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·综述·

脉冲电磁场对骨髓间充质干细胞作用研究进展

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摘要：目的 旨在探究脉冲电磁场对骨髓间充质干细胞作用条件及机制，以促进其临床应用。**方法** 由第一作者应用计算机检索 PubMed、中国期刊全文数据库(CNKI)、维普数据库和万方数据库 1997-05/2012-03 相关文献。在标题、摘要、关键词中以“pulsed electromagnetic field(PEMFs), bone marrow mesenchymal stem cells(BMMSCs), differentiation, proliferation”或“脉冲电磁场，骨髓间充质干细胞，分化，增殖”为检索词进行检索。选择文章内容与脉冲电磁场有关者，同一领域文献则选择近期发表在权威杂志文章。初检得到 184 篇文献，根据纳入标准选择 41 篇文献进行综述。**结果与结论** 在一定条件下，脉冲电磁场对骨髓间充质干细胞的增殖及分化有促进作用，对于骨质疏松、骨不连等临床应用有一定意义。

关键词：脉冲电磁场；骨髓间充质干细胞；分化；增殖

Research progress of mechanism of pulsed electromagnetic field on bone marrow mesenchymal stem cells

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Abstract: Objective To explore the mechanism of pulsed electromagnetic field on bone marrow mesenchymal stem cells in order to promote its clinical application. **Methods** A computer-based online search of PubMed database, CNKI database, VIP database, and Wanfang database from May 1997 to May 2012 was performed to search related articles with the key words of pulsed electromagnetic fields (PEMFs), bone marrow mesenchymal stem cells (BMMSCs), differentiation, and proliferation in English or Chinese. Literatures related to pulsed electromagnetic field were selected. Articles published lately in authorized journals were preferred in the same field. A total of 184 literatures were primarily selected, and 41 documents were involved for summary according to inclusion criteria. **Results and Conclusion** Under certain conditions, pulsed electromagnetic fields promote proliferation and differentiation of bone marrow mesenchymal stem cell. This can be used for osteoporosis, bone non-union, and other clinical applications.

Key words: Pulsed electromagnetic field (PEMFs); Bone marrow mesenchymal stem cells (BMMSCs); Differentiation; Proliferation

电磁技术在骨科治疗中的应用已经历一个多世纪的探索，自 20 世纪 70 年代起脉冲电磁场开始应用于临床，随着电磁技术的发展，近年来已有学者开始研究脉冲电磁场对于骨髓间充质干细胞增殖及分化的影响。但目前文献仅集中于对实验现象的描述，对脉冲电磁场频率对骨髓间充质干细胞影响的研究较少，并且对于脉冲电磁场如何促进骨髓间充质干细胞增殖及向成骨细胞分化的机制尚未明确。本文总结了不同频率脉冲电磁场对骨髓间充质干细胞的影响，及脉冲电磁场促进骨髓间充质干细胞增殖、向成骨细胞分化的作用机制，以促进其临床应用。

1 不同频率脉冲电磁场对于骨髓间充质干细胞影响

研究发现，PEMF 对干细胞的影响，直接取决于

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脉冲的时间,频率和电场强度[1]。在电磁场的各项参数中,频率对电磁场所产生的生物学效应有较大的影响[2]。有研究认为,电磁场产生生物学效应的频率范围大约在 1 ~ 100HZ[3]。骨骼系统的内生性活动频率范围在步态频率(1 ~ 5HZ)到肌肉收缩的动力频率(10 ~ 100HZ)间变化。Lee 等[4]认为,最有效的电磁场频率范围应接近机体正常功能活动频率。Sudeepta 等[5]研究表明一定"窗口"内的磁场能促进活细胞增殖反应及细胞转化,能使细胞表面蛋白分子产生电泳作用,从而调节受配体结合信号转导系统,能使细胞内的 cAMP 水平呈现升高而促发一系列的磷酸化生物信号放大反应,进而调控细胞增殖。

大量的国内外研究表明,低频脉冲电磁场具有促进成骨及细胞增殖的作用,而高频磁场的促成骨及细胞增殖能力则较弱甚至有负面影响[6]。Ragbetli 等[7]研究表明高频脉冲电磁场(> 300 MHz)干预下的 BMSCs 增殖活性有所下降。Kaszuba 等[8]研究表明高频脉冲电磁场干预组细胞凋亡率升高,总蛋白量下降。Chang 等[9]研究表明高频脉冲电磁场对干细胞增殖和分化的负面影响可能与热效应有关。Tsai 等[10]发现高频脉冲电磁场致使 DNA 发生断裂,放慢了干细胞周期的进程,致使增殖延迟。Hao 等[11]发现高频脉冲电磁场阻滞了干扰了细胞的信号传导,影响了细胞膜功能。Belyaev 等[12]研究表明高频干扰了基因的转录和翻译,从而使蛋白质表达谱发生变化。

因此找到合适频率的电磁场,在干细胞分化和增殖的合适时间给予适当的刺激,对于调控干细胞增殖分化具有重要的临床价值[13]。有研究表明。15 ~ 30 Hz 的脉冲电磁场促进成骨作用最强[6]。Simmons 等[14]认为 MSCs 经 12 Hz,1.1mT 的 PEMFs 合理刺激后,细胞增殖加速,符合成骨细胞的形态特征和生物学特性。Tsai 等[15]研究表明 7.5HZ 的脉冲电磁场通过调节细胞活性,促进成骨。

2 脉冲电磁场对骨髓间充质干细胞增殖的影响

研究显示,脉冲电磁场具有促进骨髓间充质干细胞(BMSCs)增殖的作用。Sun 等[16]研究了脉冲电磁场照射对骨髓间充质干细胞(BMMSCs)增殖的影响,发现 BMSCs 每天接受 8 h 脉冲电磁场的处理后,在接种密度为 1000 和 3000 个细胞/cm^2 的培养皿中的存活率分别增加了 59% 与 40%,BMSCs 在指数增长期的细胞密度增加了 2060%,细胞周期分析表明在脉冲电磁场处理的第 12 ~ 16 h 出现很多新分裂的细胞;在另一项脉冲电磁场照射对骨髓间充质干细胞(BMMSCs)增殖影响的研究中发现在分化的第 1 天曝光于脉冲电磁场的 BMMSCs 细胞比未经处理的细胞增殖增加 29.6%[17]。这些结果表明,脉冲电磁场在早期增强 BMMSC 介导的成骨细胞增殖,并加快成骨。研究还表明电磁场暴露可以提高 BMMSC 细胞指数阶段的增殖[16]。对于脉冲电磁场如何对细胞产生促增殖效应,目前有许多说法。Callaghan 等[18]认为脉冲电磁场通过物理效应直接促进细胞增殖与分化,但研究认为脉冲电磁场主要通过离子通道、骨形态发生蛋白-2、环磷腺苷等促进 BMMSC 增殖。

2.1 离子通道

在正常情况下,细胞遵循着一定的细胞周期,通过自我复制进行增殖,磁场对细胞周期的影响主要表现在对细胞的 S、G2 期进程起促进或阻断作用。Deng[19]等研究表明离子通道的表达对细胞增殖有一定影响,在未分化 BMMSCs 中观察到从 G1 期到 S 期 Ca^{2+} 通道活性增加而 K^+ 通道活性下降,从而促进细胞增殖。Sammons 等[20]研究表明脉冲电磁场通过增加 Ca^{2+} 内流,调节胞内 Ca^{2+} 浓度,影响细胞周期,促进细胞增殖。

2.2 骨形态发生蛋-2(BMP-2)

Selvamurugan 等[21]研究表明电磁场通过促进细胞分泌骨形态发生蛋白 2(BMP-2)促进骨髓间充质干细胞的增殖。Pountos 等[22]研究表明人骨形态发生蛋白-2 可以促进骨髓间充质干细胞的增殖。Kessler 等[23]也报道,rhBMP-2 不但能够促进 BMSCs 的分化,同时也能刺激其增殖,同时提出,rhBMP-2 体外单层培养条件下刺激 BMSCs 增殖效应的理想浓度是 50 ~ 100g/L。Liu 等[24]通过实验表明 rhBMP-2 显着增加 IL-6、IL-7、IL-11、G-CSF、M-CSF 和 SCF 等的表达,从而在体内和体外促进骨髓间充质干细胞的增殖。

2.3 环磷腺苷

Zhou 等[25]研究表明环磷腺苷除了具有刺激骨代谢能力,还能够促进骨髓间充质干细胞的增殖。Denaro 等[26]认为脉冲电磁场可以促进 MSCs 的 DNA 的合成并促进环磷腺苷升高,从而进一步促进骨髓间充质干细胞的增殖。

3 脉冲电磁场对骨髓间充质干细胞向成骨细胞分化的影响

脉冲电磁场具有很好的促成骨效应,并且可以促进骨髓间充质干细胞向成骨分化,如促

进骨髓间充质干细胞碱性磷酸酶、骨钙素、骨唾液蛋白等的表达[27]。有研究发现[17] BMSCs 暴露在脉冲电磁场下,细胞增殖与对照组相比增加了 29.6%,与成骨作用相关的一些基因表达也发生显著改变,包括对成骨作用具有关键调节作用的 cbfa1 基因,其表达与对照组相比增加了 2.7 倍。另外脉冲电磁场还能显著增加碱性磷酸酶表达以及骨基质矿化。Jansen 等[28]提出脉冲电磁场能够增加骨形成蛋白-2、转化生长因子-β1、骨保护素、基质金属蛋白酶-1 和基质金属蛋白酶-3、骨钙素、骨涎蛋白的 mRNA 水平。Esposito 等[29]研究表明人骨髓基质干细胞(BMSC)每天接受电磁场照射 8 h,连续照射 14 d 后,通过碱性磷酸酶定量和组织化学染色结果表明,经电磁场处理的骨髓基质细胞开始分化比未经处理的骨髓基质细胞早。ALP 是成骨细胞的早期标志酶,可标志成骨分化的开始。有研究发现,MSCs 向成骨细胞分化的过程中,ALP 水平有时间依赖性,随着诱导时间的延长表达量增加[20]。Jansen 等[28]发现电磁场刺激骨髓间充质干细胞成骨细胞标记基因的上调促进矿物沉积从而促进其向成骨细胞分化。近年来,许多科学家热衷于脉冲电磁场对于骨髓间充质干细胞向成骨细胞分化机制的研究。

3.1 环磷腺苷

环磷腺苷是细胞内重要的信号分子,环磷腺苷及其依赖的信号通路同多个细胞的分化密切成熟相关。De 等[30]研究表明脉冲电磁场能促进细胞释放转化生长因子-β、前列腺素 E_2 等,前列腺素 E 可通过环磷腺苷依赖的蛋白激酶 A、蛋白激酶 C 通路抑制其向软骨细胞分化。Wu 等[27]用脉冲电磁场刺激骨髓间充质干细胞后发现细胞内环磷酰苷水平明显升高,骨形态蛋白-2 的表达也增加。此外研究表明,骨形态蛋白-2 是通过激活环磷腺苷依赖的蛋白激酶 A 通路来促进成骨[31]。

3.2 基质金属蛋白酶(MMPs)

基质金属蛋白酶(MMPs)是降解细胞外基质成分,如胶原蛋白等的酶蛋白,在骨重塑过程发挥关键作用。以往的研究表明,脉冲电磁场可以诱导基质金属蛋白酶在成骨细胞中的表达活性,从而促进成骨[32]。研究表明电磁场在促进人骨髓间充质干细胞向成骨细胞分化过程中诱导基质金属蛋白酶上调。基质金属蛋白酶的上调加快胶原基质重塑,促进骨转换,此外电磁场同时上调细胞外基质的标记蛋白、骨钙素和骨涎蛋白的表达[28]。

3.3 骨保护素(OPG)/受体激活的 NF-κB 配体(RANKL)

骨保护素(OPG)和受体激活的 NF-κB 配体(RANKL)对于骨重塑系统有重要影响。OPG / RANKL 比值增加使得破骨细胞减少,促进成骨[33]。Chang 等[34]人研究表明电磁场诱导调控 OPG 的同时使得 RANKL mRNA 表达下调,导致增加的 OPG / RANKL 比值升高。电磁场照射骨髓间充质干细胞后 OPG 的 mRNA 表达增加,而 RANKL 的改变不显着,使得 OPG / RANKL 比值上升,从而与促进成骨有关。

3.4 骨形态发生蛋白

研究表明脉冲电磁场可以诱导 TGF-β 在成骨细胞内的表达[35],这种细胞因子在骨折修复的重要作用。骨形态发生蛋白是 TGF-β 家族的一员,已被临床成功用于治疗非联合骨折,体外研究表明经骨形态发生蛋白治疗后可以促进大鼠原代成骨细胞和人类间充质干细胞的成骨细胞分化[36]。研究表明脉冲电磁场可以通过上调骨形态发生蛋白水平促进成骨。此外,骨形态发生蛋白已被证明为独立于其他已知的刺激骨髓间充质干细胞诱导成骨细胞分化的因素[37]。Wang 等[38]研究表明脉冲电磁场可以增加 BMP-2 mRNA 水平从而诱导其他骨祖细胞向成骨细胞分化。

目前研究已证实脉冲电磁场可以通过改变传导通路和生长因子作用于骨髓间充质干细胞,促进其分化及增殖,随着对其作用机理的不断深入研究,其在临床应用方面的价值将愈加显著。全球范围内,现有 2 亿多骨质疏松患者,亚洲地区已成为骨质疏松的高发地区。而我国人口正急速老龄化,骨质疏松发病率更是呈快速上升趋势[1],将骨髓间充质干细胞用于骨质疏松及骨不连的治疗,对于改善这一现状有极为重要的意义。

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同的糖基化形式存在,及 TRAP-5a 和 TRAP-5b,TRAP-5a 主要来源于炎性巨噬细胞,而 TRAP-5b 主要来源于破骨细胞,本研究中测定的抗酒石酸酸性磷酸酶为 TRAP-5b,其含量反应破骨细胞活性。

本研究发现,骨转换指标 BAP、TRAP 在糖尿病组也较对照组升高,表明糖尿病组骨转换较对照组活跃,可能的原因是,维生素 D 受体存在于体内多种组织细胞,其中包括骨骼肌、胰岛 β 细胞等,维生素 D 与细胞内受体结合引起胰岛素释放、外周组织葡萄糖利用等降低血糖,从而影响糖代谢过程,此外维生素 D 缺乏引起甲状旁腺功能亢进,甲状旁腺功能亢进引起骨吸收加速,骨转换速度加快[10,11]。两组间 TRAP 水平的差异无显著统计学意义,其可能原因是本研究入组的 2 型糖尿病患者病程相对较短,2 型糖尿病对破骨活性的影响尚未充分体现;但是本研究发现糖尿病组与对照组在骨转换指标 BAP 及 TRAP 含量上的差异在男性组显著,而女性组差异不显著,分析原因是本研究入组的女性糖尿病患者有较多的绝经早期患者,绝经早期雌激素水平下降引发的骨代谢高转换在 NDM 对照组也表现得非常明显,完全覆盖了糖尿病对骨转换指标的影响。

在 25(OH)VD 与糖代谢指标的相关性研究中,看到在 2 型糖尿病患者中,25(OH)VD 与空腹血糖呈显著负相关,而与 HbA1C 的相关性不明显,此结果尚有待于今后大样本的研究以论证。

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脉冲电磁场对骨髓间充质干细胞作用研究进展

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