STEM CELLS TRANSLATIONAL MEDICINE®

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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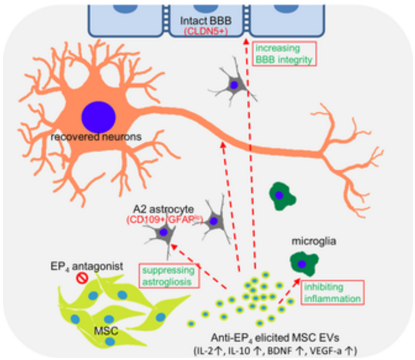
The subgranular zone of the hippocampus, a narrow layer of cells found between the granule cell layer and hilus of the dentate gyrus, represents one of the very few sites where adult mammalian neurogenesis is currently known to occur. The hippocampus itself is part of the limbic system and plays important roles in the consolidation of information from short-term memory to long-term memory, and in the spatial memory that enables navigation. Neural progenitor cells (NPCs) present in the hippocampus proliferate to generate large progenitor pools that mature into granule neurons whose extraordinary plasticity is vitally important for the formation and retrieval of memories [1]. The fact that traumatic brain injury or hippocampal degeneration can significantly impair memory and other intellectual functions is compounded by the limited level of self-regeneration displayed in the central nervous system [2]. Therefore, understanding adult hippocampal neurogenesis may allow the development of improved therapeutic strategies to treat damage/degeneration in the hippocampus. Said strategies currently include mesenchymal stem cell (MSC)-based treatments; however, studies have suggested that implanted MSCs do not differentiate into replacement tissues, thereby proposing paracrine signaling and the enhanced activity of endogenous repair mechanisms as the primary therapeutic mechanisms of MSCs post-transplantation [3]. In our first Featured Article in *Stem Cells Translational Medicine* this month, Chen et al. discovered that blocking a specific signaling pathway in MSCs promoted the release of extracellular vesicles with the ability to significantly reduce the damaging consequences of hippocampal damage in mice [4]. In a Related Article from *Stem Cells*, Leeson et al. report on how the P2X7 receptors expressed by adult murine hippocampal NPCs control cell death, niche formation, and cell proliferation and thereby influence adult neurogenesis [5].

The platelets (or thrombocytes) present in mammalian blood react to bleeding by initiating blood clotting with the help of various coagulation factors; therefore, patients presenting with defective platelets or low blood platelet counts (thrombocytopenia) are at high risk of spontaneous bleeding or poor responses to surgical procedures. Human volunteer donors currently represent the source of platelets for transfusions, although this approach is limited by various concerns, including the requirement for storage conditions, fluctuating supply, the risk of contamination, and immune-related concerns [6]. To solve this problem, researchers have sought to isolate and culture CD34-positive hematopoietic stem/progenitor cells (HSPCs) from various sources to then generate the megakaryocytes that eventually produce proplatelets, the precursors to platelets [7]. However, the development of optimal in vitro culture conditions to generate a high number of megakaryocytes from each HSPC currently represents a significant hurdle [8]. Further applications of in vitro-derived platelets include the modeling of interactions between blood components and intravenously administered stem cell therapies in the hope of generating safer and more effective treatment approaches for a range of conditions. In our second Featured Article in *Stem Cells Translational Medicine* this month, Martinez and Miller report on the utility of a gas-permeable culture surface employing fed-batch media dilution schemes for the enhanced generation of megakaryocytes from HSPCs for the ex vivo production of platelets [9]. In a Related Article from *Stem Cells*, Sheriff et al. demonstrate how the tissue origin of MSCs influences their adhesive behavior under flowing conditions and their interaction with platelets in the blood in a study with potential implications for intravenous MSC therapies [10].

## FEATURED ARTICLES

### Extracellular Vesicles from Mesenchymal Stem Cells Aid Recovery from Hippocampal Damage

Previous studies from the laboratory of Hua-Jung Li (National Health Research Institutes, Miaoli, Taiwan, China) discovered that blocking prostaglandin E2/prostaglandin E2 receptor 4 signaling in mammary epithelial stem cells prompted the secretion of extracellular vesicles with the ability to induce mouse mammary gland formation [11]. In their new study in *Stem Cells Translational Medicine* [4], the team sought to discover if blocking this pathway in MSCs [12] could also promote the release of proregenerative extracellular vesicles for the treatment of the impairments in cognition, learning, and memory observed following the hippocampal damage associated with central nervous system diseases and traumatic brain injury. Chen et al. revealed that treating MSCs with a




prostaglandin E2 receptor 4 antagonist prompted the secretion of extracellular vesicles carrying a cargo of anti-inflammatory cytokines and factors with the potential to modulate astrocyte function, blood–brain barrier integrity, and microglial migration into the damaged hippocampus. Encouragingly, the systemic administration of these extracellular vesicles following hippocampal damage in mice reversed deficiencies in cognition, learning, and memory, inhibited reactive astrogliosis, attenuated extensive inflammation, reduced microglial infiltration into the damaged hippocampus, and increased blood–brain barrier integrity. In comparison, extracellular vesicles from untreated MSCs failed to elicit these reparative/regenerative responses following hippocampal damage. Overall, the authors suggest that antagonist-treated MSC extracellular vesicles may represent a safe and effective approach for the effective treatment of diseases and disorders of the central nervous system.

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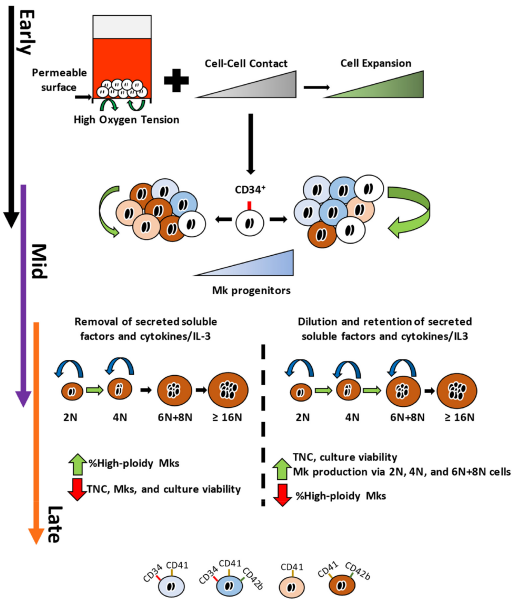
## New Cell Culture Technology Boosts in Vitro Platelet Formation from Hematopoietic Stem/Progenitor Cells




Efforts to delineate new and improved strategies to generate large numbers of megakaryocytes for platelet formation have investigated various sources of CD34-positive HSPCs [13]; meanwhile, technological developments have included a free-falling three-dimensional culture environment to enhance the number of mature megakaryocytes from cord blood HSPCs [14]. Now, Andres F. Martinez and William M. Miller (Northwestern University, Evanston, IL) report on the potential of a commercially available gas-permeable silicone rubber membrane system that provides efficient gas exchange and fed-batch media dilution schemes as a means to produce large numbers of megakaryocytes from peripheral blood HSPCs. In their *Stem Cells Translational Medicine* article [9], the duo describe how culturing CD34-positive HSPCs at a density of $40 \times 10^3$ cells per $cm^2$ on a gas-permeable soft silicone rubber membrane surface and employing media dilutions provided a significant increase in megakaryocytes per input HSPC compared with employing standard culture surfaces and full media exchanges. The megakaryocyte population produced displayed high viability and contained a greater proportion of high-ploidy megakaryocytes. Encouragingly, the megakaryocytes also produced proplatelets and platelet-like-particles that activated and aggregated upon stimulation. Given the encouraging results generated with this cell culture technology, the authors now wish to explore different cell densities, altered cytokine concentrations, the potential for cord blood HSPCs, and roles of different oxygen levels and cell-to-cell contact to further increase the yield of megakaryocytes and, therefore, the number of platelets produced.

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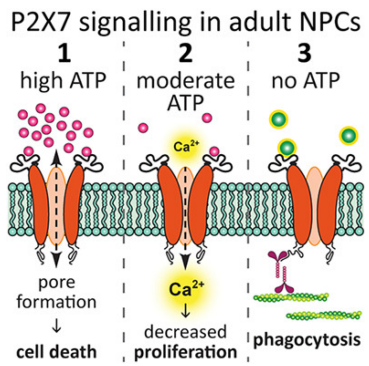
### Related Articles




## Delineating the Role of P2X7 Receptors in Neural Progenitor Cells of the Adult Hippocampus

Recent research from the laboratories of Michael W. Weible (Griffith University, Nathan, QLD) and Ben J. Gu (University of Melbourne, Victoria, Australia) discovered that cultured fetal NPCs employ P2X purinoceptor 7 (P2X7) receptors to phagocytose cellular debris, suggesting that they may aid neurogenic niche development [15]. In their subsequent *Stem Cells* article, Leeson et al. investigated the regulatory roles of P2X7 receptors in NPCs from adult murine hippocampal subgranular and cerebral subventricular zones in the hope of elucidating their possible involvement in neurogenic niche formation in the mammalian brain [5]. To this end, in vitro and in vivo assessments revealed the presence of proliferating P2X7-positive NPCs and that, in response to high concentrations of ATP that may be present during an inflammatory event [16], P2X7 receptors in NPCs promoted cell death via transmembrane pore formation. In the absence of ATP, live cell and

confocal microscopy revealed the ability of NPCs to phagocytose fluorescent beads through P2X7 activity and thereby contribute to niche maintenance; however, the presence of low to moderate levels of ATP resulted in calcium influx, low phagocytosis, and a dose-dependent decrease in NPC proliferation. The authors hope that the three distinct physiological roles described in their study will represent a crucial step toward understanding how inflammation may regulate adult neurogenesis by NPCs resident in the hippocampal subgranular and cerebral subventricular zones.

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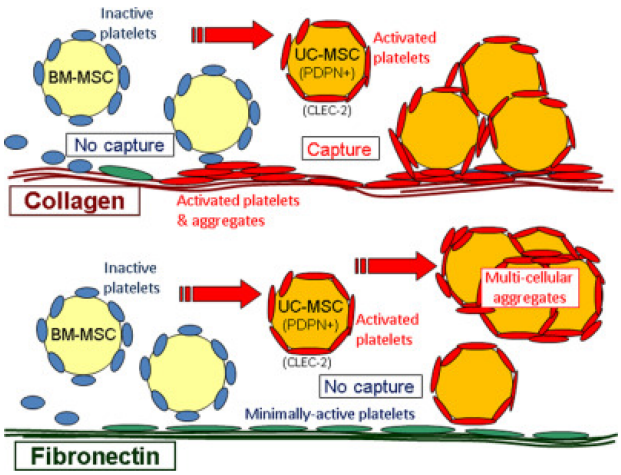
## Tissue-of-Origin Mediates the Interaction Between Mesenchymal Stem Cells and Platelets




Studies have implicated platelets in the recruitment of MSCs from the bloodstream into target tissues; one study established infused MSCs in contact with neutrophil–platelet clusters in inflamed ear dermis [17], whereas another discovered platelet activation-dependent MSC deposition in the lung of a rat model of pulmonary arterial hypertension [18]. In a recent *Stem Cells* article, researchers led by Gerard B. Nash (University of Birmingham, Birmingham, U.K.) explored the interaction of MSCs and platelets as a means to better understand and perhaps improve intravenous MSC therapy [10]. Sheriff et al. discovered that the interaction of platelets with MSCs under flowing conditions depended on their tissue-of-origin: bone marrow MSCs bound to inactive platelets and failed to adhere to platelets deposited on fibronectin or collagen matrix proteins; however, umbilical cord blood MSCs bound to and activated platelets, prompting their binding to activated platelets on collagen. Although this may allow umbilical cord blood MSCs to extravasate and pass into damaged tissues, binding to activated platelets may drive wider-spread activation and aggregation of platelets, thereby leading to a reduction in the platelet count. Interestingly, the authors discovered the expression of podoplanin, an activating ligand for platelet C-type lectin-like receptor 2 (CLEC-2), explained these differences, and revealed that treatment with recombinant soluble CLEC-2 inhibited platelet aggregation by umbilical cord blood MSCs. Overall, the authors anticipate that their findings will have important implications for therapeutic infusions of MSCs for a range of disease and disorders.

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