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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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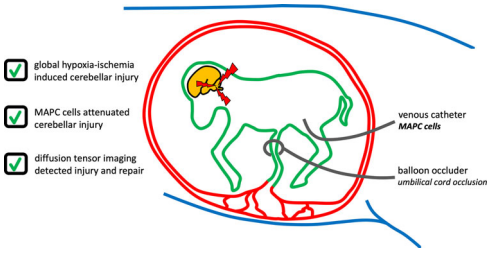
Multipotent adult progenitor cells (MAPCs), a plastic-adherent bone marrow-derived population of human multipotent adult stem cells, can undergo long-term culture expansion without significant losses in potency or genomic and epigenetic stability.[1] Furthermore, MAPCs, which are distinct from mesenchymal stem cells, do not evoke an immune response and display potent immunomodulatory/anti-inflammatory and regenerative properties.[2,3] The therapeutic potential of MAPC therapy has been supported by the improvements to neurological outcomes observed in preclinical models of hypoxic-ischemic encephalopathy, traumatic brain and spinal cord injury, and stroke, among other conditions. Of particular note, a clinical-grade MAPC product known as MultiStem (Athersys, Inc, Cleveland, Ohio) is currently under evaluation for safety and efficacy in a double-blind, placebo-controlled clinical trial for the treatment of ischemic stroke in human patients.[4] These promising results have driven the further exploration of MAPC therapy as a means to treat brain injuries and improve neurodevelopmental outcomes in preterm neonates, while complementary research has sought to understand the mechanisms by which MAPC therapy improves outcomes. In our first Featured Article published this month in *STEM CELLS Translational Medicine*, Gussenhoven et al report that systemic MAPC therapy reduces cerebellar injury after asphyxia in fetal sheep in a study that extends previous observations that MAPCs afford cerebral neuroprotection.[5] In a Related Article published recently in *STEM CELLS*, Yang et al discovered that systemic MAPC therapy enhanced recovery after stroke by altering the expression of immune-related genes and reducing pro-inflammatory signaling in the spleen.[6]

Yes-associated protein 1 (YAP1 or YAP) is a transcriptional coactivator of the Hippo pathway that transduces mechanical cues such as extracellular matrix (ECM) rigidity, strain, and shear stress to regulate biological processes that include cell growth and fate decision, organ size control, and regeneration.[7] The activation of the Hippo signaling pathway prompts the phosphorylation and inactivation of YAP1; however, the inhibition of Hippo signaling prevents YAP1 phosphorylation and promotes the relocation of YAP1 from the cytoplasm to the nucleus, where it functions as a transcriptional coactivator for genes associated with cell proliferation, survival, mobility, stemness, and differentiation. Multiple studies have highlighted an important role for YAP1 in controlling the differentiation of various stem and progenitor cell types - specifically, activated YAP1 supports the maintenance of the self-renewing state of pluripotent stem cells[8] and the proliferation of tissue-resident stem cells,[9] whereas YAP1 inactivation can promotes efficient stem cell differentiation. Therefore, a deeper understanding of YAP1 function in stem cell biology may permit the enhanced in vitro expansion of stem cells and their efficient differentiation into therapeutically relevant cell types. In our second Featured Article published this month in *STEM CELLS Translational Medicine*, Yamashita et al demonstrate that the inactivation of YAP1 during the differentiation of human induced pluripotent stem cells (iPSCs) on a laminin-fragment culture substrate significantly improves chondrogenesis and cartilage formation.[10] In a Related Article published recently in *STEM CELLS*, Xia et al characterized YAP1 as a crucial mechanotransduction signaling mediator that promotes the expansion of inner ear progenitor cells (IEPCs) via the regulation of Wnt/β-catenin activity.[11]

FEATURED ARTICLES

Protecting the Preterm Cerebellum with Systemic MAPC Therapy



Researchers led by Reint K. Jellema (Maastricht University Medical Center, The Netherlands) previously demonstrated how systemic MAPC therapy protected cerebral structure and function in a fetal sheep model of hypoxic-ischemic encephalopathy,[12] an important cause of mortality and morbidity in preterm neonates,[13] using a specialized form of diffusion-weighted magnetic resonance imaging known as diffusion tensor imaging. In their more recent *STEM CELLS Translational Medicine* article,5 Gussenhoven et al sought to assess the

neuroprotective potential of systemic MAPC therapy in the preterm sheep cerebellum following global hypoxia-ischemia induced by umbilical cord occlusion. The authors intravenously delivered MAPCs one hour after injury and assessed cerebellar responses through histopathology and diffusion tensor imaging. Hypoxia-ischemia induced noticeable cortical injuries in the cerebellum, which included disrupted cortical strata, histopathological microgliosis, hypomyelination, and the disruption of white matter organization; however, early systemic MAPC therapy modulated injury patterns in the preterm cerebellum, as evidenced by the prevention of cortical injury and attenuation of white matter injury. Additionally, the authors provided evidence supporting diffusion tensor imaging in detecting microstructural alterations associated with injury and therapeutic response in the preterm cerebellum. While this article represents the first description of improvements to cerebellar injuries following early systemic MAPC therapy in a relevant large animal model of global hypoxia-ischemia, these exciting findings also support the clinical value of diffusion tensor imaging as a more accurate injury detection strategy.

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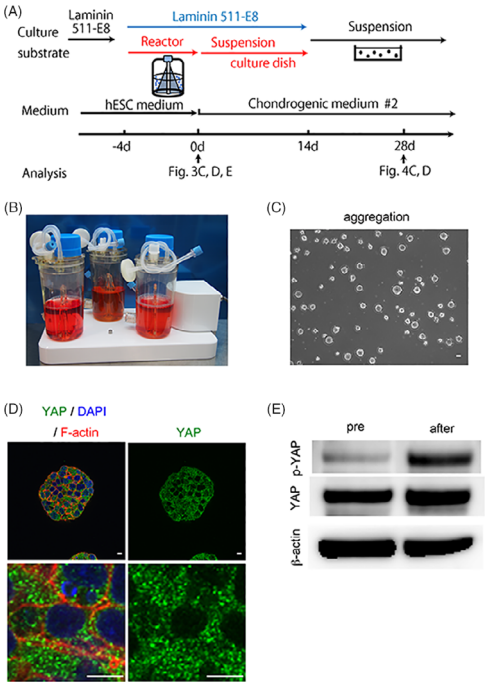
YAP1 Modulates the Articular Cartilage-Forming Potential of Human iPSCs

Researchers seeking to boost the chondrogenic differentiation of human iPSCs and improve the treatment of cartilage-related conditions such as osteoarthritis have begun to explore the critical role of the cell culture substrate. In the place of undefined substrates such as Matrigel, several studies have provided evidence for the chondrogenic potential of substrates composed of defined laminin fragments.[14,15] To explore this strategy further, researchers from the laboratory of Noriyuki Tsumaki (Kyoto University, Japan) analyzed the differential effects of culture substrates during the exposure of iPSCs to chondrogenic differentiation medium and discovered a key role for YAP1 in regulating cartilage formation. In their new *STEM CELLS Translational Medicine* article,[10] Yamashita et al explored the potential of a specific laminin fragment (laminin 511-E8) as a pro-chondrogenic growth substrate; however, the team discovered that iPSCs more efficiently formed cartilage on a Matrigel substrate. Growth on the laminin substrate prompted iPSCs to take on a more rounded cell morphology when compared to Matrigel, which suggested the involvement of YAP1. The authors subsequently confirmed that the laminin substrate prompted YAP1 activation, which inhibits differentiation; however, transient knockdown of YAP1 in iPSCs during early chondrogenic differentiation permitted the formation of cartilage on laminin, whereas the exposure of iPSCs cultured on laminin to YAP1 inhibitors also increased cartilage formation. While this exciting new study highlights a crucial role for YAP1 modulation in the chondrogenic differentiation of iPSCs, these findings also advise the careful choice of culture substrate to improve differentiation efficiency.



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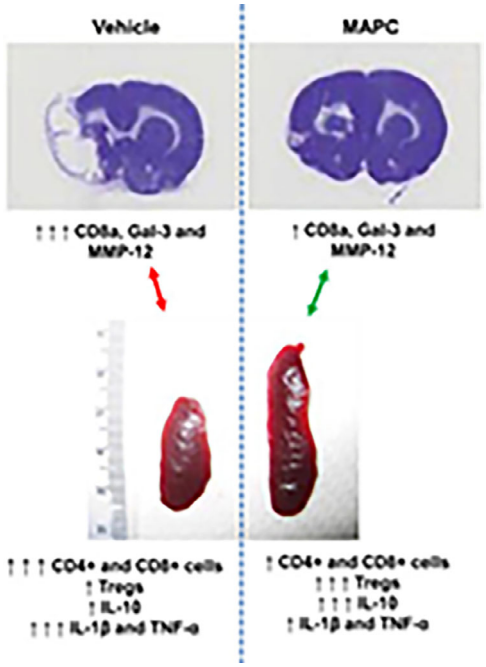
RELATED ARTICLES

Systemic MAPC Therapy Enhances Recovery from Stroke via the Spleen

Brain injuries can prompt overt responses in the spleen, including an increase in size or the release of immune cells and pro-inflammatory mediators that can exacerbate damage in the central nervous system[16,17]; however, spleen-mediated immune responses after stroke and the possibility of employing stem cells to counteract said responses remained relatively unexplored. To fill this knowledge gap, researchers led by Sean I. Savitz (McGovern Medical School at UT-Health Houston, Texas) assessed splenic activation and peripheral immune responses after ischemic stroke in adult rats and evaluated the impact of systemic MAPC therapy. Reporting in a recent *STEM CELLS* article,[6] Yang et al discovered that ischemic injury prompted an increase in spleen size and the overexpression of genes related to inflammation and immune responses in the brain and spleen. Encouragingly, systemic MAPC therapy enhanced recovery from stroke, which associated with the restoration of normal spleen size and the modulation of important immune responses,which included an increase in immunosuppressive T regulatory cells within the spleen and an increase in anti-inflammatory (IL10) and a decrease in pro-inflammatory (IL-1β) interleukin release from splenocytes.

Finally, the importance of the spleen was underscored by the lack of effect of systemic MAPC therapy after stroke in rats lacking spleens. Overall, the authors hypothesized that the immunomodulatory influence of systemic MAPC therapy on the spleen creates an enhanced pro-regenerative environment in the damaged brain that fosters recovery after stroke.



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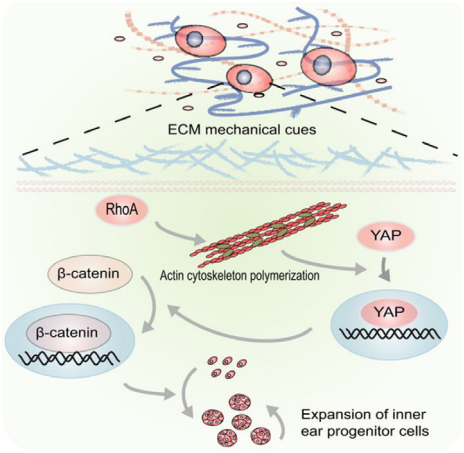
YAP1-Dependent Mechanotransduction Promotes Inner Ear Progenitor Cell Expansion

The ability to effectively expand IEPCs during long-term in vitro culture could foster the development of enhanced strategies for mechanosensory hair cell regeneration and the restoration of hearing. Although the formation of progenitor-derived spheroids and their differentiation has provided a tractable research model for the study of inner ear development,[18,19] the lack of an ECM scaffold, which provides structural integrity and biological cues, remains a significant problem to the exploration of how mechanical cues and mechanotransduction signaling affect IEPC culture. To remedy this situation, researchers from the laboratories of Wenyan Li and Huawei Li (Fudan University, Shanghai, China) compared IEPCs in traditional suspension culture to those grown within an encapsulated three-dimensional culture system employing Matrigel, an ECM-based culture substrate. Reporting in *STEM CELLS*,[11] Xia et al discovered that encapsulation promoted the survival and expansion of IEPCs thanks to the mechanical cues from the ECM that induced Ras homolog family member A (RhoA) accumulation and polymerization of the actin cytoskeleton. In turn, these alterations prompted the nuclear localization of YAP1, which enhanced IEPC expansion through the upregulation of the Wnt/β-catenin signaling pathway. Overall, the authors suggest that the transduction of mechanical signals from the ECM through the RhoA-YAP1-β-catenin signaling axis regulates the survival, proliferation, and differentiation of IEPCs. While these findings should contribute to the improvement of the in vitro culture of IEPCs, they may also prompt the development of pharmacological strategies to induce hair cell regeneration in the inner ear.



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