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PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

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Mitogen-activated protein kinases (MAPKs or MAP kinases) are serine-/threonine-specific protein kinases that phosphorylate substrates that control cellular functions such as proliferation, gene expression, differentiation, mitosis, survival, and apoptosis in response to various stimuli. In mammals, MAPKs comprise three subfamilies—the extracellular signal-regulated kinase (ERK) MAPKs, which are activated by growth factors and mitogens, and the c-Jun N-terminal kinase (JNK) and p38 (p38) MAPKs, which are activated by cellular stressors and inflammatory cytokines. A large body of work has explored the importance of MAPK signaling to early development and the function of stem cell populations such as embryonic stem cells,[1] skeletal muscle stem cells,[2] and lung stem cells.[3] Given the importance of MAPKs and the specific importance of p38/MAPKs in response to several types of stress, targeting MAPK signaling pathways may represent an interesting means of supporting exogenous stem cell therapies or promoting endogenous stem cell-mediated regeneration and tissue repair in patients suffering from a range of diverse conditions. In the first of our featured articles published this month in *STEM CELLS Translational Medicine*, Liang et al report that ferulic acid treatment alleviates irradiation-induced impairments in skeletal stem cells (SSCs) and promotes bone regeneration through p38/MAPK and ERK/MAPK signaling pathway reactivation and so may promote bone repair following skeletal tumor treatment.[4] In a related article published recently in *STEM CELLS*, Shafiquzzaman et al demonstrated, for the first time, the role of the Tak1 (mitogen-activated protein kinase kinase kinase 7)-p38/MAPK pathway in club cell regeneration and bronchiolar epithelial repair and, in doing so, highlighted a potential therapeutic target for bronchiole-related disorders.[5]

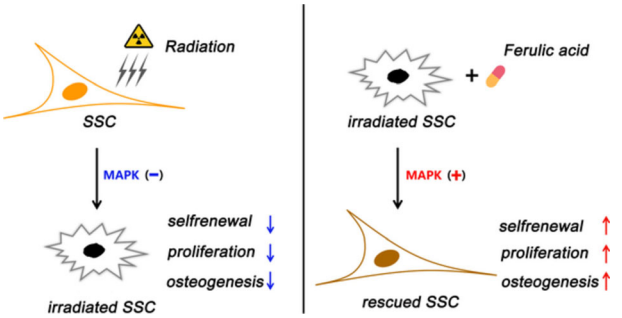
The platelet-derived growth factor (PDGF) family primarily regulates the growth and division of mesenchymal cells such as fibroblasts and smooth muscle cells. The four polypeptide chains encoded by the *PDGFA*, *PDGFB*, *PDGFC*, and *PDGFD* genes form five different dimeric glycoproteins: PDGF-AA, -BB, -AB, -CC, and -DD. The binding of PDGFs to receptors that possess differential binding affinities induces the dimerization of PDGFR-α and -β chain isoforms to form homodimeric and heterodimeric receptors and the activation of receptor tyrosine kinase activity. PDGFR activation stimulates a range of crucial intracellular signaling pathways that promote cell proliferation and migration[6] and plays essential roles during embryogenesis, controlling the development of the lungs, intestines, skin, testis, kidneys, hematopoietic system, and blood vessels. While PDGF also plays a vital role in wound healing in later life,[7] PDGF signaling can contribute to the development of cancer, inflammatory disease, pulmonary fibrosis, atherosclerosis, asthma, and chronic obstructive pulmonary disease.[8] In the second of our featured articles published this month in *STEM CELLS Translational Medicine*, Shaw et al explore how aging and injury impact the responses of kidney mesenchymal cells through a detailed analysis of marker protein/gene expression, which includes the specific expression of PDGFR-α and PDGFR-β by renal myofibroblasts.[9] In a related article published recently in *STEM CELLS*, Zhou et al reported on how synergistic interactions between mesenchymal stem cells (MSCs) and endothelial cells could improve bone regeneration and how the differentiation of MSCs into pericytes through the PDGF-BB/PDGFR-β signaling pathway supported blood vessel formation.[10]

FEATURED ARTICLES

MAPK Signaling Controls Skeletal Stem Cell-Mediated Tissue Regeneration After Irradiation

Previous research from Heng Zhu (Beijing Institute of Radiation Medicine) and Li Ding (Air Force Medical Center, PLA, Beijing, China) established a role for SSCs in targeting host immune cells to control inflammation[11] and regulating bone remodeling by suppressing inflammatory osteoclastogenesis.[12] Their subsequent research sought to improve bone reconstruction strategies following skeletal tumor treatment by radiotherapy/surgery by exploring the effect of irradiation on SSC biology and bone regeneration and the potential for ferulic acid, a phytochemical with antioxidant and therapeutic activities, to alleviate any potential radiation-induced stem cell damage.[13,14] As reported in their *STEM CELLS Translational Medicine* article,[4] Liang et al discovered that irradiation suppressed proliferation, colony formation, and the osteogenic differentiation of SSCs and induced a general decrease in their number. Furthermore, subsequent proteomic and transcriptomic analyses revealed that irradiation reduced the activation of the p38/MAPK and ERK/MAPK signaling pathways and inhibited the expression of crucial tissue regeneration-associated

genes. Importantly, ferulic acid treatment of irradiated SSCs induced the reactivation of the p38/MAPK and ERK/MAPK signaling pathways to significantly rescue radiation-induced stem cell impairments; furthermore, the specific activation of these pathways by ferulic acid treatment also improved SSC-mediated bone repair in an irradiated bone defect mouse model. Overall, the authors propose a crucial role for the p38/MAPK and ERK/MAPK signaling pathways in regulating the self-renewal of SSCs and SSC-mediated tissue regeneration following irradiation, thereby underscoring the relevance of these findings to the treatment of skeletal cancer patients.



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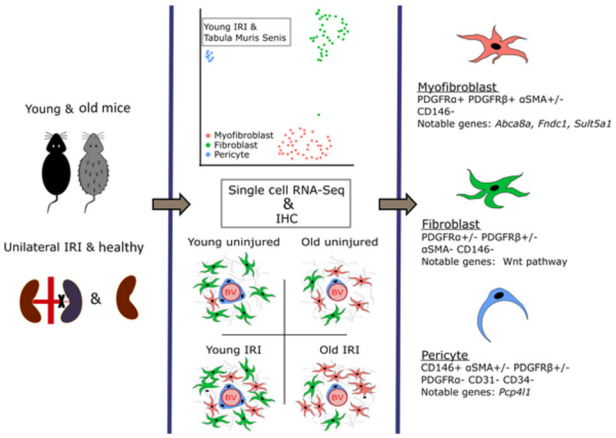
Analysis of Mesenchymal Cells Helps to Define Age-Related Differences in Kidney Injury Responses

The impact of acute kidney injury[15] on the renal mesenchyme can reduce peritubular capillary density to worsen the loss of nephrons and promote fibrosis, a hallmark of chronic kidney disease.[16] The mesenchymal cells of the kidney significantly influence these disease-associated processes; however, we understand little regarding how aging impacts mesenchymal cells and their response to injury. In the hope of filling this knowledge gap, researchers led by Bruno Péault (University of California, Los Angeles, California, USA) and David A. Ferenbach (University of Edinburgh, UK) characterized renal mesenchymal cell heterogeneity in young and aged mice under normal conditions and after ischemia-reperfusion-injury using multiplexed immunolabeling and single-cell transcriptomics. In their recent *STEM CELLS Translational Medicine* article,[9] Shaw et al discovered that the expression profiles of a range of perivascular cell marker proteins correlated well with their location within the complex architecture of the renal mesenchyme; of note, PDGFR-α and PDGFR-β co-expression efficiently labeled renal myofibroblasts (formed during kidney fibrosis) while CD146 was identified as an optimal renal pericyte marker. Notably, single-cell RNA sequencing of murine kidneys demonstrated that mesenchymal cells segregated into three subtypes with distinct expression patterns with aging and following injury (pericytes, fibroblasts, and myofibroblasts); overall, uninjured aged kidneys resembled injured young kidneys. The authors hope that their integrated description of how marker expression in the renal mesenchyme changes with age and in response to injury may allow the more accurate definition of renal mesenchymal cell populations and the identification of age-specific pathways and potential therapeutic targets.



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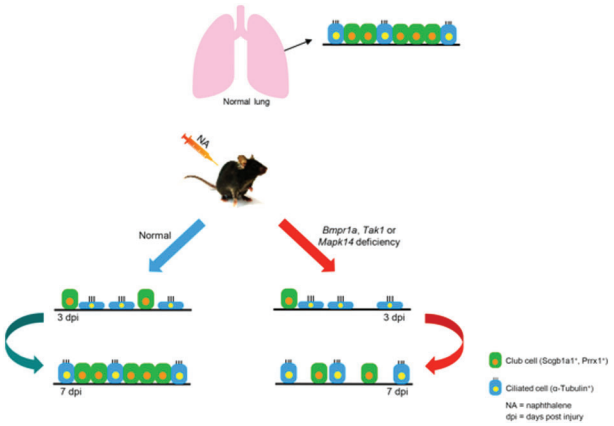
RELATED ARTICLES

MAPK Signaling Controls Club Cell Regeneration and Bronchiolar Epithelial Repair

The club cells of the small airways (bronchioles) protect the bronchiolar epithelium and detoxify inhaled harmful substances. Self-renewing progenitor-like club cells differentiate into ciliated epithelial cells and contribute to the repair of the bronchiolar epithelium, which represents a significant site for the development of life-threatening disorders, such as chronic obstructive pulmonary disease and lung adenocarcinoma.[17,18] In a recent *STEM CELLS* article,[5] researchers led by Huijuan Liu (Shanghai Jiao Tong University, Shanghai, China) explored the identity of progenitor club cells and the mechanisms by which these cells regenerate the bronchiolar epithelium. Shafiquzzaman et al now report that a noncanonical bone morphogenic protein (BMP) pathway involving Tak1 and MAPK[19,20] plays a crucial role in bronchiolar epithelium regeneration by promoting club cell proliferation and expansion. The authors employed lineage tracing and conditional gene knockout mouse studies to establish the homeobox transcription factor Prrx1 as a marker for adult mouse club cells during homeostasis and regeneration. Their analyses also established the importance of a noncanonical signaling pathway comprising BMPs and a BMP receptor type 1A (BMPR1A)-Tak1-p38/MAPK signaling pathway in club cell regeneration; while the loss of *Bmpr1a*, *Tak1*, or *Mapk14* (encoding p38α) expression in Prrx1-expressing club cells had negligible impact under homeostatic conditions, gene deficiencies significantly impacted club cell regeneration and bronchiole repair in adult mice by reducing the proliferation and expansion of regenerating

club cells. Overall, these findings represented the first description of the BMPR1A-mediated Tak1-p38/MAPK pathway as a regulatory mechanism affecting club cell regeneration and bronchiolar epithelium repair and a potential therapeutic target for bronchiole-related disorders.



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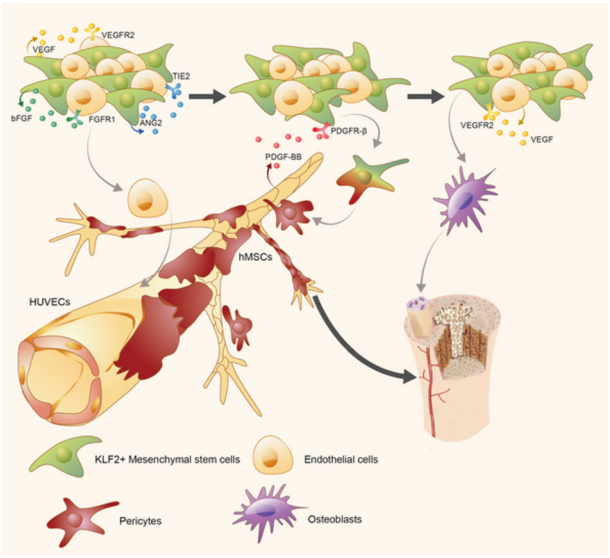
Exploring the Synergy of MSCs and Endothelial Cells in Bone Regeneration Strategies

As MSC and endothelial cell coculture-based studies suggested a reciprocal increase in MSC-derived osteogenesis[21] and endothelial cell-derived angiogenesis,[22] researchers from the laboratories of Mengfei Yu and Huiming Wang (Zhejiang University, Hangzhou, China) explored this synergistic interaction to develop enhanced bone regeneration strategies. As reported in their recent *STEM CELLS* article,[10] Zhou et al evaluated the interaction of human MSCs expressing *Krüppel-like factor 2* (*KLF2*), which codes for a zinc-finger transcription factor, and human umbilical vein endothelial cells cultivated in conventional two-dimensional and advanced three-dimensional gelatin methacrylate hydrogel coculture systems with optimized media formulations. The authors highlighted the crucial role of *KLF2* expression in maintaining the stem-like nature of MSCs and enhancing the MSC-mediated induction of endothelial cell-mediated angiogenesis, which itself subsequently stimulated MSC-mediated osteogenesis. Interestingly, the secretion of a range of crucial angiogenic factors by MSCs (including basic fibroblast growth factor, vascular endothelial growth factor, and angiopoietin-2) enhanced endothelial cell-derived angiogenesis; however, this also prompted the differentiation of MSCs into pericytes through the PDGF-BB/PDGFR-β signaling pathway to promote the formation of maturing blood vessels. Meanwhile, the increased expression of vascular endothelial growth factor by maturing endothelial cells enhanced the osteogenic potential of the remaining MSCs. Overall, the findings of this exciting study suggested that the implantation of *KLF2*-expressing human MSCs and endothelial cells within advanced three-dimensional cell scaffolds may represent an efficient means of significantly enhancing bone defect regeneration.



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