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Placental Cells and Derivatives: Advancing Clinical Translation

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The placenta is an intriguing and mysterious organ, starting from its role during pregnancy. A temporary organ perceived as exhausted and normally discarded as biological waste, the placenta has sparked much attention from researchers and clinicians for its potential uses in regenerative medicine. Just over a decade ago, a few researchers had the notion that placental tissues such as the amniotic membrane, chorion, and umbilical cord tissue could contain cells with stem cell properties and therapeutic potential. Since then, scientific research is beginning to provide an understanding of the mechanisms through which placental tissues, cells, and their derived factors exert therapeutic actions in different preclinical disease models. Even more, this is an exciting moment in the history of placental cell research as we are at the dawn of investigating their safety and efficacy in several clinical trials.

This special issue in *Cell Transplantation* is dedicated to the understanding of the therapeutic potential of placental tissues, cells, and factors derived from the cells.

The issue opens with focus on the amniotic membrane. A few contributions focus on mapping the amniotic membrane in terms of mitochondrial activity and regenerative potential. Banerjee et al. show that the placental and reflected regions of the human amniotic membrane possess different mitochondrial properties and suggest that differences in energy metabolism could impact therapeutic applications. Centurione et al. show that human amniotic epithelial cells isolated from different regions of the amniotic membrane possess different pluripotency and proliferation marker expression, underlining the heterogeneity of the cell population. Serra et al. also focus on human amniotic epithelial cells showing that they can respond to pro-angiogenic signals in vitro and differentiate into hepatic sinusoidal endothelial cells in vivo.

Other studies in the issue focus on the understanding of the immune-modulatory properties of placental cells, a well-known Trojan horse that has been attributed to their regenerative properties in inflammatory-based disorders. Magatti et al. review the widely recognized immunosuppressive properties of amniotic cells and conditioned medium and also show that these cells possess the ability to induce immune responses, underlining the need to understand the mechanisms underlying these bipolar properties in order to identify the optimal therapeutic applications. Several contributions have also highlighted the paracrine, immune-modulatory actions exerted by amniotic cells through extracellular vesicles. Lange-Consiglio et al. demonstrate that microvesicles from equine amniotic mesenchymal stromal cells (MSCs) contain micro-ribonucleic acid (miRNAs) involved in regulating the inflammatory processes, suggesting their significant role in the immune-modulatory ability of amniotic MSCs. Cavallini et al. show that modulation of the extracellular milieu through lipid supplementation can impact the dynamics of intracellular vesicle trafficking as well as the quality and functional properties of secreted exosomes. Silini et al. demonstrate that the immune-modulatory properties of amniotic MSCs are retained after the encapsulation of cells in a pectin gel cell carrier, suggesting their use in novel osteochondral regenerative strategies. Other regenerative medicine applications using the amniotic membrane are reviewed by Zeleznik et al., who focus on the use of amniotic membrane in reconstructive urology, from preparation and storage of the membrane and preclinical studies up to standardization for clinical use. Barboni et al. review the translational potential of placental cells in veterinary medicine, with a particular focus on their potential for the treatment of musculoskeletal diseases in domestic animals.

The use of placental cells in hematopoietic disorders is also discussed in this issue. Lo Iacono et al. demonstrate

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that Wharton's jelly MSCs support the expansion of multipotent as well as committed hematopoietic stem/progenitor cells. Kumar et al. demonstrate the preclinical feasibility of in utero transplantation of genetically modified, first trimester chorionic villus MSCs as a cell-mediated gene therapy in hemophilia A. Sher et al. discuss the ability of Pluristems's GMP-approved placental cells to enhance hematopoietic cell counts after bone marrow failure and ongoing studies to treat hematopoietic syndrome of acute radiation as well as incomplete engraftment after bone marrow transplantation.

Other contributions focus on the use of placental cells in neurodegenerative diseases. Pischiutta et al. review the beneficial effects of placenta-derived stem cells in acute brain injury, with a focus on the experimental studies on traumatic brain injury and stroke, the engineering strategies pursued to foster cell potential, use of the placental cell secretome as an alternative, cell-free strategy, and the latest results from clinical trials using placenta-derived stem cells for acute brain injury. Joerger-Messerli et al. show that exosomes from Wharton's jelly MSCs have the potential to prevent and resolve hypoxic–ischemic-induced apoptosis in neuronal cells in immature neonatal brain through the transfer of let-7-5p miR. Finally, in this issue Taghizadeh et al. describe the cell isolation process from umbilical cord tissue using the Auxo-Cell Processing System, or AC:Px® that allows for processing of solid tissue using mechanical means to liberate cells, avoiding the use of any biochemical, enzymatic digestion.

This special issue showcases the rapidly expanding potential applications of placental cells and derivatives, while underscoring the need to understand the therapeutic mechanisms of actions.