN编码基因*SPPI*是1型糖尿病的易感基因之一^[18,19]。OPN可以调节BMSC的分化方向, OPN敲除小鼠的BMSC更易分化为脂肪细胞并表现出较高的体脂含量^[20]。高脂肪饮食的小鼠中OPN的含量增加, 且

OPN主要储存在脂肪组织中。然而You等人发现, 尽管肥胖青少年的血清OPN在运动后显著下降, 但其体脂率未发生明显变化^[21], 这表明血清OPN可能受到脂肪组织以外其他组织的更大影响。鉴于骨组织是OPN的重要来源且运动可改善骨代谢, 骨代谢的动态变化可能会对血清OPN水平产生影响。骨源性OPN对机体整体能量代谢的具体影响值得进一步研究。

骨可以通过分泌炎症因子调节能量代谢。慢性低度炎症与代谢综合征的发病密切相关^[22], 炎症可激活如核因子 κ B(nuclear factor kappa-B, NF- κ B)和c-Jun氨基末端激酶(c-Jun amino-terminal kinase, JNK)等炎症信号通路, 进一步干扰胰岛素信号转导并导致胰岛素抵抗^[23]。成骨细胞分泌的IL-6可以调节骨吸收^[24], BMSC可能比成骨细胞更能产生炎症因子, 许多炎症因子如IL-6、巨噬细胞炎症蛋白-1 α 、粒细胞集落刺激因子和粒细胞巨噬细胞集落刺激因子, 均被证明由BMSC分泌^[25]。

骨组织内几乎所有类型的细胞都分泌外泌体^[26,27], 其囊泡内成分极为丰富, 包括NF- κ B、NF- κ B配体受体致活剂(Receptor activator of nuclear factor kappa-B ligand, RANKL)、ephrinA2、miR-146a和miR-214-3p等。BMSC来源外泌体中RNA的表达与干细胞来源的脂肪细胞产生的外泌体的表达相似^[28], 表明这两种外泌体可能具有相似的调节全身能量代谢的能力。此外Su等人的研究证实BMSC可以通过外泌体影响胰腺、肝脏和其他代谢相关器官的功能, 他们发现BMSC分泌的含有miR-29b-3p的外泌体随着年龄的增长而显著增加^[29]。外泌体内多种生物活性物质也赋予了它们治疗潜力, 例如注射BMSC来源外泌体到糖尿病小鼠体内后, 其内的miRNA可通过抑制转化生长因子- β (transforming growth factor- β , TGF- β)/Smad家族成员3(Smad family member 3, Smad3)信号通路来改善葡萄糖耐量^[30]。

2 成骨细胞

成骨细胞通过合成类骨质和分泌基质囊泡来促进矿化和骨形成。成熟的成骨细胞可分泌OCN参与糖代谢, OCN是一种由46~50个氨基酸残基组成的直链多肽, 翻译修饰后形成羧化OCN。骨基质中的羧化OCN通过提高破骨细胞的活性进而调节骨吸收和重塑, 然

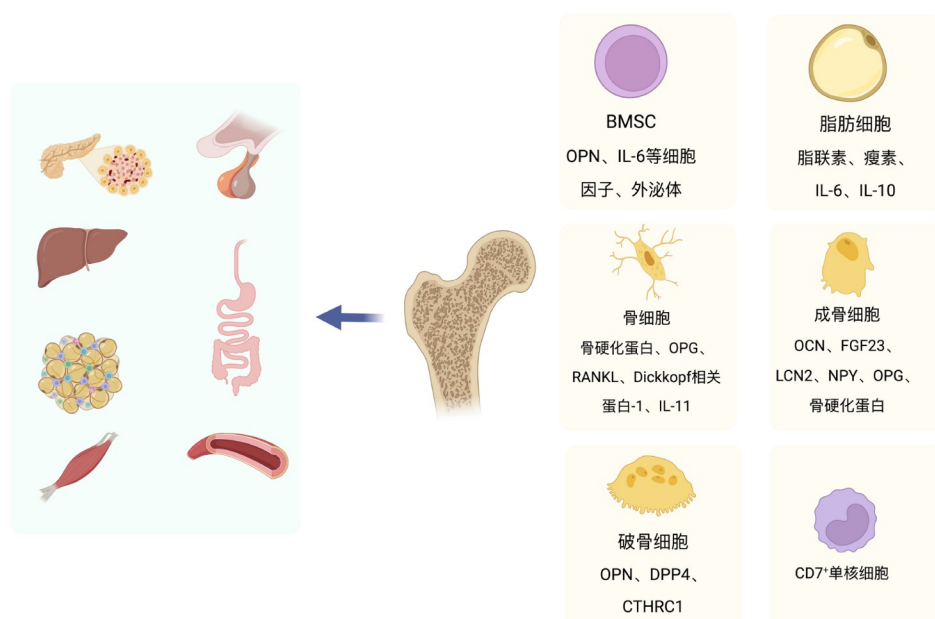


图 1 骨组织内的细胞包括骨细胞、成骨细胞和破骨细胞, 以及骨髓腔内的骨髓间充质细胞、骨髓脂肪细胞和免疫细胞等。不同类型的细胞能够分泌各种因子通过旁分泌或者内分泌作用调节体内多个器官的功能。这些细胞通过复杂的相互作用, 共同维持骨骼乃至全身的能量稳态。

Figure 1 Cells within bone tissue include osteocytes, osteoblasts, osteoclasts, bone marrow mesenchymal cells, bone marrow adipocytes, and immune cells. Different types of cells secrete various factors that regulate the function of multiple organs in the body through paracrine or endocrine mechanisms. Through complex interactions, these cells collectively maintain the energy homeostasis of the skeleton and the entire body.

而羧化OCN在骨形成及吸收中的作用及机制仍存在争议^[31,32]。OCN也能以未羧化的形式分泌到外周循环中, 通过促进葡萄糖的摄取和参与胰岛素信号转导, 调节全身的能量代谢^[33-35]。未羧化OCN直接抑制胰岛β细胞中固醇调节元件结合蛋白1c(sterol regulatory element binding protein 1c, SREBP1c)和碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, ChREBP)的表达, 从而促进β细胞增殖^[36]。未羧化OCN还可以通过调节其他激素来促进胰岛素分泌。在肠上皮细胞中, 未羧化OCN可以增加胰岛素刺激蛋白胰高血糖素样肽-1基因的表达^[37]。在非胰岛组织中, 未羧化OCN还可以提高葡萄糖的利用率, 并增强细胞对胰岛素的敏感性。未羧化OCN通过激活PI3K/AKT/NF-κB信号通路来缓解内质网应激, 从而改善脂肪细胞、肌细胞和血管内皮细胞的胰岛素抵抗。

成纤维细胞生长因子(fibroblast growth factor, FGF)家族在调节生物体的生长发育过程中发挥重要作用^[38,39], 其中FGF19, FGF21和FGF23被称为内分泌成纤维细胞生长因子, 因为它们的功能与代谢调节密切相关^[40]。FGF23是一种主要由成骨细胞和骨细胞分

泌的骨源性蛋白质^[41], 成骨细胞和骨细胞特异性敲除FGF23的小鼠血清中无法检测到FGF23^[42]。FGF23既可以作为自分泌或旁分泌因子直接作用于骨组织, 也可调节其他组织的功能以影响能量代谢。FGF23对FGFR/Klotho共受体复合物具有高度亲和力, 该复合物主要存在于肾脏和甲状旁腺中^[43,44], Klotho可与膜受体结合并抑制胰岛素抵抗^[45]。此外FGF23可增加小鼠血清和肝细胞中炎症因子的表达, 从而加重炎症引起的肝损伤; 循环中高水平的炎症因子可以诱导骨细胞中FGF23的分泌, 促进炎症因子和FGF23间的正反馈循环^[46-48]。肝细胞中FGF23异常升高可激活PLCγ/钙调磷酸酶(calcineurin, CaN)/活化T细胞核因子(nuclear factor of activated T cells, NFAT)信号通路, 促进更多炎症因子的释放。另一项临床研究显示血清FGF23水平与BMI、腰围、腰臀比、血脂和脂肪质量呈正相关^[47]。由于慢性炎症是导致肥胖的因素之一, FGF23与炎症因子之间的关系可能揭示了肥胖和脂质代谢的潜在机制。由于FGF23和FGF19/21在结构上具有同源性, 而FGF19/21参与胆汁酸稳态的维持和全身胰岛素敏感性的调节, 故推测FGF23可能具有类似效

果,这也为其调节能量代谢提供了另一潜在机制^[49-51]。

成骨细胞还能通过脂运载蛋白2(Lipocalin-2, Lcn2)调控糖脂代谢和食欲。尽管Lcn2以前被认为仅由脂肪组织分泌并与肥胖有关,但近期研究发现Lcn2在成骨细胞中高表达,且成骨细胞中Lcn2的表达水平至少比白色脂肪组织或其他器官高10倍^[52]。Lcn2对小鼠和人类的能量代谢具有一定益处。禁食后小鼠Lcn2浓度增加了3倍, Lcn2缺乏小鼠的摄食量大大增加,提示Lcn2对于食欲的调控作用。黑皮质素受体4(melanocortin-4 receptor, MC4R)是Lcn2的受体,控制体内的食欲、体重和能量平衡^[53], Lcn2可穿透血脑屏障并与下丘脑中脑室旁核的MC4R结合,进而激活MC4R依赖性抑制食欲信号通路。Lcn2对维持脂代谢和线粒体功能具有重要作用。Lcn2缺乏会导致含有长链多不饱和脂肪酸的心磷脂水平增加,含有单不饱和脂肪酸的心磷脂水平降低,从而破坏棕色脂肪组织中线粒体的动态平衡,导致线粒体功能障碍进而影响整体能量代谢及相关信号通路,尤其是mTOR通路^[54]。此外Lcn2缺陷还改变了磷脂酸的产生,这与磷脂代谢酶和mTOR信号通路的变化有关^[54]。Lcn2对脂代谢的另一作用表现在促进白色脂肪棕色化。用重组Lcn2处理成熟的3T3-L1脂肪细胞导致产热标记物和米色及棕色脂肪细胞标记物标记物的上调,并增加了线粒体活性^[55]。此外,与野生型小鼠相比,全身性Lcn2基因敲除小鼠的体重增加和内脏脂肪沉积速率更快,体现了Lcn2抗肥胖的作用^[55]。然而一些实验结果表明了Lcn2可能具有不利作用。例如Lcn2处理后脂肪细胞中葡萄糖转运蛋白1和葡萄糖转运蛋白4的水平及葡萄糖摄取显著下降^[56]。与野生小鼠相比, Lcn2敲除小鼠的空腹血糖明显降低,葡萄糖耐量升高^[57]。Lcn2可能通过上调IL-6的表达、减少过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor gamma, PPAR γ)和脂联素的表达来影响葡萄糖的利用^[58]。进一步研究发现, 2型糖尿病患者的Lcn2水平明显高于正常个体,其表达与C反应蛋白、IL-6和肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)等炎症标志物水平呈正相关^[59]。这些研究结果的差异可能与Lcn2信号通路的复杂性和研究方法的不同有关,也可能是因为不同组织分泌的Lcn2具有不同功能。例如全基因组Lcn2敲除小鼠的葡萄糖耐量增加且胰岛素敏感性不变^[60],而成骨细胞特异性敲除小鼠则表现出葡萄糖耐量降低和胰岛素敏感性受

损^[52]。

神经肽Y(neuropeptide Y, NPY)是成骨细胞调控糖代谢的另一靶点。NPY是大脑中含量最丰富的神经肽之一,由36个氨基酸组成^[61]。NPY最初被发现是一种强效的食欲刺激神经肽^[62],但后续研究发现NPY也在外周组织如脂肪组织、胰腺和骨骼中表达^[63]。在脂肪组织中, NPY可促进脂肪细胞增殖和脂肪生成;在胰腺中, NPY受体的激活可以减少 β 细胞凋亡并改善高血糖,表明外周组织分泌的NPY在内分泌系统中也具有重要调节作用^[58]。在骨骼中, NPY由成骨细胞分泌,通过自分泌和旁分泌作用于骨组织^[60]。通常认为NPY对骨形成没有直接影响,但可以减少高脂肪饮食喂养小鼠的骨质流失^[64]。也有研究表明NPY可能具有促进BMSCs增殖和抗凋亡作用^[65]。一项关于NPY受体的研究发现,小鼠早期成骨细胞谱系中Y1受体的特异性敲除可导致空腹血糖水平升高和葡萄糖耐量降低,这主要由胰岛素分泌减少所引起^[66]。但由于没有证据表明NPY会直接与胰岛细胞结合, NPY可能通过影响成骨细胞的功能间接影响其他器官的代谢,然而具体机制尚不清楚。

成骨细胞可大量分泌骨保护蛋白(osteoprotegerin, OPG), OPG是TNF受体超家族的成员,在骨、肺、肾、心血管等多个组织中均有表达^[67,68]。代谢综合征患者的OPG血清浓度显著升高,并伴有炎症标志物C反应蛋白和胰岛素抵抗的增加,以及内脏脂肪的增加^[69]。除了OPG/RANK/RANKL信号转导系统, OPG还有另一种配体,即肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)。OPG通过竞争性抑制TRAIL及其死亡受体trail-r1和trail-r2,从而抑制细胞凋亡。TRAIL及其受体也在人类胰腺 β 细胞中的表达^[70], TRAIL信号的激活可以导致正常胰腺 β 细胞的死亡,是1型糖尿病的潜在发病机制^[69]。糖尿病大鼠血管壁中的OPG/TRAIL比值显著降低^[71],表明OPG可能通过该途径调节能量代谢。近期研究发现OPG还可能通过抑制p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinases, p38 MAPK)的激活来影响胰腺 β 细胞, IL-1 β 诱导的 β 细胞死亡需要持续的p38 MAPK激活,而OPG可抑制p38 MAPK激活^[72-74]。此外, OPG可能通过影响OCN的分泌来调节骨吸收和葡萄糖代谢^[75]。研究表明血清OPG水平与代谢性疾病如非酒精性脂肪肝有关^[76]。然而

OPG或OPG/RANK/RANKL信号系统与代谢紊乱之间的关系尚不清楚。尽管成骨细胞分泌大量OPG,但由于OPG在其他组织的广泛表达,很难确定骨源性OPG是否直接影响胰腺 β 细胞。

糖尿病、肥胖症和骨质疏松症等代谢性疾病通常伴有骨形成受损和骨硬化蛋白水平升高引起的骨量低^[77]。骨硬化蛋白是一种主要由成熟骨细胞分泌的糖蛋白^[78],可抑制成骨细胞活性并维持骨骼在正常情况下的强度。骨硬化蛋白的缺乏会导致骨过度硬化,其过度表达则会抑制骨骼的形成^[79]。代谢紊乱状态下,骨硬化蛋白不仅可以作用于骨组织,还可以作为内分泌因子在远处器官中发挥作用。Daniele和Yu等人的临床研究发现骨硬化蛋白与2型糖尿病患者的空腹胰岛素水平和胰岛素抵抗有关^[80]。但也有研究表明敲除骨硬化蛋白的小鼠脂肪含量下降,胰岛素敏感性增高^[81],而骨硬化蛋白的增高可以促进米色脂肪的形成^[82]。这些结果表明骨硬化蛋白含量的上升可能不是代谢性疾病的结果,而是促使这些疾病发生的一个因素,但具体机制仍不清楚。骨硬化蛋白不仅会影响骨局部的钙化,还会影响心血管组织、肾脏、肌腱等其他部位的钙化^[83]。研究发现2型糖尿病患者的动脉粥样硬化发病率与血清硬化蛋白间存在关联;而硬化蛋白可能通过降低低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)和钙水平来减少动脉粥样硬化斑块的形成,从而保护血管内皮并抑制动脉粥样硬化^[84,85]。在2型糖尿病患者中,高血糖等促动脉粥样硬化因素会促进LDL-C的氧化,血管壁内的积累的巨噬细胞可有效识别氧化的LDL-C,导致脂质在巨噬细胞中积聚,促进动脉粥样硬化和血管硬化^[86,87]。而骨硬化蛋白可通过降低LDL-C减少脂质积累,从而减轻血管损伤。此外,硬骨蛋白还可通过抑制血管钙化起到保护作用,因为骨硬化蛋白可以抑制Wnt信号通路,进而抑制了炎症激活过程所需的Wnt/ Ca^{2+} 途径^[88]。

3 骨细胞

作为骨组织中含最丰富的细胞,骨细胞在能量代谢中发挥着关键作用,其作用不仅局限于局部的骨组织,还对全身的能量代谢产生影响。作为骨骼系统的主要机械感应细胞,骨细胞能感知机械负荷并通过分泌多种Wnt信号通路拮抗因子,如骨硬化蛋白和

Dickkopf相关蛋白-1,进而调控成骨细胞和破骨细胞的活性^[89,90]。骨细胞还通过分泌RANKL调控破骨细胞的形成和功能,从而影响骨吸收,RANKL是促进破骨细胞生成的关键细胞因子,缺乏RANKL的骨细胞会导致破骨细胞减少和骨质增厚^[91]。与此同时,骨细胞还可以通过分泌OPG来阻止RANKL与破骨细胞前体结合,抑制骨吸收^[92]。此外,骨细胞与其他组织间的相互作用同样影响着机体能量代谢。运动导致骨骼承受机械负荷,并刺激脂肪组织的能量消耗,而骨细胞分泌的因子可能是沟通机械负荷和脂肪消耗的桥梁。骨表达的IL-11在机械负荷时上调,促进骨生成并抑制脂肪生成^[93]。研究表明,全身性敲除IL-11的小鼠骨量减少,全身脂肪增加且葡萄糖耐受性降低;骨细胞和成骨细胞特异性缺乏IL-11的小鼠也表现出类似的骨生成减少和全身脂肪增加,但脂肪细胞特异性缺乏IL-11的小鼠则没有任何异常^[93]。这些发现表明骨细胞在响应机械负荷的同时可调控骨生成和全身脂肪含量,并参与全身能量代谢。

4 破骨细胞

破骨细胞是由单核-巨噬细胞融合而成的巨型多核细胞,通过骨吸收参与骨骼局部能量代谢。破骨细胞可通过旁分泌的方式调节成骨活动。破骨细胞所分泌的富含OPN的细胞外囊泡可促进BMSC的成骨分化,具体而言,OPN可激活TGF- β 和Smad3进而促使BMSC分化为成骨细胞^[94]。成熟的破骨细胞分泌胶原三螺旋重复蛋白-1(collagen triple helix repeat containing-1, CTHRC1),促进骨间充质干细胞的成骨分化,同时特异性敲除破骨细胞中的Cthrc1会导致骨量下降和骨形成减少^[95]。破骨细胞所介导的骨吸收往往与成骨相耦联,以确保在某些骨吸收部位可以形成新骨,一项临床研究将二肽基肽酶4(dipeptidyl peptidase 4, DPP-4)确定为破骨细胞所分泌的重要骨能量代谢耦联因子^[96]。在接受地诺单抗消融破骨细胞的患者中,DPP-4的循环含量显著下降,但胰高糖素样肽-1(glucagon-like peptide-1, GLP-1)的含量上升;此外,与接受双膦酸盐或钙和维生素D治疗的2型糖尿病患者相比,接受地诺单抗治疗的2型糖尿病患者糖化血红蛋白显著降低,提示DPP-4不仅参与了骨重塑,还可能对全身能量代谢造成影响^[96]。

5 骨髓脂肪组织

BMSC不仅具有成骨能力,也具有成脂潜力,且成脂能力的增加往往伴随成骨能力的下降.哺乳动物椎骨中的骨髓脂肪细胞具有类似棕色脂肪组织的产热特征,而在胫骨中则通常表现出类似白色脂肪组织的表型^[97].虽然关于这两种骨髓脂肪细胞的形成转化及其各自的内分泌功能的研究还不充分,但骨髓脂肪细胞的确可以分泌多种调控因子来发挥其功能^[98].

脂联素在调节脂肪代谢、胰岛素分泌和其他代谢途径方面具有重要作用,其受体在骨骼肌、肝脏和胰腺等组织器官中均有表达^[99, 100].脂联素与受体结合后激活PPAR α , AMPK和p38MAPK从而调节糖脂代谢^[101].此外脂联素还可穿过血脑屏障作用于中枢神经系统.虽然骨髓脂肪细胞分泌的脂联素对全身代谢的作用尚未完全证实,但其在骨骼肌细胞代谢中的作用已得到证实.脂联素可刺激钙离子的流入和肝激酶B1激活,增强AMPK活性和线粒体生物合成^[102].胰岛素可以抑制人骨髓脂肪细胞中脂联素的表达,提示高胰岛素血症可能影响骨髓脂肪细胞的功能^[103].研究发现人类成骨细胞中脂联素的转录和翻译很低,对从胫骨和股骨提取的成熟成骨细胞进行定量分析发现,其水平仅占人皮下脂肪组织中脂联素的3%^[104],因此骨髓来源脂联素在能量代谢中的作用仍有争议.

瘦素主要由白色脂肪组织分泌,与肥胖直接相关.瘦素受体在许多组织均有表达,其中在下丘脑弓状核、脾、肺、肝、肾和肾上腺中的表达量较高^[105].瘦素与其受体结合后激活下游STAT, PI3K和MAPK信号通路^[106].瘦素不仅可以直接作用于胰岛细胞并抑制胰岛素分泌,还可调节脂肪细胞,改变细胞对胰岛素的敏感性,或作用于大脑的摄食中枢,从而抑制食物摄入并减少脂肪含量^[107].最近发现,骨髓脂肪组织也能表达瘦素,并可直接作用于骨中的瘦素受体,通过激活FGF23和调节OCN的分泌来影响骨骼生长^[108].然而没有明确的证据表明MAT中的瘦素可以调节整体代谢.

IL-6和TNF- α 等炎症基因在骨髓脂肪细胞中高度表达^[109].然而这些骨源性促炎因子在血清中的水平通常较低,针对其全身效应的研究较少.体外研究发现,人类骨髓脂肪细胞可以分泌少量的IL-1 β 和TNF- α ,但分泌大量的IL-6,这表明骨髓脂肪细胞可能参与全身脂肪代谢和炎症反应.IL-10是一种具有抗炎特性的细

胞因子,其抗炎作用依赖于与受体复合物IL-10R α 和IL-10R β 结合,后者触发信号转导并激活转录激活因子3^[110].骨髓细胞也能表达IL-10,IL-10可以附着在脂肪细胞上的IL-10R α 受体.与骨髓细胞特异性IL-10敲除小鼠相比,整体IL-10敲除小鼠具有更高的白色脂肪组织含量、更高的血糖水平和更低的葡萄糖耐量,因此推断骨髓来源的IL-10是影响脂肪褐变和胰岛素敏感性的关键因素^[111].

6 骨髓免疫细胞

骨髓具有强大的造血功能,骨髓造血干细胞向髓系和淋巴系分化成粒细胞、单核细胞及淋巴细胞等从而参与机体能量代谢的调节.机体代谢紊乱会导致骨髓成分出现异常.研究表明,作为RAS-MAPK通路负调节因子的Spred1在高脂肪饮食条件下对维护造血干细胞稳态发挥重要作用,而Spred1的敲除则会使造血干细胞在面对高脂饮食压力时出现功能失调^[112].

近年来提出了一种新的骨髓免疫调控体重反弹的理论,该理论指出,骨髓CD7⁺单核细胞亚群能响应能量状态的变化,通过促进白色脂肪米色化来改善机体能量代谢,从而对抗体重反弹.体重反弹是肥胖症治疗中的一大挑战.免疫细胞能对机体摄入能量的变化作出反应,但它们在调节体重反弹中的作用仍不清楚.研究发现了干细胞样的CD7⁺单核细胞亚群在节食引起的体重减轻的小鼠和人类骨髓中聚集.这些细胞可抑制体重反弹,而CD7⁺单核细胞的消耗则会加速体重反弹^[113].CD7⁺单核细胞通过表观遗传改变获得了代谢记忆,优先迁移到皮下白色脂肪组织,并在那里分泌纤维蛋白原样蛋白2,激活蛋白激酶A信号通路,促进米色脂肪产热.然而CD7⁺单核细胞在减肥后会逐渐进入静止状态,增加体重反弹的风险.值得注意的是,FMS样酪氨酸激酶3(Fms-like tyrosine kinase 3, Flt3)配体可显著恢复CD7⁺单核细胞的活力,从而改善体重的快速反弹.这种独特的骨髓来源的代谢记忆免疫细胞群可以作为防治肥胖症的靶标.作为单核-巨噬细胞系统的另一成分,巨噬细胞也参与了能量代谢.早期研究发现,运动能够促进骨髓巨噬细胞分泌RCN2,进而促进骨髓脂肪分解及骨和淋巴细胞生成,这为治疗骨质疏松症和增强免疫力提供了新策略^[114].骨髓巨噬细胞还可通过分泌外泌体调节代谢稳态,骨髓来源M2巨噬细胞外泌体高表达

miR-690, 在体内和体外发挥胰岛素增敏作用^[115]。

机体的衰老往往伴随着多种细胞代谢功能的变化, 分泌颗粒钙蛋白(grancalcin, GCA)的免疫细胞亚群可通过分泌GCA结合Plexin-B2调节BMSC成骨-成脂命运分化, 进而调节骨衰老^[116]。骨骼干细胞衰老是导致骨再生潜力下降的主要原因, 但具体机制仍不清楚。脾脏体中的巨噬细胞在衰老过程中会分泌包括粒GCA在内的前衰老因子, 进而引发骨骨骼干细胞衰老并影响骨折愈合。向幼鼠局部注射GCA可诱导骨骼干细胞衰老并延迟骨折修复。敲除单核细胞-巨噬细胞中的Gca足以促进年老小鼠的骨折修复并缓解骨骼干细胞衰老。在具体机制方面, GCA与Plexin-B2受体结合并激活Arg2介导的线粒体功能障碍, 从而导致细胞衰老。骨骼干细胞中Plexin-B2的消耗会影响骨折愈合, 而给予GCA中和抗体则能够促进年老小鼠的骨折愈合, 因而GCA的中和可能成为治疗老年人骨折不愈合或延迟愈合的潜在方法。

7 讨论

骨骼健康与个体的能量代谢紧密相关, 如糖尿病患者患骨质疏松症的风险高于正常人、过低的体重通常伴随着骨密度下降^[117]。骨组织中的瘦素、胰岛素和脂联素受体的存在表明能量代谢对骨代谢有直接影响^[118]。此外, 骨组织在其不断更新过程中产生和消耗的能量也会影响全身的能量代谢。OCN的发现进一步证实了骨在调节全身能量代谢中的重要作用。成骨细胞分泌的Lcn2以及骨髓脂肪组织分泌的瘦素和脂联素, 可穿过血脑屏障作用于中枢神经系统, 对骨源性因子及其相互作用的进一步研究有助于了解中枢神经系统能量平衡的机制。骨源性外泌体也是近年来的一个新研究领域, 已被发现可以调节骨骼本身和其他组织^[119]。然而由于外泌体的普遍性和其内容的多样性, 骨源性外泌体的其他功能值得进一步探究。

骨对能量代谢相关器官具的调控作用极其复杂, 这可能与骨组织分泌因子受体在不同细胞表面的分布

和比例差异有关。此外, 骨源性因素发挥功能的过程中可能受到多种因素的影响, 包括遗传背景、年龄和个体健康状况。例如OCN的脱羧依赖于维生素K, 因此人体内的维生素K浓度会影响OCN的生理功能。

探究骨对能量代谢的调控的关键点之一是明确骨源性因子的变化与能量代谢改变之间的因果关系, 这包括证明那些在组织和器官中起关键作用的因子是否来自骨组织。对于OCN和FGF23等骨源性因子而言, 其来源较易确定, 因为它们主要由骨细胞分泌。但对于在多个组织和器官中表达的因子, 则往往需要通过基因工程技术进行研究。然而目前并非所有骨源性因子都有合适的特异性敲除动物模型。此外需要注意的是, 骨组织中的一些自分泌因子虽然不能分泌到血液循环并作用于其他器官, 但它们仍可以通过调节骨代谢来间接影响全身代谢。

鉴于骨对全身能量代谢的复杂调控, 未来研究将可能聚焦于骨源性因子及各种骨组织细胞亚型的临床应用。衰老的过程伴随着骨代谢和全身代谢的持续变化, 可能导致代谢紊乱并影响骨骼健康。骨骼老化的特征主要包括骨质的减少和骨髓脂肪的增多^[120], 由此导致的骨源性因子水平变化可能与葡萄糖耐量下降、胰岛素抵抗的发生和炎症反应的增强等变化有关, 并可进一步促进代谢疾病的发生。骨骼是重要的运动器官, 而运动被发现可以对骨骼代谢产生重大影响^[121]。不仅骨骼, 研究表明运动能够改善骨骼代谢, 并通过多种机制改变整体新陈代谢状态并延缓衰老^[122], 其机制之一可能是通过影响骨代谢和骨源性因子的分泌。因此运动疗法有望成为治疗或预防代谢疾病, 尤其是与衰老有关疾病的有效策略。

值得进一步探究的是, 这些骨源性因子或骨组织内免疫细胞亚型是否可作为治疗代谢性疾病及其相关并发症的新靶点。例如OPG已被发现是绝经后妇女糖尿病诊断的潜在标志物, 另有实验研究了OPG-RANKL-RANK信号传导是否会影响糖尿病患者的心血管并发症^[123]。需要更多实验进一步证实骨组织在临床治疗中的应用潜力。

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The role of bone in energy metabolism

LUO XiangHang, GUO QiaoYue & XIONG JinMing

Department of Endocrinology, Endocrinology Research Center, Xiangya Hospital of Central South University, Changsha 410008

Bone serves primarily as a support for the entire body and is the primary regulator of calcium homeostasis and hematopoietic function. An increasing number of recent studies have highlighted the importance of bone as an endocrine organ. These studies suggest that bone-derived factors regulate local bone metabolism and the body's metabolic functions. These findings could help to provide novel pathologic mechanisms for associated metabolic diseases or may help to diagnose, treat, and prevent metabolic diseases such as osteoporosis, obesity, and diabetes. This review summarizes the regulatory effects of bone and bone-derived factors on energy metabolism and discusses future research directions.

bone, energy metabolism, bone-derived factors, bone metabolism, metabolic diseases

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