脂肪干细胞及细胞因子在皮肤放射性损伤修复中的研究进展

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摘要 本文就当前脂肪干细胞（Ddipose-derived stem cells，ADSCs）与富血小板纤维蛋白（Platelet-rich fibrin，PRF）治疗皮肤软组织放射性损伤的研究概况进行探讨。相对于传统的治疗方式，ADSCs与PRF对于改善皮肤放射性损伤具有独特的优势。放射会使皮肤受到氧化损伤并产生细胞凋亡，从而引起红斑水肿、湿性脱屑等组织病理学改变；而ADSCs的抗凋亡、旁分泌生长因子、抗瘢痕的功能可以针对皮肤放射性损伤机制，减轻放射性损伤创面炎症，提高微血管密度，同时促进创面再上皮化，从而有效地改善皮肤放射性损伤；PRF释放的高浓度生长因子可明显提高创面的愈合率，并且PRF的生物特性能进一步优化ADSCs修复损伤的作用。结合ADSCs联合PRF治疗皮肤放射性损伤的研究现状，对今后的实验研究和临床治疗方向进行展望。

关键词 皮肤放射性损伤，脂肪干细胞，富血小板纤维蛋白，损伤修复，抗瘢痕

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Advances in the study of adipose stem cells and cytokines in the repair of radiation skin damage

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ABSTRACT This article discusses the current research status of adipose-derived stem cells (ADSCs) and platelet-rich fibrin (PRF) in the treatment of soft tissue radiation injury in the skin. ADSCs and PRF have unique advantages over conventional treatment modalities for improving cutaneous radiation injury. Radiation causes oxidative damage to skin and skin cells subsequently undergo apoptosis, which causes histopathological changes such as erythema edema and wet desquamation. The anti-apoptotic, paracrine growth factor and anti-scarring functions of ADSCs can concomitantly target the mechanism underlying skin radiation injury, reduce inflammation of radiation-injured wounds, increase microvascular density, and promote re-epithelialization of wounds, thereby effectively improving skin radiation injury. The high concentration of growth factors released from PRF can significantly increase the healing rate of wounds, and the biological properties of PRF can further optimize the activity of ADSCs in repairing

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skin damage. Future experimental research and clinical treatment directions may involve combining the current research status of ADSCs with PRF in the treatment of cutaneous radiation injury.

KEYWORDS Radiation skin damage, Adipose stem cells, Platelet-rich fibrin, Injury repair, Anti-cicatricial

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放射治疗是肿瘤的关键治疗方式之一，费用相对低廉，占癌症患者治疗总费用的5%左右[1]。但高达85%的放射性治疗患者不可避免地伴随着放射部位的皮肤软组织损伤[2]，红斑、水肿、溃疡等副作用会增加癌症患者的痛苦，并阻碍病情的控制。现有的放射性皮肤损伤的治疗方法多种多样，外用药物是患者常用的治疗方式，如维生素E、超氧化物歧化酶、各类消炎乳膏、重组人表皮生长因子等，以及具有“清热解毒、活血化瘀”的功效的外敷中药制剂[3]。物理方法中常见的激光治疗具有扩张局部血管，促进组织修复的作用。但是对于皮肤出现溃疡、出血或坏死的严重急性放射性皮肤损伤，或是慢性的放射性皮肤损伤所形成的瘢痕而言，传统方式只能改善症状，在减少瘢痕纤维化、防治局部功能缺陷方面作用不佳。因此，临床上需要进一步探索更有效的放射性皮肤损伤治疗策略。

脂肪干细胞（Adipose-derived stem cells，ADSCs）作为一种间充质干细胞，不仅可增殖分化成所需细胞，介导组织修复，替代受损细胞，也可通过旁分泌激活血管再生，并能抑制增生性瘢痕形成[4]。与骨髓干细胞相比，ADSCs来源丰富，获取简单方便，对机体损伤小，提取细胞率更高，脂肪中的ADSCs产量可达到同等体积中骨髓干细胞的100~500倍[5]。并且ADSCs能够明显增加创面的真皮毛细血管密度，提高创面的血供和肉芽率，因此，其长期成为组织修复与再生重建领域的研究热点。富血小板纤维蛋白（Platelet-rich fibrin，PRF）作为第二代血小板浓缩物，在2001年第一次被提出[6]，它的制备无需化学试剂，减少了过敏反应的风险，是一种完全自体生物材料。PRF能模拟伤口愈合的生理过程，释放出高浓度生长因子，从而促进组织愈合与血管形成[7]，使其在细胞生长、分化、迁移、免疫等生物学过程中发挥重要作用。ADSCs与PRF均对皮肤软组织的创伤有治疗价值，ADSCs具备再生修复的种子细胞，PRF可提供营养皮肤组织的细胞因子，因此，两者在治疗皮肤放射性损伤中具有广泛的临床应用前景。但目前较少有学者对ADSCs与PRF治疗皮肤放射性损伤作出综述，本文将具体阐述两者在皮肤放射性损伤修复中的作用（图1）。

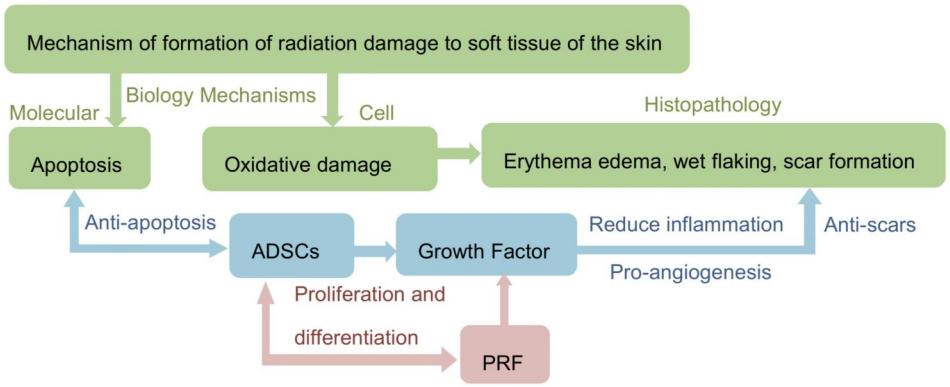

图1 ADSCs与PRF在皮肤放射性损伤修复中的作用
Fig.1 Function of ADSCs and PRF in the repair of skin radiation damage

1 皮肤软组织放射性损伤的形成机制

1.1 组织病理学改变

（1）红斑水肿。肿瘤局部放射治疗后皮肤损伤的早期阶段是表皮基底细胞损伤，进而释放各种炎症因子，引起真皮层的微血管扩张，血管腔内充满红细胞，血浆外渗致间质水肿，形成红斑水肿的外观。

（2）湿性脱屑。当放射性损伤进一步加重时，血管扩张释放更多的炎症细胞，并且血管腔内血小板

相互粘连，滞留附着于血管壁上，导致血栓形成，从而中断局部皮肤软组织的营养供给，基底细胞层修复困难，表皮屏障破坏严重，真皮层便会释放渗出物，与废旧的角质混合形成湿性脱屑[8]。

（3）瘢痕形成。皮肤软组织在放射损伤后会延长炎症期，在炎症后期，大量炎性细胞活跃引起成纤维细胞增生，并合成丰富的胶原蛋白对抗炎症因子带来的损伤，导致真皮层胶原蛋白沉积，出现纤维性变化，最终真皮萎缩，皮肤形成瘢痕[9]。

1.2 分子生物学机制

放射治疗的目的是杀死癌细胞或控制癌细胞增殖，但健康皮肤会不可避免地暴露于射线中，引起细胞凋亡。当皮肤受到辐照时，辐射会诱导肿瘤蛋白53与Bax蛋白高表达[10]，从而激活DNA启动细胞周期阻滞、凋亡，并转录DNA损伤信号激酶，引起DNA双链断裂[11]，造成皮肤基底细胞凋亡，无法更新表皮细胞。

1.3 细胞生物学机制

氧化损伤是皮肤软组织放射性损伤的重要原因之一。细胞受到辐射损伤时会释放各种炎症趋化因子，吸引炎症细胞到损伤部位，进而释放更多（如肿瘤坏死因子-α、白介素-1等）促炎因子[12]。这些促炎因子会损伤血管内皮细胞，从而导致血供不足，伤口难以愈合。HMGB1是一种重要的炎症因子，有学者发现[13]，皮肤放射性损伤可以非正常激活HMGB1通路，从而引起一系列炎症级联反应。5，6，7，8-四氢生物蝶呤作为一氧化氮合酶的关键辅助因子，其缺少便会导致一氧化氮合酶的解耦和高氧化性自由基的产生，而电离辐射可破坏5，6，7，8-四氢生物蝶呤[14]。此外，电离辐射可与水分子相互作用形成活性氧自由基，进而激活细胞凋亡信号通路，引起细胞破坏凋亡[15]。Cao等[16]发现，用基质细胞衍生因子-1α/趋化因子受体4抑制剂可以减轻大鼠的放射性皮肤损伤和纤维化，这表明基质细胞衍生因子-1α/趋化因子受体4通过激活促纤维化转化生长因子-β/Smad信号通路，参与了辐射诱发皮肤急性损伤和纤维化。

2 ADSCs在皮肤软组织放射性损伤修复中的作用

ADSCs是由Zuk等[17]在2001年发现并命名的间充质干细胞，其具有自我更新潜力、增殖能力和成骨、成脂和成软骨的三系分化潜力，是促进组织创伤修复和组织重建的重要工具。近年来，用ADSCs修复放射性损伤一直是研究的热点。ADSCs的定向分化和旁分泌功能可针对皮肤软组织放射性损伤的机制，进行组织修复再生。结合国内外最新研究，ADSCs治疗放射性损伤的作用机制归纳如图2所示。

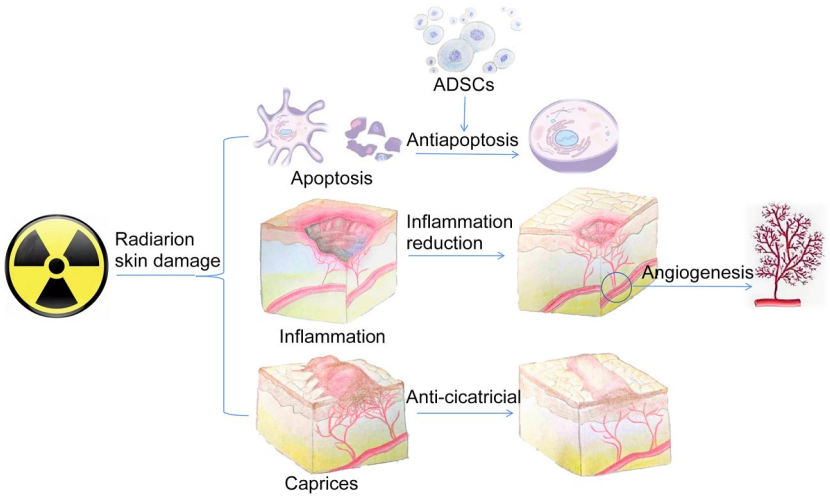

图2 脂肪干细胞治疗皮肤放射性损伤的示意图
Fig.2 Schematic diagram of ADSCs treating skin radiation damage

2.1 抗凋亡作用

细胞凋亡是肿瘤局部放射诱导皮肤损伤的一个重要特征。Lin等[18]发现ADSCs可通过减轻心室肌细胞的氧化应激来减少凋亡。在细胞凋亡过程中组织蛋白酶F（Cathepsin F，CTSF）起重要作用。有

研究[19]发现，当ADSCs移植到放射性皮炎的大鼠体内时，与对照组相比，ADSCs组能下调CTSF的表达，同时上调相关抗凋亡蛋白，从而减弱放射诱导的细胞凋亡，并促进毛囊和皮脂腺再生。也有研究[20]表明，ADSCs可减少顺铂诱导的上皮性卵巢癌细胞的凋亡，用ADSCs处理后的透明细胞癌ES2细胞和腺癌SKOV3细胞，其凋亡细胞的比例与对照组相比，分别降低了约50%和30%。一项动物实验研究[21]也发现，ADSCs可降低促凋亡蛋白Bax，并升高抗凋亡蛋白Bcl-2的水平。因此，ADSCs的抗凋亡作用是减轻皮肤软组织放射性损伤重要原因之一。

2.2 分泌生长因子促进损伤组织修复

ADSCs分泌的生长因子不仅可以加速创面修复，还可被成纤维细胞吸收，从而刺激成纤维细胞中I型胶原蛋白、III型胶原蛋白、基质金属蛋白酶1、碱性成纤维细胞生长因子和转化生长因子-β1的信使RNA和蛋白质水平增加[22]，进一步促进伤口愈合。组织损伤修复的过程包括炎症、增殖和重塑3个过程，而ADSCs分泌的生长因子可影响组织修复的每个过程。

（1）减轻炎症作用。当皮肤组织的放射性损伤发生时，会产生促炎因子，诱导ADSCs与炎症细胞迁移至损伤部位，ADSCs会产生不同的细胞因子进行免疫调节，通过下调炎症反应来减轻组织损伤。辅助性T淋巴细胞1是介导许多炎症反应和自身免疫的主要效应细胞。Bowles等[23]发现，ADSCs可通过干扰转录因子STAT1的合成，降低辅助性T淋巴细胞1细胞转录因子的基因表达，从而抑制其分化，进而影响促炎因子干扰素-γ、肿瘤坏死因子-α的水平，促进转化生长因子-β等抗炎因子的分泌。而巨噬细胞可被抗炎因子所激活，从而下调炎症反应，有利于组织修复过程[24]。因此，ADSCs在减轻炎症反应上发挥了重要的作用。

（2）促血管生成作用。电离辐射会减少血管供应，造成皮肤损伤和组织功能丧失，而ADSCs可参与血管的形成，有效增加微血管密度。已有研究[25]证实，ADSCs分泌的转化生长因子-β、碱性成纤维细胞生长因子、肝细胞生长因子、白介素-1β、血管内皮生长因子等可介导大量的内皮细胞在创面部位增殖，从而增加新生毛细血管形成。有动物实验[26-27]表明，经ADSCs治疗后能促进大鼠放射性溃疡的血管生成，明显增加创面血供，从而加速其愈合。在一项小猪的放射与烧伤创面研究中[28]，ADSCs能加速伤口的再上皮化，相比对照组，ADSCs可使再上皮化时间平均加快3.5倍，并增加67%的血管密度和30%的胶原蛋白含量。ADSCs也成功应用于困难棘手的放射性损伤治疗案例中。临床上有4名顽固性辐射损伤的患者曾多次接受分期人工真皮植皮、游离皮瓣等手术，虽然伤口可以闭合，但作用时间有限，几个月后便会创伤复发。而Akita等[29]给该4名患者局部注射自体ADSCs，在术后75 d放射性创面可完全愈合，6个月后超声复查可见注射ADSCs部位的局部血液循环增加。此外，ADSCs促血管作用还可通过增加特定血管生成潜能来进一步增强。用流式细胞术分离得到$CD34^+CD146^+$的ADSCs，相比$CD34^-CD146^-$的ADSCs对照组，可以使脂肪移植物血管化程度明显升高，增加脂肪存活率[30]。在电离辐射造成血管减少，引起局部组织缺氧的情况下，进一步增强ADSCs分泌细胞因子的能力。M2巨噬细胞可释放多种细胞因子促进血流再灌注和提高组织存活率，在缺氧诱导因子-1α的介导下，ADSCs内的白介素-10基因表达被增强，进而激活STAT3/Arg-1信号通路，从而诱导更多的M2巨噬细胞形成[31]。

（3）抗瘢痕形成作用。慢性皮肤放射性损伤的纤维化反应会引起细胞外基质的异常沉积和重塑，通常会造成审美缺陷和局部功能限制。而ADSCs可通过调整过多的胶原表达来达到抑制瘢痕化目的。转化生长因子-β1是胶原合成的关键调节因子。Xie等[32]认为，ADSCs可能是通过抑制转化生长因子-β1/Smad通路，在体外抑制各类瘢痕成纤维细胞的增殖、迁移及细胞外基质蛋白的表达，从而减少增生性瘢痕形成。Borrelli等[33]发现，富含CD74的ADSCs可减少慢性辐射诱导的皮肤纤维化，因为$CD74^+$ADSCs能表达更多的肝细胞生长因子、成纤维细胞生长因子-2和转化生长因子-β3，减少转化生长因子-β1的表达，从而降低了皮肤硬度、真皮厚度和皮肤的胶原含量，改善放射性损伤后的软组织重建。因此，ADSCs可降低I型胶原蛋白、III型胶原蛋白和α-平滑肌肌动蛋白的表达，使胶原沉积变少，进而抑制瘢痕形成。Wush等[34]也指出，ADSCs不仅能促进放射性溃疡愈合，也显著减少创面纤维化。与这些研究不同的是，Zho等[35]在小鼠皮肤伤口模型中发现，ADSCs能使成纤维细胞增殖活性增强，并增加I型胶原蛋白、III型胶原蛋白，从而加快伤口愈合速度。在伤口修复的早期阶段，胶原的增加可促进伤口愈合，这与ADSCs的抗瘢痕能力并不冲

突。因为瘢痕的主要特征是微血管发育不良伴炎症细胞浸润[36]。放射会造成血管缺乏，组织不足以提供充足的营养物质来进行创面修复再生，因此，在后期的伤口重塑阶段，只能依靠胶原过度沉积、老化形成瘢痕来修补创口。ADSCs应用于放射性损伤修复的研究见表1。

表1 脂肪干细胞应用于放射性损伤修复的研究汇总

Table 1 Summary of studies on the application of adipose stem cells for radioactive injury repair

研究作者 Study authors	年份 Year	研究对象 Research subjects	研究方法 Research methods	研究结果 Study results
Huang *et al*[26]	2013	大鼠 Rats	单次照射背部（50 Gy剂量），3~4周后形成溃疡，放射3周后局部注射ADSCs Single irradiation of the back (50 Gy dose), ulcer formation after 3~4 weeks, local injection of ADSCs after 3 weeks of radiation.	ADSCs能增加创面的血供和肉芽率 ADSCs increase the blood supply and granulation rate of traumatic surfaces
Foubert *et al*[28]	2017	小猪 Piggy	少量多次全身放射（总剂量1.2 Gy）+ 背部全层热烧伤，伤后3 d局部及静脉注射ADSCs Small amount of multiple whole body radiation (total dose 1.2 Gy) + full back thermal burns, local and intravenous ADSCs injections 3 d after injury	ADSCs促进伤口的再上皮化，并增加血管密度和胶原蛋白 ADSCs promote wound re-epithelialization and increase vascular density and collagen
刘志燕等[27] Liu Z Y *et al*	2019	大鼠 Rats	单次照射大鼠左大腿内侧皮肤（90 Gy剂量），放射14 d出现溃疡，放射24 h后局部注射ADSCs Single irradiation of rat left medial thigh skin (90 Gy dose), ulceration appeared 14 d after radiation, local injection of ADSCs 24 h after radiation	ADSCs促进血管生成和溃疡愈合 ADSCs promote angiogenesis and ulcer healing
Borrelli *et al*[33]	2020	小鼠 Mice	少量多次放射小鼠头皮（总剂量30 Gy），放射后4周出现慢性纤维化效应，放射4周后局部注射CD74阳性的ADSCs Small amount of multiple radiation to the scalp of mice (total dose 30 Gy), chronic fibrotic effect 4 weeks after radiation, local injection of $CD74^+$ ADSCs 4 weeks after radiation	ADSCs具有明显的抗纤维化作用 ADSCs have a significant anti-fibrotic effect
Wu *et al*[34]	2018	裸鼠 Naked rats	不同剂量照射裸鼠背部（最高剂量15 Gy×3），放射4周后创造皮肤伤口，并局部注射ADSCs Irradiation of the back of nude mice at different doses (maximum dose 15 Gy×3), creation of skin wounds after 4 weeks of radiation, and local injection of ADSCs	ADSCs加速了伤口愈合并减少纤维化 ADSCs accelerate wound healing and reduce fibrosis
Khademi *et al*[48]	2020	大鼠 Rats	单次照射臀部皮肤（30 Gy剂量），放射24 h后局部注射ADSCs Single radiation of buttock skin (30 Gy dose), local injection of ADSCs 24 h after radiation	单独使用ADSCs并不能明显对减少辐射引起的皮肤损伤 The use of ADSCs alone does not significantly reduce radiation skin injury

续表

研究作者 Study authors	年份 Year	研究对象 Research subjects	研究方法 Research methods	研究结果 Study results
Akita *et al*[29]	2012	4名女性患者 4 female patients	几十年慢性骶尾骨、颈部等部位的放射性溃疡和组织严重纤维化，清创后人造真皮覆盖创面，并局部注射自体ADSCs Decades of chronic sacrococcygeal and neck ulcers and severe fibrosis of the tissues, with artificial dermis covering the wound after debridement and local injection of autologous ADSCs	术后75 d创面可完全愈合，局部血液循环增加 Complete healing of the wound can be achieved 75 d after surgery, with increased local blood circulation

3 PRF在皮肤软组织放射性损伤修复中的作用

PRF的生物学作用与其组成结构有关，含有丰富的血小板、白细胞和生长因子，并被一个特殊结构的纤维蛋白网所聚集。PRF促进创面愈合的机制主要有细胞因子和纤维蛋白支架两个方面。

3.1 细胞因子

PRF具备创面修复和组织再生所必需的因子。血小板在浓缩的过程中会释放出大量的生长因子，而PRF可模拟伤口愈合的生理过程释放生长因子，PRF含有的白细胞如中性粒细胞也能释放血管内皮生长因子来诱导新血管生成，并加快组织愈合。有学者[37]报道了PRF可通过增加再生表皮的厚度和上调血管内皮生长因子的表达来诱导创面愈合。PRF在临床创面治疗上也取得了惊喜的效果，Fortunato等[38]把PRF局部应用于治疗坏疽性脓皮病，发现PRF可促进溃疡的缩小和症状的改善，并能减少全身皮质类固醇的使用，在45 d后溃疡可完全愈合。在另一项随机、三盲的烧伤治疗临床试验中[39]，PRF凝胶在敷于烧伤创面后的第8天、15天，其创面愈合率显著高于对照组，且疼痛程度显著下降。说明PRF不仅能增加供体伤口愈合速度和愈合率，也能减轻疼痛水平。此外，一项研究[40]发现，PRF中的血小板衍生生长因子、纤维母细胞生长因子、转化生长因子-β等能显著上调I型胶原蛋白、III型胶原蛋白的基因表达，使胶原纤维更具条理性。

3.2 纤维蛋白支架

在凝血的最后阶段，纤维蛋白起着稳定最初的血小板簇的作用。这样的支架作用可把细胞因子纳入其网状结构，扫描电镜可以观察到大约97%的血小板和50%的白细胞聚集其中[41]，这些细胞既是各种生长因子的储存库，也作为细胞因子的传递载体。有学者[42]把PRF联合阿司匹林用于修复大鼠牙周骨，发现PRF与阿司匹林复合物可在37 ℃下持续48 h缓释水杨酸，促进牙周膜间充质细胞的增殖和迁移，并且纤维蛋白结构可模拟细胞外基质的结构和功能，为细胞附着、增殖和分化提供合适的三维环境。所以，PRF能持续维持细胞因子水平，不仅是由于血小板与白细胞的持续释放，也与PRF的三维立体结构能保持其生物活性有关。PRF的纤维支架作用见图3。

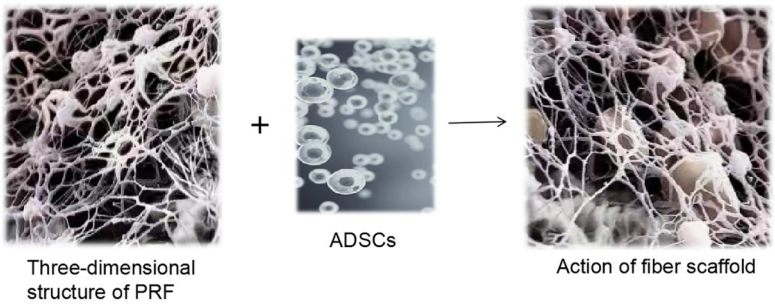

图3 富血小板纤维蛋白的纤维支架作用示意图
Fig.3 Schematic diagram of the action of PRF fibrous scaffolds

PRF对治疗牙周修复、骨及软骨再生、肌腱修复、整形美容等均有重要价值，但目前PRF对皮肤软组织放射性损伤研究较少，多被颌面学科用于修复放射性骨坏死。有学者[43]用PRF治疗放、化疗后出现的牙周溃疡感染，发现在2周内牙周伤口可愈合。有研究[44]发现，PRF对上颚放射性骨坏死效果显著。但也有学者[45]指出，PRF并不能预防放疗后颌骨放射性骨坏死的发生，在长达180 d的临床评估中，PRF并没有带来比常规手术和药物结合治疗有更好的疗效，这可能由于难以控制放射剂量及术后口腔护理，也与样本量较少的局限性有关。PRF应用于放射性损伤修复的研究见表2。

表2 富血小板纤维蛋白应用于放射性损伤修复的研究汇总

Table 2 Summary of studies on the application of PRF to the repair of radiation injury

研究作者 Study authors	年份 Year	研究对象 Research subjects	研究方法 Research methods	研究结果 Study results
Chen *et al*[43]	2019	1名53岁男性，口腔放疗后右上颌出现放射性骨坏死 A 53-year-old male with radiation osteonecrosis of the right maxilla after oral radiotherapy	牙槽清创后把PRF敷于患处、移植皮瓣后一期缝合 PRF was applied to the affected area after alveolar debridement, and the flap was grafted and sutured in one stage	术后3周内黏膜愈合，术后10个月随访X射线显示骨愈合良好 Mucosal healing within 3 weeks post-operatively and follow-up X-ray showed good bone healing at 10 months post-operatively
Maluf *et al*[44]	2020	1名65岁女性，口腔放疗后右上颚后部出现放射性骨坏死 A 65-year-old female with radionecrosis of the right posterior maxilla after oral radiotherapy	清创后放置两片PRF膜 Placement of two PRF membranes after debridement	术后2周黏膜愈合，39个月的随访未见复发 Mucosal healing at 2 weeks post-operatively and no recurrence at 39 months follow-up
Palma *et al*[45]	2020	23名头颈部肿瘤患者，60~70 Gy剂量放疗 23 patients with head and neck tumors treated with 60~70 Gy dose of radiotherapy	拔牙后PRF凝块填充牙窝 PRF clots filling of dental sockets after tooth extraction	临床评估180 d，两组在疼痛评分和放射性骨坏死发生率中无明显差异 No significant differences between the two groups in pain scores and incidence of radiation osteonecrosis at 180 d of clinical evaluation

4 ADSCs与PRF联合用于放射性损伤修复

PRF可增强ADSCs增殖、分化和旁分泌的生物学功能[46-47]，因此，ADSCs与PRF联合使用具有一定的协同作用。Khademi等[48]局部用ADSCs治疗大鼠臀部的放射性皮肤损伤后2~4周，治疗组的创面大小与对照组无明显差异，因此，他们认为ADSCs与生长因子联合使用可能效果更佳。Wang等[49]也发现，ADSCs联合PRF析出液可恢复放射引起的唾液腺组织的永久性损伤，而单独的ADSCs或PRF析出液则达不到该治疗效果。在2014年，Chen等[50]把ADSCs联合PRF皮下注射到猪模型的放射后腮腺部位，6个月后发现软组织缺损区的血管密度显著增加，凋亡细胞减少，表明PRF可作为辅助剂来提高ADSCs组织修复的疗效。也有报告[51]称PRF联合自体脂肪组织可辅助坏死骨切除术来治疗难治性下颌骨骨坏死。目前ADSCs与PRF联合用于放射性损伤修复的研究较少，但已有大量实验[52-53]证实，两者联合治疗神经修复、软骨缺损和骨质疏松的效果更显著。

基质血管凝胶（Stromal vascular fraction gel，SVFG）于2016年由我国学者鲁峰教授[54]提出，其经过1 200 g离心3 min后进行机械乳化，再经2 000 g离心3 min制备而成。SVFG在机械乳化过程中去除了成熟脂肪细胞，保留了约80.5%的ADSCs和74.2%的内皮细胞，从而增加了5~6倍的ADSCs浓度[55]。并且SVFG中含有的细胞外基质可为ADSCs提供天然的生长环境。因此，SVFG被认为是ADSCs的优秀替代品，在临床应用中有很大的潜力。大量

研究证实了SVFG具有促进血管生成和创面修复的作用[56-57]，并且SVFG在治疗放射性损伤中也有一定的效果，不仅能提高放射性骨折的愈合率[58]，还能治疗临床上严重的辐射导致的皮肤损伤，促进创面愈合[59]。Li等[60]研究表明，SVFG与PRF析出液通过下调白介素-8和上调白介素-10、血管内皮生长因子、缺氧诱导因子-1α等因子的表达水平减轻创面炎症，提高创面的微血管密度，刺激胶原蛋白形成，从而促进大白兔皮肤放射性损伤创面的再生修复，并且SVFG联合PRF析出液的效果更好。因此ADSCs或SVFG与PRF联合有望成为临床上治疗皮肤放射性损伤的重要策略之一。ADSCs联合PRF应用于放射性损伤修复的研究见表3。

表3　脂肪干细胞联合富血小板纤维蛋白应用于放射性损伤修复的研究汇总
Table 3　Summary of studies on the application of ADSCs combined with PRF in the repair of radiation injury

研究作者 Study authors	年份 Year	研究对象 Research subjects	研究方法 Research methods	研究结果 Study results
Chen *et al*[50]	2014	小猪 Minipig	单次照射右侧腮腺区域（20 Gy剂量），4个月后局部注射PRF联合ADSCs Single irradiation of the right parotid area (20 Gy dose), followed by local injection of PRF combined with ADSCs after 4 months	6个月后软组织缺损区的血管密度显著增加，凋亡细胞减少 Significant increase in vascular density and decrease in apoptotic cells in the soft tissue defect area after 6 months
Wang *et al*[49]	2018	小鼠 Mice	单次照射小鼠头部和颈部（18 Gy剂量），12周后局部注射ADSCs和PRF析出液 Single irradiation of the head and neck of mice (18 Gy dose), followed by local injection of ADSCs and PRF extract after 12 weeks	12周后联合组的唾液腺腺泡细胞损伤和萎缩更少，淀粉酶水平与微血管密度增加更明显 The combined group had less salivary gland follicle cell damage and atrophy and a more pronounced increase in amylase levels and microvessel density after 12 weeks
Lawb *et al*[51]	2020	1名69岁男性 A 69-year-old male	右下颌骨放射性骨坏死，切除坏死下颌骨后放置两片PRF膜+自体脂肪移植 Radiation osteonecrosis of the right mandible, removal of necrotic mandible and placement of two PRF membranes + autologous fat graft	3周后黏膜完全愈合，2个月后创面区血液灌注明显改善 Complete mucosal healing after 3 weeks and significant improvement in blood perfusion in the trabecular area after 2 months

5　结论

本文一方面总结了皮肤软组织在被照射后出现急性反应及慢性损伤表现的机制，另一方面指出ADSCs可以减少细胞凋亡，并分泌细胞因子下调急性放射性损伤炎症反应，促进新生血管形成，加快组织修复过程，还可在放射性损伤慢性期进行抗纤维化，干扰瘢痕形成。因此，ADSCs可在皮肤软组织放射性损伤中发挥重要作用。而PRF拥有丰富的生长因子，可控制炎症，促进皮肤软组织创面愈合，提高皮瓣和移植物的成活率，从而减少伤口愈合时间和并发症的发生率，亦是软组织重建的有力工具。并且PRF的生长因子和纤维蛋白支架，为ADSCs的增殖和分化提供更好的微环境，因此ADSCs联合PRF的协同作用为改善急性与慢性放射性皮肤损伤提供一种研究方向。但目前对于ADSCs联合PRF运用于皮肤放射性损伤修复的研究较少，两者联用的相关机制在未来有待进一步探索。

生物技术的发展提高了对ADSCs的利用，但ADSCs仍有潜在的促进肿瘤复发的风险。一些基础实验认为，ADSCs能以旁分泌的方式促进肿瘤细胞的增殖、侵袭性迁移。Zha等[61]在小鼠模型上发现ADSCs通过肝细胞生长因子（Hepatocyte growth factor，HGF）旁分泌和参与HGF/c-MET信号通路来促进宫颈癌细胞的生长和侵袭。Sharaf等[62]也发现，头颈部癌患者的ADSCs的上清液可促进食管鳞状细胞癌的增殖和新血管生成，但也有很多应用富含ADSCs的脂肪进行乳房重建的临床研究证明了ADSCs具备安全性[63-65]。因此，ADSCs应避免用于与肿瘤较接近的放射性皮肤损伤，更适用于（如食管癌、宫颈癌等）与表皮无关的肿瘤，从而保证

ADSCs治疗的安全性。此外，高龄或偏瘦的病人的脂肪较少，可考虑采用同种异体移植的方式来获取有效的自体干细胞。因此，ADSCs的广泛使用仍面临诸多挑战，ADSCs的高效操作、低温保存及相关风险因素还需深入的探索和研究。

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