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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.

STEM CELLS TRANSLATIONAL MEDICINE

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Microglia are the resident macrophages of the brain and spinal cord and represent the primary immune defense in the central nervous system. Deriving from yolk sac erythromyeloid progenitors during development,[1,2] large numbers of microglia (approximately 10%-15% of all cells in the brain) continually scavenge the central nervous system to detect and remove protein plaques that disrupt communication and cause inflammation, damaged or unnecessary neurons and synapses, and various types of infectious agents. Overall, these vitally important immune cells support brain development and maintain proper function during adulthood; however, microglia also play critical roles in the onset and progression of various central nervous system pathologies, including psychiatric disorders and tumorigeneses/metastasis.[3,4] Current aims in microglial research involve the development of efficient strategies for their ex vivo generation/amplification (but forgo the potential problems associated with pluripotent stem cell use) for use in transplantation-based therapies and the exploration of how microglia impact disease pathology and mediate responses to various treatment strategies. In the first of our Featured Articles published this month in *STEM CELLS Translational Medicine*, Bruzelius et al describe the discovery of microglia-like precursors in the human bone marrow that may represent the starting point for the development of novel patient-centered microglial approaches and in vitro modeling.[5] In a Related Article published recently in *STEM CELLS*, L'Episcopo et al demonstrated that the transplantation of syngeneic neural stem cells (NSCs) within the substantia nigra pars compacta in an aged mouse model of Parkinson's disease prompted the restoration of functionality thanks, in part, to the induction of Wnt/β-catenin signaling in microglia.[6]

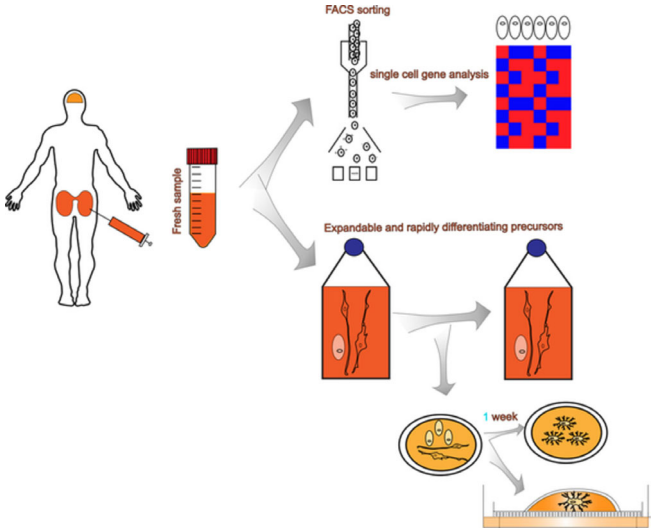
Although the bone morphogenetic protein (BMP) family of ligands were originally identified as osteoinductive components, they are now understood to impact a range of processes associated with embryonic development (including cardiogenesis, neurogenesis, and osteogenesis) and adult homeostasis by regulating cell lineage commitment, morphogenesis, differentiation, proliferation, and apoptosis of various types of cells throughout the body.[7] BMPs form part of the transforming growth factor β (TGFβ) family and signal through types I and II serine-threonine kinase receptors and intracellular downstream effectors, such as the Smad proteins, which can induce specific gene expression programs. For example, BMP2 signaling represents a vital component of many developmental processes, such as digit formation, cardiogenesis, and neuronal growth.[8] BMP2 also plays critical roles in the musculoskeletal system, with the presence of BMP2 driving the differentiation of bone-resident stem cells into osteoblasts (cells that form new bone) via the induced expression of crucial osteogenic genes that include Runt-related transcription factor 2 and Osterix.[9] Further insight into BMP-mediated signaling may aid the efficient differentiation of stem/progenitor cells into therapeutically relevant somatic cell types and further our understanding of diverse human pathologies associated with aberrant BMP pathway regulation.[10] In the second of our Featured Articles published this month in *STEM CELLS Translational Medicine*, Mejia et al identify a highly replicating stem-like cell (RSC) as the early stem/progenitor cell that initiates BMP2-induced heterotopic bone formation.[11] In a Related Article published recently in *STEM CELLS*, Dries et al systematically profiled multiple components of the TGFβ signaling pathway during neural differentiation to reveal the existence of cell-stage specific networks of individual components.[12]

FEATURED ARTICLES

Human Bone Marrow-Derived Microglial Progenitors as a Starting Point for Microglial Therapies and Modeling

The generation of microglia from pluripotent stem cells or their derivation from bone marrow monocytes suffers from various problems that have impeded their therapeutic application. As a recent study had reported that murine bone marrow-derived microglia possessing a yolk sac microglial signature could populate the diseased central nervous stem,[13] researchers led by Tania Ramos-Moreno (Lund University, Sweden) recently sought to examine the human bone marrow in the hope of identifying cells that may foster the rapid and reliable generation of human microglia for therapeutic purposes. In their recent *STEM CELLS Translational Medicine* article,[5] Bruzelius et al report on the detection, isolation, and characterization of intermediately-specified myeloid microglial progenitors present within the human bone marrow stroma that express human-specific consensus adult microglial genes. Encouragingly, the authors also described protocols

for the efficient in vitro expansion of these microglial progenitors (which employs a stromal cell feeder layer) and the generation of microglia that retain the expression of important marker genes. Importantly, progenitor-derived microglia phagocytosed latex beads and Alzheimer's disease-associated Aβ amyloid fibrils, underwent immune polarization after relevant stimulation, and exhibited a microglial-like morphology. Furthermore, progenitor-derived microglia also survived when cultured in an ex vivo human brain organotypic model containing glioblastoma and exhibited morphological characteristics that suggested functional polarization in a brain tumor environment. The authors hope that this newly described microglial progenitor population may represent a safe and efficient starting point for the production of the large numbers of microglia required for in vitro modeling and the development of therapies.



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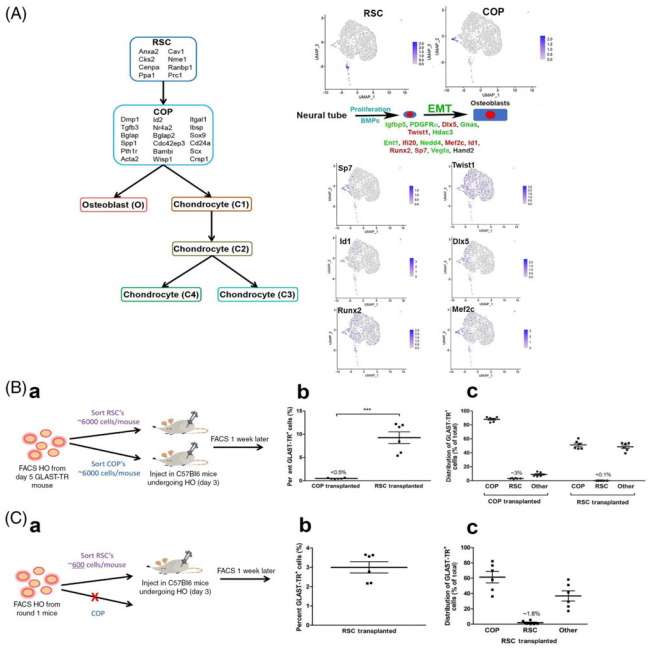
BMP2-Induced Heterotopic Bone Formation by Newly Identified Highly Replicating Stem Cells

Previous studies that attempted to identify the stem/progenitor cells controlling BMP2-induced heterotopic bone formation suggested a role for glial high-affinity glutamate transporter (GLAST)-expressing chondro-osseous progenitor cells.[14,15] To confirm these findings, researchers led by Alan R. Davis (Baylor College of Medicine, Houston, Texas) employed a mouse reporter model (GLAST-Tomato Red) to identify the exact progenitor population responsible for BMP2-induced heterotopic bone formation. As reported in their *STEM CELLS Translational Medicine* article,[11] Mejia et al employed highly sensitive single-cell RNA sequencing of fluorescently labeled chondrocytes and osteoblasts after BMP2-induced heterotopic bone formation and identified a highly replicating stem-like cell or RSC as a candidate for study. The authors demonstrated that RSCs undergo an epithelial-to-mesenchymal transition (like neural crest stem cells) to produce mesenchymal stem cell-like cells that express osteoblast and chondrocyte transcripts and generate bone and cartilage tissue. RSCs also engrafted, survived, amplified, and differentiated into mesenchymal stem cell-like and mature cell types following their intramuscular injection in mice undergoing heterotopic bone formation; furthermore, the isolation of RSCs from transplanted animals allowed for similar findings after transplantation into a second mouse, which strongly suggests that RSCs initiate BMP2-induced heterotopic bone formation. Overall, their highly replicative nature, when combined with the limited presence of cell surface antigens, suggests the application of these newly-identified GLAST-expressing RSCs in advanced strategies to improve musculoskeletal regeneration or amplify bone formation.



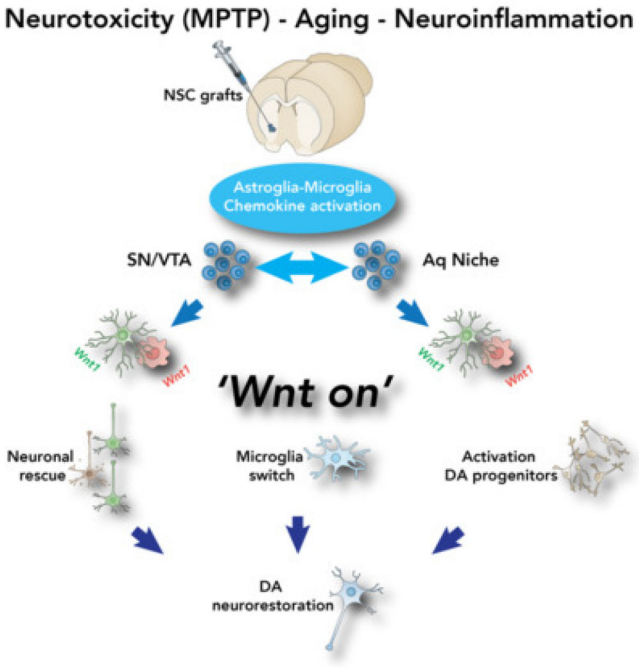
https://doi.org/10.1002/sctm.20-0378

RELATED ARTICLES

NSC Transplantation Restores Neuronal Function in Aged Parkinson's Disease Mice Via Microglial Signaling

Recent research led by Bianca Marchetti (University of Catania, Italy) and Stefano Pluchino (University of Cambridge, UK) highlighted a significant role for reactive astrocytes and Wnt/β-catenin signaling in alterations to midbrain dopaminergic neuron plasticity and brain repair in Parkinson's disease model mice during aging,[16,17] a leading disease risk factor. In a more recent *STEM CELLS* article, the authors explored how the transplantation of syngeneic NSCs into the substantia nigra pars compacta of an aged mouse model of Parkinson's disease may rejuvenate the host microenvironment and promote the recovery of dopaminergic neuron function.[6] L'Episcopo et al discovered that NSCs

transplanted into the brains of neurotoxin-lesioned aged mice (sporadic Parkinson's disease model) engrafted and migrated to the dopaminergic neuron niche, with a significant proportion acquiring an astroglial phenotype. Subsequently, Wnt1-expressing endogenous and exogenous astrocytes triggered Wnt/β-catenin signaling pathway activation in both dopaminergic neurons and microglia to induce neurotrophic and anti-inflammatory/anti-oxidative mechanisms to rejuvenate the aged inflammatory microenvironment and favor a neurorestorative program in the aged Parkinson's disease brain. Notably, the abolishment of neurorestorative potential and immunomodulation associated with NSC transplantation following the inhibition of Wnt/β-catenin signaling highlighted the overall importance of this signaling pathway. Overall, the authors believed that their findings, which underscored the impact of transplanted NSCs on nigrostriatal functionality in the aged Parkinson's disease brain in part via microglial-mediated immune responses, may have therapeutical implications for dopaminergic neuron restoration.



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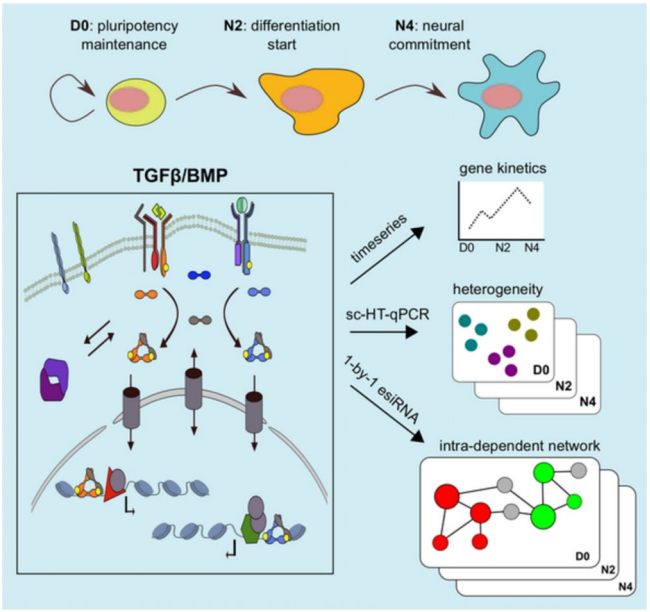
In-Depth Analysis of TGFβ Pathway Highlights Complex Transcriptional Regulation During Fate Transitions

Signaling via TGFβ family ligands (including BMPs and Activin/Nodal, among others) imparts both cell-type-specific and context-dependent transcriptional changes during embryonic development to regulate cellular transitions.[18,19] In the hope of providing a better understanding of this complex process, researchers led by Danny Huylebroeck (Erasmus University Medical Center, Rotterdam, The Netherlands) and Ruben Dries (Dana-Farber Cancer Institute, Boston, Massachusetts) explored the transcriptional regulatory network of nearly one hundred TGFβ-related components via a systematic high-throughput perturbation approach in mouse ESCs differentiating into neural progenitors. As reported in their recent *STEM CELLS* article,[12] Dries et al perturbed one TGFβ component at a time via the expression of endoribonuclease-prepared small interfering RNAs and evaluated the effect on the mRNA levels of the other components at various stages (which correlated to three cell types—pluripotent ESCs, primed epiblast-like cells, and early neural progenitors). Their systematic analysis revealed the existence of intricate systems of multilevel regulation where gene-gene interactions generally occurred in a cell-stage specific manner. Single-cell RNA-profiling during the distinct stages of mouse ESC neural differentiation also demonstrated the presence of coexpression modules and subpopulations possessing stable coexpression modules, with the core pluripotency genes given as an example of a module present at all stages. Overall, the findings generated from this fascinating combinatorial experimental approach advised the careful interpretation of single-gene perturbations or knockouts in differentiating stem/progenitor cells or during embryogenesis.



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