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骨髓间充质干细胞在组织工程研究中的应用新进展 *

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摘要:骨髓间充质干细胞又称为骨髓源性间充质干细胞,是指存在于骨髓基质细胞系统中的一类干细胞,具有高度稳定的体外扩增能力和多向分化潜能等特点。骨髓间充质干细胞因其取材方便,易于分离和培养,以及在适当条件下可诱导分化为皮肤、骨骼、内脏、血液、神经等多种组织细胞的独特优势,目前被广泛应用于药物开发、免疫调节、组织修复、器官重建等多个研究领域。近年来,骨髓间充质干细胞作为种子细胞在组织工程领域有着非常诱人的潜在应用前景。本文就骨髓间充质干细胞在组织工程学研究中应用的最新进展作一综述。

关键词:骨髓间充质干细胞;诱导分化;组织工程;种子细胞

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New Application of Mesenchymal Stem Cells in the Field of Tissue-engineering Scientific Research*

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ABSTRACT: Bone marrow mesenchymal stem cells (BMSCs) also might be called bone marrow-derived mesenchymal stem cells, is a sort of stem cells existing in the bone marrow stromal cells system, and has general characteristics of stem cells, the highly stable amplification ability in vitro and the potential of multi-directional differentiation. Given that BMSCs are convenient, easy to be isolated and cultured, and can be induced to differentiate into bones, blood, skin, gut, neural cells under appropriate conditions. BMSCs are widely used in many research fields, such as regenerative medicine, immune regulation, tissue repairing, organ reconstruction and so on, BMSCs as seed cells in tissue engineering field have a very promising potential application prospect. This paper reviewed the latest progress in tissue engineering applications of BMSCs.

Key words: Bone marrow mesenchymal stem cells; Inducing differentiation; Tissue engineering; Seed cells

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前言

骨髓间充质干细胞 (bone marrow mesenchymal stem cells, BMSCs)是最早发现的干细胞,也是目前研究最广泛的成体间充质干细胞群,兼有体内、外多向分化潜能,不仅能够分化为骨细胞、软骨细胞、脂肪细胞和骨骼肌细胞,还可以分化为心肌细胞、神经细胞、表皮细胞、血管内皮细胞和肝细胞等。近年来,随着组织工程技术和基因工程技术的迅猛发展,BMSCs 以其易于获得、取材方便、免疫原性低等优势,成为组织工程研究中的优良种子细胞,目前已被广泛应用于消化系统^[1,2]、循环系统^[3]、呼吸系统^[4]、泌尿系统^[5]、骨骼肌系统^[6,7]、血液系统^[8]、免疫系统^[9]等各大系统疾病的基础研究及临床应用领域。本文综述近年来 BMSCs 在组织工程研究中的应用新进展。

1 BMSCs 结合生物材料在组织工程研究中的应用

大量研究表明,BMSCs 结合生物材料作为移植复合体,在组织缺损的替代治疗方面的治疗效果明显优于单纯的生物材料,这种方法尤其适用于骨组织和软骨组织的损伤修复。动物模型研究^[10]中,研究员将人骨髓间充质干细胞和人脐带血间充质干细胞均接种于大孔磷酸钙泥上,分别将含有以上细胞的生物支架植入大鼠缺损的颅骨中,对照组为单纯移植大孔磷酸钙泥治疗,在第 4、12 和 24 周末用微型 CT 和组织解剖方法测定三组的骨骼再生。结果表明,和单纯的大孔磷酸钙泥组相比,前两组产生的新生骨组织和新生血管均明显多于后者。另有实验表明^[11],与市场上硫酸钙为基础材料的人造骨移植相比,含有羟基磷灰石的三维多聚纳米生物材料联合骨髓间充质干细胞

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修复大鼠长骨缺损过程中, BMSCs 结合生物材料起着更为显著的作用。BMSCs 结合丝蛋白生物支架治疗坐骨神经缺损^[12]和 BMSCs 结合电纺纳米材料应用于皮肤组织工程学研究^[13]等报道更是证实了新型可吸收的组织工程材料结合 BMSCs 在组织工程研究中的重要应用价值。

2 BMSCs 结合细胞因子在组织工程研究中的应用

BMSCs 与细胞因子之间的关系错综复杂, 其中涉及的众多机制问题目前尚不清楚, 较明确的是多种细胞因子可以通过促进和调节 BMSCs 的增殖、诱导分化和趋化过程, 以增强 BMSCs 对宿主组织损伤的修复能力。金世柱等^[14]对近年来关于粒细胞集落刺激因子 (granulocyte colony-stimulating factor, G-CSF) 的一系列研究予以归纳总结, 发现 G-CSF 能够动员骨髓间充质干细胞向损伤的肝脏组织 "归巢", 在特定的病理环境下分化为肝组织从而有效治疗肝脏疾病。Pulavendran S 等^[15]在体外小鼠 BMSCs 培养体系中加入肝细胞生长因子 - 壳聚糖纳米颗粒复合物 (hepatocyte growth factor-chitosan nanoparticles, HGF-CNP), 21 天后发现原先的 BMSCs 变成了典型的圆形肝细胞, 且研究者用免疫荧光技术检测出了白蛋白的表达, 由此证明 HGF 能够诱导小鼠 BMSCs 向肝细胞分化。苏雪莲等^[16]应用不同浓度的成纤维细胞生长因子 (basic fibroblast growth factor, b-FGF) 将山羊 BMSCs 成功诱导为成纤维细胞样细胞, 并成功检测到糖胺聚糖和 I 型胶原的表达, 从而证实了 BMSCs 作为工程化关节盘种子细胞的可行性。此外, 有学者曾将胰岛素样生长因子 (insulin-like growth factor-I, IGF-I) 和转化生长因子 $\beta 1$ (transforming growth factor $\beta 1$, TGF $\beta 1$) 联合应用于软骨组织工程学研究^[17]而得到较好效果。综上可见, 以骨髓间充质干细胞为基础的细胞替代治疗辅以单个或多个细胞因子共同应用于组织工程学研究已成为当今生命科学领域研究的热点科学问题。

3 BMSCs 结合中药在组织工程研究中的应用

中药是中国医药界几千年来的伟大成果, 它以其独特功效广泛应用于心脑血管疾病、内分泌代谢疾病、自身免疫性疾病及肿瘤等疾病的防治。近年来, 随着对干细胞研究的深入, 中药在组织工程研究中的优势亦得到挖掘, 不少研究^[18,19]证实部分中药单体和中药可以有效的促进 BMSCs 向各器官的趋化并诱导分化为多种组织细胞。张金生等^[20]利用大鼠心肌梗死模型研究发现, 三七皂甙可以促进 BMSCs 的归巢从而对心肌梗死区及周围损伤组织达到修复作用。另有学者研究发现中药配方同样可通过促进 BMSCs 归巢至病灶区从而加强 BMSCs 对大鼠骨关节炎的治疗效果^[21]。人参皂苷 Rd (Ginsenoside Rd) 作为一种中药单体, 其对神经系统、循环系统的保护作用已得到医学界广泛认可。郝秀华等^[22]以羟丙基- β -环糊精作为载体, 制成人参皂苷 Rd-羟丙基- β -环糊精包合物, 明显提高了人参皂苷 Rd 在水中的溶解度和生物利用度, 这将会明显影响该中药单体在科研领域及临床研究的应用范围, 也为人参皂苷 Rd 在组织工程研究的应用提供了有效的参考方法。中医药理论与 BMSCs 研究方法的结合, 是对我国中西医结合方针政策的完美诠释, 代表着当代组织工程学进入了一个无民族、无国界、多学科交

叉互补、共同发展的新时代。

4 BMSCs 结合基因重组技术在组织工程研究中的应用

BMSCs 作为组织工程研究的种子细胞, 不仅具有干细胞的多种优势, 还易于外源基因的导入和表达, 因而也是基因工程学重要的种子细胞之一。其中多数研究模式是将体外培养的 BMSCs 选择性的导入目的基因, 再移植入动物模型或人体内, 以协同参与机体组织损伤的修复。此方法将细胞治疗与基因治疗巧妙地结合起来, 为多种疾病的治疗提供了一个崭新的平台。鉴于细胞因子在组织工程中的重要应用价值, 在导入目的基因的选择方面, 研究人员将视线转向了各类细胞因子基因。杨进福等^[23]成功地利用阳离子脂质体将人血管内皮生长因子基因 (human vascular endothelial growth factor165, hVEGF165) 转染至大鼠 BMSCs, 并获得有效的表达。研究^[24]发现, 和单纯应用 BMSCs 治疗大鼠脊髓损伤组相比, 表达神经营养因子-3 (neurotrophin-3, NT-3) 的基因工程化 BMSCs 组显现出更强有意义的疗效。除此之外, 也有肿瘤学研究者旨在构建基因工程化的 BMSCs 作为自杀基因载体以用于恶性肿瘤转移灶的靶向治疗, 并在体内试验中取得了良好的效果^[25]。微小核糖核酸 (micro RNA, miRNA) 对生物基因表达的调控作用近年来得到医学界的广泛证实, 研究人员将 miRNA-124 转染 BMSCs, 证明 miRNA-124 在 BMSCs 诱导分化为心肌细胞过程中主要是通过靶向调节 STAT3miRNA 的表达而发挥调节作用^[26], 并对其具体调节过程进行了研究, 成为干细胞组织工程学由宏观迈向微观的代表之一。

5 BMSCs 结合光生物学技术在组织工程研究中的应用

光生物学 (photobiology) 是指从宏观作用机制与微观量子过程不同水平研究光和生物相互作用的一门科学, 光生物学相关的干细胞组织工程研究则是目前最具前景的新兴领域之一。相关研究^[27]发现低水平可见光可促进 BMSCs 的增殖。另有研究人员在体外用小鼠 BMSCs 为细胞骨架的三维培养体系制造出皮肤类似物, 成功地通过光调节过程和纳米微粒释放光感物质来控制搔抓反应后的皮肤创伤愈合过程, 证实了低水平激光在皮肤创口愈合过程中的重要作用, 为光生物学应用于皮肤组织工程研究奠定了基础^[28]。

6 BMSCs 在组织工程血管研究中的应用

机体组织器官损伤的修复很大程度上依赖于器官或组织新生血管的形成, 因而构建有效的小直径血管移植术一直以来是生物医学的重点及难点问题。而近年来, 经过科研人员的不懈努力, 组织工程学为其提供了诱人的解答, 以 BMSCs 为种子细胞联合生物支架形成的组织工程血管为此打开了新局面。体外研究的 BMSCs 不仅能够分化为成骨细胞、软骨细胞和脂肪细胞系, 还可以可塑性诱导分化为血管表型细胞。Centola. M 等^[29]将 BMSCs 贴附于不断释放肝素的新型生物支架, 从而将 BMSCs 诱导分化为血管内皮细胞。有研究证明^[30]人 BMSCs 可以代替平滑肌细胞成为组织工程血管的新细胞来源。另外, 更鼓舞人心的是研究人员用 BMSCs 构建的组织工程血管已经初

步用于动物活体实验并证明其能发挥一定的作用^[31]。

7 展望

综上所述,BMSCs 自发现以来,作为组织工程研究中优先选择的种子细胞,不仅具有高度的体、内外自我复制能力和多向分化潜能,且取材方便,可源于自体,免疫原性低,已广泛应用于生命科学各个领域。近年来,随着新型生物技术的不断开发,BMSCs 相关研究及应用将不再局限于简单的细胞学水平及单纯性体外功能实验,而是走向了一个与生命科学技术相结合,多学科交叉运用的新领域。尤其是基因重组技术在 BMSCs 的应用更是实现了组织工程学从宏观现象到微观机制的完美衔接。

另外,BMSCs 在组织工程研究中尚有一些问题亟待解决,首先,BMSCs 鉴定及纯化方法有待进一步完善。其次,BMSCs 体、内外作用机制尚需更深层次的探讨。再者,BMSCs 活体内成瘤性、对机体凝血机制的影响等安全性问题有待更多的理论支持。但相信随着生物技术的发展及干细胞研究的逐渐深入,以 BMSCs 为基础的组织工程技术与方法将有望成为临床上各系统疾病治疗的强有力工具。

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