· 综述 ·

外周血干细胞联合富血小板血浆在组织修复中的研究进展

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摘要: 随着再生医学的发展, 外周血干细胞(peripheral blood stem cell, PBSC)与富血小板血浆(platelet-rich plasma, PRP)作为细胞治疗与生长因子疗法的代表, 在组织工程与临床修复领域中展现出巨大的应用潜力。PBSC 具有多向分化潜能、强大的旁分泌功能及归巢能力, 而 PRP 则含多种生长因子, 可诱导细胞增殖与分化、促进基质形成及抑制细胞凋亡。二者联合应用已在骨、软骨、肌腱、皮肤及神经等多种组织修复中展现出显著的协同效应, 这一效应主要通过以下机制协同推动组织再生进程: 调控局部炎症反应、促进细胞迁移与分化, 以及增强细胞外基质的重建。然而, 目前该联合疗法面临采集制备标准缺失、深层分子机制研究不足、高质量临床证据匮乏及监管与成本控制等挑战。未来应着重加强机制研究与临床试验, 推动制备工艺标准化与治疗策略个体化, 从而促进两者向临床常规治疗转化。

关键词: 外周血干细胞; 富血小板血浆; 组织修复; 再生医学; 细胞治疗; 协同作用

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Progress in the application of peripheral blood stem cells combined with platelet-rich plasma in tissue repair

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Abstract: With the advancement of regenerative medicine, peripheral blood stem cells (PBSC) and platelet-rich plasma (PRP), as representatives of cell-based therapies and growth factor-based therapies, respectively, have demonstrated significant application potential in tissue engineering and clinical repair. PBSCs possess multilineage differentiation potential, robust paracrine function, and homing capacity, while PRP contains a variety of growth factors that can induce cell proliferation and differentiation, promote extracellular matrix formation, and inhibit apoptosis. The combination of the two has shown notable synergistic effects in the repair of various tissues, including bone, cartilage, tendon, skin, and nerve. This synergy primarily drives tissue regeneration through the following mechanisms: modulation of local inflammatory responses, promotion of cell migration and differentiation, and enhancement of extracellular matrix remodeling. However, this combined therapy currently faces challenges such as a lack of standardized collection and preparation protocols, insufficient investigation into the underlying molecular mechanisms, a paucity of high-quality clinical evidence, as well as regulatory and cost-control issues. Future efforts should focus on strengthening mechanistic research and clinical trials, advancing the standardization of preparation processes, and promoting individualized treatment strategies to facilitate its translation into routine clinical practice.

Key words: peripheral blood stem cells; platelet-rich plasma; tissue repair; regenerative medicine; cell therapy; synergistic effect

1　组织修复的需求与方向

1.1　组织修复的临床需求与现状

随着人口老龄化加剧, 退行性疾病(如骨关节炎)及代谢性疾病(如糖尿病)的患病率显著上升, 这些疾病常伴随慢性难愈性创面或组织缺损, 对患者生活质量产生影响, 其治疗面临着巨大的挑战[1]。

目前, 传统的组织修复手段主要包括物理康复、清创缝

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合等方法,然而,这些方法无法做到功能性再生,尤其对于不可逆的退行性改变、大面积损伤或伴有基础疾病的复杂病例,其疗效常显不足。此外,自体移植的来源限制与二次损伤都严重制约了其在解决难愈性损伤这一重大临床难题中的应用[2]。

1.2 细胞治疗与生长因子疗法成为再生医学新策略

面对传统疗法的局限性,再生医学致力于修复受损或丢失的组织成分,细胞治疗[3]与生长因子疗法[4]作为组织修复的两大关键,为组织工程提供了全新的治疗思路。外周血干细胞(peripheral blood stem cell,PBSC)与富血小板血浆(platelet-rich plasma,PRP)作为细胞治疗与生长因子疗法的代表,正逐渐成为研究热点。与既往间充质干细胞(mesenchymal stem cell,MSC)或造血干细胞(hematopoietic stem cell,HSC)的研究不同,本综述聚焦于外周血这一更为微创的细胞来源,旨在系统阐述涵盖 MSC 及 HSC 等的 PBSC 联合 PRP 的应用潜力。PBSC 具备多向分化潜能与强大的旁分泌功能,且可通过动员剂高效采集,避免了侵入性的骨髓穿刺[5];而 PRP 则富含高浓度生长因子,制备简便且完全自体化[6],在骨科、运动医学、口腔科及整形外科等领域已得到广泛应用。将 PBSC 与 PRP 相结合,旨在发挥“细胞+因子”的双重优势,通过协同作用推动组织再生。本文将对 PBSC 联合 PRP 在组织修复中的研究进展进行全面梳理与展望。

2 PBSC 与组织修复

2.1 PBSC 的定义、种类及生物学特性

PBSC 指存在于外周血循环中的具有自我更新和多系分化潜能的细胞群体,主要包含 HSC、MSC 以及少量内皮祖细胞(endothelial progenitor cell,EPC)。与骨髓来源干细胞(bone marrow-derived stem cell,BMSC)相比,PBSC 可通过血细胞分离机以成分血单采方式获取,无需侵入性骨髓穿刺,具有来源广泛、便于自体化等优势[7]。目前,PBSC 的相关采集流程和并发症处理方案已经较为成熟,安全性高,而且研究显示,经动员获取的 PBSC 比 BMSC 具有更强的增殖潜力与损伤响应能力[8]。

2.2 PBSC 采集技术

PBSC 采集技术一般指通过药物动员将骨髓中的干细胞释放至外周血,并进行分离收集的过程。由于正常情况下外周血中干细胞含量极低,临床需使用动员剂提高其数量[8]。目前,最常用的动员剂是粒细胞集落刺激因子(granulocyte colony-stimulating factor,G-CSF),它通过破坏 HSC 与骨髓基质之间的黏附(如 VCAM-1)和趋化信号($CXCR_4$/$CXCL_{12}$ 轴),促进 HSC 进入外周血[9-10]。动员一般需连续皮下注射 45 天,在外周血 $CD34^+$ 细胞达到峰值时进行采集。然而,单独使用 G-CSF 存在动员周期长、个体差异大以及可能增加心血管事件等风险[11-12]。为此,新兴动员策略的探索和应用至关重要。其中,CXCR4 拮抗剂(如普乐沙福)可特异性阻断 $CXCR_4$/$CXCL_{12}$ 轴,与 G-CSF 联用可协同提升 $CD34^+$ 细胞产量,并缩短动员时间[13-14]。此外,莫替沙福肽等长效 $CXCR_4$ 抑制剂的研究也显示出快速、持续动员更原始干细胞亚群的潜力[12,15]。其他如靶向 VLA-4/VCAM-1 轴的药物也处于探索阶段[16]。

采集过程通过血细胞分离机进行,连续处理大量全血,收集富含目标细胞的成分,其余血液成分则被回输到体内[17]。

2.3 PBSC 在组织修复中的作用

PBSC 参与组织修复是一个多机制协同的过程,主要涉及靶向归巢、细胞分化、旁分泌调节及免疫调控等途径。首先,PBSC 通过表面的趋化因子受体感知损伤处释放的信号分子如基质细胞衍生因子-1(stromal cell-derived factor-1,SDF-1),精准迁移至损伤区域,以便发挥修复作用[18-19]。在修复机制上,一方面,PBSC 可分化为特定功能细胞,直接替代受损细胞[20]。另一方面,旁分泌作用是 PBSC 实现修复的核心途径。其分泌的多种生物活性因子,如血管内皮生长因子(vascular endothelial growth factor,VEGF)、肝细胞生长因子(hepatocyte growth factor,HGF)等能够促进细胞增殖和血管新生[21];胰岛素样生长因子-1(insulin-like growth factor-1,IGF-1)、白细胞介素-6(interleukin-6,IL-6)有抗氧化和抗凋亡作用[22];而转化生长因子-β(transforming growth factor-β,TGF-β)、前列腺素 E_2(prostaglandin E_2,PGE_2)等能够调节免疫反应,抑制过度炎症,并促使巨噬细胞极化为抗炎表型[23-24],同时 SDF-1 招募更多修复相关细胞到损伤部位[25]。此外,PBSC 来源的外泌体可通过传递 miRNA、mRNA 及蛋白质等,调控靶细胞功能,从而促进修复[26]。同时,PBSC 能够通过细胞间接触及分泌活性因子,调节免疫细胞功能,形成利于修复的免疫微环境[27-29]。上述机制相互作用,使 PBSC 在组织修复中展现出巨大潜能。

3 PRP 与组织修复

3.1 PRP 的定义、主要生物活性成分

PRP 指通过自体全血离心而获得的血小板浓缩物,其血小板浓度通常为基础水平的 26 倍或更高[30]。PRP 在制备后通常处于“休眠”状态,通过加入凝血酶、氯化钙或接触组织胶原等方式被激活。活化过程包括血小板脱颗粒释放生长因子及纤维蛋白原聚合形成支架[31]。

PRP 的修复能力主要源于其复杂的生物活性成分,主要包括:血小板衍生生长因子(platelet-derived growth factor,PDGF)、TGF-β、VEGF、表皮生长因子(epidermal growth factor,EGF)、成纤维细胞生长因子(fibroblast growth factor,FGF)、IGF、HGF 以及细胞因子、趋化因子和黏附蛋白[32]。此外,PRP 中还含有具有生物调节功能的微囊泡和外泌体,共同参与并促进组织修复过程[33]。

3.2 常用 PRP 采集技术

PRP 的制备核心原理是密度梯度离心,即利用血液中

各成分的比重差异进行分离，最终得到含有高浓度血小板的血浆。PRP 的采集技术主要分为开放和封闭技术。

开放技术手工制备 PRP 通常采用二次差速离心法。抗凝全血轻离心得到富含血小板的血浆后再通过重离心去除贫血小板血浆，即得 PRP[34]。开放技术成本低、灵活性高，但存在细菌污染、血小板损耗与提前激活的风险，而且存在难以标准化质控等规范化操作程序，因此一般不建议用于临床。

封闭技术主要包括商业套装法、血袋法和单采法。商业套装法是使用专用的 PRP 制备套装和配套离心机制备 PRP。这种方法稳定安全且高效，但成本较高，灵活性较低，而且在收集和浓缩血小板的能力方面存在较大差异[35]。血袋法是一种利用封闭式多联血袋制备 PRP 的传统方法，其原理与手工法类似，但过程在无菌的血袋管路系统中进行。该方法兼具了标准化与灵活性，成本低于商业套装，且安全性显著优于手工法；该法已广泛应用于血站系统，用于制备手工浓缩血小板制剂供临床使用，且已有整套质量控制体系；不过其步骤未脱离人工操作，制备效率低，不同个体制备之间差异较大，一致性弱。单采法是利用血细胞成分分离机，通过体外循环方式制备 PRP 的技术，也是血站系统生产、制备浓缩血小板制剂的常用方法。其原理基于成分单采技术，在血液流动和离心过程中，实时分离并收集高浓度血小板，同时将其余血液成分回输给患者。该方法的核心优势为精确控制产品规格，血小板浓度和纯度高，能一次采集、多次使用[36]，且易于质控和规范化操作。

3.3　PRP 在组织修复中的多重作用

组织修复通常分为三个相互重叠的阶段：炎症期、增殖期和重塑期[37]。在炎症期，PRP 促进巨噬细胞从促炎 M1 型向抗炎促修复 M2 型极化，减轻过度炎症，创造修复环境[38]。此外，PRP 所含的抗菌肽等成分亦能在早期发挥一定的局部抗感染作用[39]。在增殖期，PRP 通过 VEGF、FGF 等因子促进新生血管形成，为修复区域提供营养支持[40]，同时还能驱动干细胞、成纤维细胞等向损伤部位迁移、增殖，并分化为功能细胞，合成细胞外基质（extracellular matrix，ECM），为组织重建提供结构基础[20,32,41]。在重塑期，PRP 促进成纤维细胞合成胶原蛋白并引导其有序排列，提升组织强度[42]。此外，它还能通过调控胶原比例，起到抗纤维化的作用[43]。

4　PBSC 与 PRP 联合应用的生物学基础及其相互作用

PBSC 与 PRP 联合应用的核心在于二者的协同效应，这种协同并非功能的简单叠加，而是在细胞与分子层面构建了一个互补的修复体系。PRP 为 PBSC 的存活与功能发挥提供微环境支持，而 PBSC 则在修复中响应并放大 PRP 的生物学信号。

4.1　PRP 对 PBSC 生物学行为的调控作用

损伤部位的恶劣微环境不利于移植 PBSC 的存活。首先，PRP 通过分泌活性成分，促进 ECM 形成，并为 PBSC 提供黏附位点，帮助其在损伤区“锚定”，从而获得营养与生存支持[44-45]。同时，PRP 释放 PDGF、FGF、EGF 和 IGF-1 等生长因子，可通过激活 MAPK、PI3K/Akt 等信号通路，驱动 PBSC 从静息期进入细胞周期，促进其增殖[46]。PBSC 需要精准归巢至损伤部位才能发挥修复作用。PRP 活化后释放的趋化因子（如 SDF-1），可在局部形成并维持强大的化学梯度，表达 CXCR4 受体的 PBSC 能够感知此梯度，从而定向趋化至损伤区域[18,47]。此外，PRP 还可通过分泌 HGF 和 VEGF 增加血管通透性，加强 PBSC 的迁移能力[48-49]。最后，PRP 中生长因子的组合与释放时机能有效引导具有多向分化潜能的 PBSC 向目标细胞谱系分化。例如，在骨修复中 TGF-β 和 IGF-1 等细胞因子可诱导 PBSC 中 HSCs 和 MSCs 向软骨及成骨细胞分化[50-51]。在血管新生过程中，VEGF 和 PDGF 能有效引导 MSCs 或 EPCs 向内皮细胞分化，促进功能性血管形成[52-54]。

4.2　PBSC 与 PRP 协同修复组织的分子机制

PBSC 与 PRP 的协同修复作用，建立在二者于分子与细胞层面形成的精密网络之上，其核心机制包括信号通路激活、免疫微环境调节、ECM 重构以及旁分泌网络的整合。

PRP 提供的多种生长因子与 PBSC 膜上相应受体结合，共同激活细胞内多条信号转导通路。PI3K/Akt 通路的激活可提升 PBSC 在损伤微环境下的存活率；MAPK/ERK 通路则驱动细胞周期蛋白表达，促进修复细胞增殖[46,55]；在损伤中，TGF-β-Smad 通路引导干细胞向目标细胞（如软骨细胞）定向分化[56]。这些通路的激活与调控，影响损伤部位细胞的行为。并且它们之间并非简单地独立运行，而是复杂的交叉对话：例如，PI3K/Akt 信号可负向调控 TGF-β/Smad 通路，防止干细胞过度分化[57]；而 MAPK/ERK 的过度激活则可能抑制干细胞保持未分化且无衰老状态[58]。因此，PRP 与 PBSC 的协同效应依赖于信号通路的动态平衡，而非单一通路的持续激活。

另外，二者联合能更有效地推动损伤局部环境从炎症状态向修复状态转换。这一过程具有显著的时序性，首先在炎症期 PBSC 通过分泌肿瘤坏死因子 α 刺激基因 6 蛋白（TNF-α-stimulated gene 6 protein，TSG-6）、白细胞介素-10（interleukin-10，IL-10）等介质，下调肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、白细胞介素-1β（interleukin-1β，IL-1β）等促炎因子表达[59]。同时，PRP 的生长因子与 PBSC 的分泌组协同作用，共同驱动巨噬细胞从促炎 M1 型向抗炎促修复 M2 型极化[38,60]，并促进调节性 T 细胞扩增，从而有效控制过度炎症，为再生创造有利条件[27,29,61]。进入增殖期后，二者协同作用的重心转向组织构建，PRP 与 PBSC 共同确保了 ECM 的功能性再生。首先，PRP 活化后形成的纤维蛋白支架为细胞迁移和组织修复提供结构支撑[62]。随后，二者通过刺激成纤维细胞及引导 PBSC 分化，协同促进 I 型、III 型胶原等 ECM 核心成分的合成与分泌[63-65]。此外，它们通过调控基质金属蛋白酶（matrix metalloproteinases，MMPs）及组织金属蛋白酶抑制剂（tissue inhibitors of metallo-

proteinases,TIMPs)的表达平衡,来控制 ECM 的降解与更新,避免病理性纤维化[43,66]。

PBSC 与 PRP 协同效应的核心在于其强大的旁分泌能力,两者释放的同类因子产生叠加效应,协同调控细胞的抗炎、增殖与分化[21-25,32]。更重要的是,两者均可释放能被周围靶细胞摄取的外泌体,从基因表达层面改变生物学行为,协调修复进程[26,33]。研究表明,PRP 甚至可通过激活 Akt/Rab27 等通路,进一步促进 PBSC 的外泌体分泌,从而放大其旁分泌修复效应[67]。

但是,PRP 与 PBSC 的联合应用并非在所有条件下都会起协同增强作用,有些情况下可能会有潜在的拮抗作用。例如,PRP 中高浓度的 TGF-β 虽然可以促进 MSCs 向骨、软骨细胞分化,但可能会抑制 MSCs 肌源性分化,从而影响肌肉愈合,因此在肌损伤修复中需优化 PRP 浓度或者联合 TGF-β 抑制剂使用[68-69]。其次,过度活化的血小板会释放高浓度的炎性因子,从而抵消 PBSC 的免疫调节作用,加剧局部炎症[70]。所以还需要更多的研究给出规范治疗的证据。

5 PBSC 联合 PRP 在组织修复中的临床应用

基于上述的理论基础,PBSC 与 PRP 联合策略已在多个组织修复领域从概念验证走向临床探索(表 1)。

在骨、关节与肌肉的治疗中,PRP 趋化 PBSC 至损伤部位后促进其增殖分化并刺激血管生成[71-73]。临床研究证实,外周血 $CD34^+$ 细胞已被证明是治疗骨折不连的一种可靠方法[74]。与单纯植骨或单用 PRP 相比,联合 PBSC 能加速骨痂成熟,提高新生骨密度及愈合速度[75]。另外,向关节腔内注射 PRP 与 PBSC 的混合物,PRP 可改善关节滑液环境并引导 PBSC 靶向归巢至损伤区[44,76],PBSC 则通过免疫调节抑制炎症,并分泌营养因子保护软骨细胞,并在损伤部位分化为软骨细胞[7,77-78]。与 MSCs 相比,外周血 $CD34^+$ 细胞在增殖能力和血管生成方面更有优势,可显著改善骨关节炎患者的疼痛程度、关节功能及活动能力[79]。临床研究显示,PBSC 与 PRP 联合疗法能显著改善患者膝关节功能评分,影像学检查也提示形成了质量更优的修复软骨组织[51]。在肌损伤中,PBSC 中 $CD34^+$ 细胞能促进韧带愈合和重塑[80],而 PRP 形成纤维蛋白支架为 PBSC 提供支撑,还可释放生长因子增强 PBSC 的肌源性分化潜能[81-82]。二者协同作用不仅促进肌纤维功能再生,还通过调节胶原代谢抑制病理性纤维化,从而提高新生组织的力学强度[43,66]。

此联合疗法在其他损伤中也展现出应用潜力,PRP 凝胶可直接覆盖在难愈溃疡表面并刺激成纤维细胞增殖,促进创面愈合[83],同样外周血 $CD34^+$ 细胞可增加血流灌注从而加速创伤愈合[84]。联合使用后,PRP 能进一步增强 EPCs 的血管生成能力,并提高 MSCs 在创面的存活率与增殖能力[85-86]。研究证实,联合治疗可显著增加肉芽组织形成、胶原沉积及血管密度,加速创面闭合并改善愈合质量[87-88]。另外,在神经修复中,PRP 提供神经营养支持并引导修复细胞迁移[89]。联合 PBSC 可协同促进施旺细胞增殖、上调神经营养因子(nerve growth factor,NGF)表达,进而有效保护神经元、促进轴突再生和髓鞘形成[90]。动物面神经损伤模型中,联合疗法在功能恢复、电生理及组织学结果上均优于单一成分治疗,显示出良好的神经修复潜力[91]。

表 1 联合疗法在不同组织修复中的研究汇总

Table 1 Summary of research on combination therapies for tissue repair in various tissues

修复领域	模型/疾病	干预方式	结果	证据等级	参考文献
骨	骨缺损	M-MSCs/PRP 凝胶联合治疗	再生能力显著增强	动物实验	[75]
软骨与关节	关节软骨损伤	PRP/PBSC 凝块贴壁注射软骨损伤处	促进关节软骨再生,5 年随访临床结局改善	临床研究	[51]
肌肉与韧带	骨骼肌损伤	PRP 培养骨骼肌来源的人 MSCs	显著促进增殖和成肌分化	机制研究	[82]
皮肤创伤	糖尿病创面	注射脂肪 MSCs 生理盐水溶液+活化的 PRP	促进伤口再上皮化和肉芽组织形成,创面愈合效果优于单一治疗	动物实验	[87]
神经	神经横断	应用 PRP+神经诱导的人 MSCs	促进面神经再生	动物实验	[91]

6 临床应用的挑战、对策与未来展望

6.1 当前临床应用的主要瓶颈

尽管 PBSC 与 PRP 联合疗法在组织修复中展现出广阔前景,但其临床应用仍面临多重挑战。首先,从 PBSC 的动员方案(如 G-CSF 剂量、细胞采集目标)到 PRP 的制备系统、活化方法,均缺乏国际统一的“金标准”,导致产品质量与成分批次间差异大,研究结果难以比较和重复[92-93]。而且,现有证据缺乏大规模、随机双盲、安慰剂对照的临床试验来确证长期疗效和安全性。此外,联合策略会形成更加复杂的机制作用网络,对于最佳治疗时机、细胞与 PRP 比例、递送方式等关键参数,需要深入的机制研究作为精准化方案的设计依据[94]。

更为重要的是,疗法的安全性与监管难度。尽管两者均为自体来源,风险相对较低,但治疗过程仍存在潜在副作用。PBSC 动员可能引起骨痛、血小板减少等罕见事件[95];因此,能否不使用动员剂来采集少量 PBSC 用于骨关节炎等治疗开始受到关注。此外,PRP 注射亦有感染、过敏、局部炎症的报告[96],因此,能否在密闭条件下混合 PBSC 和 PRP 也至关重要。PBSC 与 PRP 制备、质量控制和临床应用面临严格的监管审查,流程复杂且成本高昂[97-98]。利用单采技术一次性采集两者的联合成分将有效打破这种壁垒,同时,这也是输血医学科作为治疗平台服务临床的契机与优势。

6.2 应对策略与未来研究方向

面对上述诸多挑战,多方面的应对策略至关重要。首

先,应着重技术创新,针对不同治疗靶位,研发非动员采集 PBSC 的方法;同时,开发更安全、高效的一体化采集技术,实现对干细胞、血小板浓度等关键参数的精确控制和实时监测。一体化采集的核心目标是在单次成分血单采过程中,同步获取高浓度的 PBSC 与 PRP,从而避免多次穿刺、降低污染风险、提高治疗便捷性。其实现的关键在于研发双目标单采程序以及配套采集耗材。本研究团队目前已通过调整程序参数和改变管路夹闭等方式实现非动员状态下 PBSC 与 PRP 同步单采。其次,推动标准化与质控体系建设,强化其作为输血和血液治疗类产品的独特属性,按照血液及血液成分质量管理体系要求,以确保产品的安全和质量一致性。另外,增加临床试验与机制研究为其进一步应用提供理论支撑,扩大临床治疗的适应证,探索个性化的采集和治疗方案。在成本方面,未来研究要在验证联合疗法有效性与安全性的基础上,将成本效益分析纳入研究,为制定合理的定价和医保支付标准提供参考依据,推动该疗法在临床实践中的稳定应用。

利益冲突说明/Conflict of Interests

所有作者均声明不存在利益冲突。

伦理批准及知情同意/Ethics Approval and Donor/Patient Consent

本文不涉及伦理审批和知情同意。

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