物理疗法调控骨髓间充质干细胞成骨分化治疗骨质疏松症的研究进展

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摘　要　骨质疏松症(osteoporosis,OP)的发生与成骨细胞介导的骨形成和破骨细胞介导的骨吸收之间的平衡被打破密切相关,而骨髓间充质干细胞(bone mesenchymal stem cell,BMSC)成骨分化对维持二者平衡至关重要。物理疗法治疗 OP 具有疗效好、安全性高等特点,在临床上逐渐被广泛使用。多项研究表明,多种物理疗法治疗 OP 的作用机制与调控 BMSC 成骨分化密切相关。本文对运动疗法、全身振动、脉冲电磁场、体外冲击波等物理疗法调控 BMSC 成骨分化治疗 OP 的研究进展进行了综述。

关键词　骨质疏松;物理治疗方法;间质干细胞;细胞分化;骨生成;信号传导;综述

骨质疏松症(osteoporosis,OP)是一种以骨量减少、骨组织微结构破坏,导致脆性骨折风险增高为特征的全身性骨代谢疾病[1]。目前,临床治疗 OP 主要以药物治疗和物理疗法为主。药物治疗周期长、不良反应多,患者依从性不佳,影响临床疗效[2-3]。物理疗法主要包括运动疗法和物理因子疗法,其中物理因子疗法包括全身振动、脉冲电磁场、体外冲击波等[4]。有研究[5-6]表明,物理疗法能够促进骨小梁重塑、提高骨密度,延缓 OP 进展,其作用机制与调控骨髓间充质干细胞(bone mesenchymal stem cell,BMSC)成骨分化密切相关。本文对运动疗法、全身振动、脉冲电磁场、体外冲击波等物理疗法调控 BMSC 成骨分化治疗 OP 的研究进展进行了综述。

1　运动疗法调控 BMSC 成骨分化治疗 OP

目前尚无统一的运动疗法治疗标准,临床上多根据患者自身情况进行个性化定制。多项研究表明[7-11],运动疗法在提高 OP 患者骨密度、减少骨丢失、降低骨折风险方面疗效显著。Watson 等[7]研究发现,高强度抗冲击训练能够提高绝经后低骨密度女性腰椎和股骨的骨密度。Filipovic 等[8]针对绝经后 OP 患者制定了 12 周的运动计划,结果显示其可改善绝经后女性骨强度,降低骨折风险。Ng 等[9]的研究结果表明,16 周的单侧跳跃冲击运动能够改善绝经后女性股骨颈、胫骨远端的骨密度。Harding 等[10]针对中老年骨质疏松患者开展了为期 8 个月的运动治疗,每周进行 2 次高强度抗冲击训练和等距轴向压缩训练,结果显示治疗结束后患者股骨近端骨密度较治疗前提高。

运动过程中产生的肌肉张力和机械应力能够作用于骨骼,引起骨内压力变化,组织液通过腔隙小管系统自高压区流向骨细胞所在的低压区,组织液流动刺激骨细胞,导致骨细胞内钙浓度、环磷酸腺苷(cyclic adenosine monophosphate,cAMP)、肌醇三磷酸、前列腺素等物质增加[11]。这些物质一方面能够促进骨膜细胞的矿化作用,另一方面能够促进 BMSC 向成骨细胞转化,增加骨形成。BMSC 属于机械刺激敏感型细胞,运动治疗过程中产生的机械刺激能够通过多条信号通路发挥作用,从而影响 BMSC 成骨分化[12]。Case 等[13]研究发现,运动疗法能够增加小鼠 BMSC 的数量,并促使其成骨分化,其作用机制与 β-连环蛋白的激活以及过氧化物酶增殖物激活受体-γ(per-oxisome proliferater-activated receptor-γ,PPAR-γ)的表达抑制有关。Li 等[14]研究发现,运动疗法能够促进 Runx 相关转录因子 2(Runt-related transcription factor 2,Runx2)、成骨相关转录因子 Osterix 以及 Wnt/β-连环蛋白信号通路相关蛋白的表达,抑制 PPAR-γ、转录因子 CCAAT/增强子结合蛋白(CCAAT/enhancer-binding protein,C/EBP)的表达,从而能够促进 BMSC 成骨分化,抑制其成脂分化。Runx2 是骨形成蛋白(bone morphogenetic protein,BMP)家族的靶基因,是 BMSC 成骨分化的重要调节因子[15]。Yuan 等[16]研究发现,运动疗法能够激活 BMP 家族,进而诱导 Runx2 表达,发挥促进 BMSC 成骨分化的作用。Chen 等[17]研究发现,循环拉伸能够

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激活 AMP 活化蛋白激酶(AMP - activated protein kinase,AMPK),上调沉默信息调节因子 1(silence information regulator 1,SIRT1),通过 AMPK - SIRT1 信号通路上调 Runx2 的表达,进而促进 BMSC 成骨分化。此外,miRNAs 在运动疗法调控 BMSC 成骨分化过程中发挥重要的作用。Mao 等[18]研究发现,运动疗法还可下调靶向 BMSC 成骨分化相关基因的 miRNAs、上调靶向 BMSC 破骨分化相关基因的 miRNAs,促进成骨细胞的增值与分化,抑制破骨细胞的增殖与分化。母系表达基因 3(maternally expressed gene 3,MEG3)是长链非编码 RNA(long noncoding RNA,lncRNA)的一员,可调控 BMSC 成骨分化;Zhu 等[19]研究发现,拉伸应变可上调 lncRNA - MEG3 的表达,抑制 BMSC 中 miR - 140 - 5p 的表达,促进 BMSC 成骨分化。

2 全身振动调控 BMSC 成骨分化治疗 OP

全身振动是一种能够改善肌肉 - 骨骼系统的训练方法,其主要通过机械振动和外部负荷激活相应的神经反射,促进肌肉收缩的同时对骨骼产生反复的压力刺激[20]。相关研究[21]表明,全身振动能够促进骨形成、抑制骨吸收,进而提高骨强度和骨密度,降低发生骨质疏松性骨折的风险。Eldeeb 等[22]采用全身振动治疗绝经后低骨密度患者,在治疗 24 周后,患者腰椎、股骨骨密度均增加。Luo 等[23]的研究结果也表明,绝经后低骨密度患者在进行全身振动训练后,腰椎、股骨骨密度增加。Yu 等[24]研究发现,采用加速度 <1 g、频率 20 ~ 90 Hz 的低强度振动能够有效促进 BMSC 成骨分化,增强骨形成。Wysocki 等[25]研究发现,低强度振动能够通过 miR - 378a - 3p 增强 Runx2、碱性磷酸酶(alkaline phosphatase,ALP)、Ⅰ型胶原蛋白及骨钙素的表达,进而促进 BMSC 成骨分化。Li 等[26]研究发现,低强度振动一方面能够上调 Runx2、成骨相关转录因子 Osterix、Ⅰ型胶原蛋白及骨钙素 mRNA 和蛋白的表达,下调 PPAR - γ 的表达,另一方面能够上调雌激素受体的表达,并激活 Wnt 信号通路,进而促进 BMSC 成骨分化。Zhao 等[27]研究发现,低强度高频率振动能够抑制 PAR - γ、转录因子 C/EBP、脂联素的表达,促进 p38、促分裂原活化的蛋白激酶磷酸化,进而促进 BMSC 成骨分化,增强骨形成。此外,Wen 等[28]研究发现,低强度振动能够促进大鼠的骨形成,并能够通过 SIRT1/p53/p21 信号通路抑制成骨细胞的衰老。

3 脉冲电磁场调控 BMSC 成骨分化治疗 OP

脉冲电磁场是一种治疗 OP 的非侵入性物理因子疗法,目前已在临床上广泛应用,并取得良好疗效[29]。Ebid 等[30]采取脉冲电磁场结合运动疗法对 95 例 OP 男性患者进行了 12 周的治疗,结果显示患者髋关节和腰椎骨密度显著增加。Liu 等[31]分别采用阿仑膦酸钠口服和脉冲电磁场治疗绝经后 OP 患者,治疗 24 周后 2 组患者腰椎和股骨近端骨密度均显著提高,且 2 组提高率无显著差异。Catalano 等[32]采用脉冲电磁场治疗 43 例绝经后 OP 患者,结果显示核因子 κB 受体活化因子配体与骨保护素(osteoprotegrin,OPG)的比值显著降低,Dkk - 1 表达量降低、β - 连环蛋白表达量升高。BMSC 具有向成骨细胞、软骨细胞及脂肪细胞等多种细胞分化的潜能。脉冲电磁场能促进 BMSC 中 ALP、BMP - 2 的表达,并抑制脂肪因子、激活蛋白 2 等成脂分化相关的转录因子的表达,从而促进 BMSC 成骨分化、抑制 BMSC 成脂分化[33]。BMP - 2 是骨基质中的酸性蛋白,属于转化生长因子(transforming growth factor,TGF) - β 超家族成员[34]。Martini 等[35]将人 BMSC 暴露于频率 75 Hz、强度 1.5 mT 的脉冲电磁场中,结果表明脉冲电磁场可促进 BMP - 2、BMP - 6 和 BMP Ⅰ型受体基因表达,增强人 BMSC 成骨分化。白细胞介素(interleukin,IL) - 6 是趋化因子家族的一种细胞因子,也是炎症因子之一。Wang 等[36]研究发现,IL - 6 能够激活 Toll 样受体(Toll - like receptor,TLR)2、TLR4 和 Akt 通路,从而抑制 β - 连环蛋白、Setd7 的表达,抑制成骨分化。脉冲电磁场则能够上调腺苷受体 A2a、A3 的表达,降低 IL - 6、IL - 8 等炎症因子的表达,增加 cAMP、IL - 10 等的表达,进而促进成骨分化[37]。此外,De Mattei 等[38]研究发现,脉冲电磁场能够通过上调 miR - 26a 和 miR - 29b 的表达、降低 miR - 125b 的表达,促进 BMSC 成骨分化。因此,脉冲电磁场不仅能够通过调控成骨分化及成脂分化相关蛋白的表达促进 BMSC 成骨分化,同时还能够通过抑制炎症因子的表达、调控相关 miRNA 的表达来促进 BMSC 成骨分化,进而影响 OP 的进展。

4 体外冲击波调控 BMSC 成骨分化治疗 OP

体外冲击波是一种高能量压力波,能够对人体组织产生空化效应,在细胞水平产生力学刺激,从而促

进多种生长因子的表达[39-41]。Huang 等[42]研究发现,体外冲击波能够增强骨质疏松大鼠骨折区域 OPG 和 BMP-2 的表达,促进骨形成。Wölfl 等[43]研究发现,体外冲击波能够提高低骨密度患者的骨转换标志物的表达水平。Shi 等[44]研究发现,体外冲击波可诱导氧化还原反应,增加胞外信号调节激酶的信号转导,激活内皮型一氧化氮合酶,从而促进成骨分化。Wang 等[45]研究发现,体外冲击波可引起膜扰动,并激活 Ras 信号通路,诱导核心结合因子 a1、Ⅰ型胶原蛋白和骨钙素 mRNA 表达,促进 BMSC 成骨分化。Li 等[46]研究发现,体外冲击波能够通过 TGF-β/Sma 和 Mad 相关蛋白(Sma-and Mad-related protein,Smad)2 途径促进 BMSC 成骨分化;Smad 家族介导 BMP 信号通路,其中 Smad2 可转化 TGF-β 信号,诱导 BMSC 成骨分化相关基因表达。

5　小　结

OP 的发生与成骨细胞介导的骨形成和破骨细胞介导的骨吸收之间的平衡被打破密切相关,而 BMSC 成骨分化对维持二者平衡至关重要。BMSC 属于机械刺激敏感型细胞,其能够将生物力学信号转化为生物化学信号,影响其增殖分化。物理疗法治疗 OP 取得了显著的临床疗效,其能够通过调控 BMSC 成骨分化来达到增加骨密度和骨强度、降低脆性骨折发生率的目的。然而,目前已有研究表明,运动疗法、全身振动、脉冲电磁场、体外冲击波等物理疗法能够通过多条信号通路调控 BMSC 成骨分化,但其具体作用机制较为复杂,尚未完全明确。因此,对于不同物理疗法调控 BMSC 成骨分化的具体机制,尚需进一步开展动物实验、细胞实验等进一步深入研究。

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