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Enhancing translational potential of Mesenchymal Stem Cell (MSC) therapies for cancer with 3D culture

Mesenchymal stem cells (MSCs) have many potential applications in cancer therapy and regenerative medicine. In particular, there is interest in exploiting the notable tumor-tropic properties of MSCs to deliver suicide genes directly into tumors. Recently, we prepared a standardized bank of iPS cell-derived MSCs (iPSC-MSCs) engineered to stably express the suicide gene that codes for cytosine deaminase (CD), an enzyme that converts the inert prodrug 5-fluorocytosine (5-FC) into the cytotoxic agent 5-fluorouracil (5-FU). These genetically modified cells constitutively expressed high levels of CD through numerous passages and following cryopreservation and maintained features characteristic of tissue-derived MSCs. IPSC-MSCs expressing CD showed robust bystander activity and dose-dependent killing of all cancer cell lines tested *in vitro* and/or *in vivo* in the presence of 5-FC. The translational potential of MSC-based therapies for cancer has been hindered by low cell viability and microvascular entrapment following intravenous injection. Here we showed that when CD-expressing iPSC-MSCs were prepared as multicellular spheroids in 3D hanging drop cultures, cell size was markedly reduced similar to tissue-derived MSCs and cell resiliency was improved. Apparently as a result, greater numbers of viable cells were able to avoid obstructing lung microvasculature following tail vein injection in mice. As expected, lung inflammation was less severe following intravenous injection of the cells from 3D cultures versus cells prepared in standard adherent 2D cultures. Interestingly, expression of CD, as well as the anti-cancer factor TRAIL, was augmented in the sphere-derived iPSC-MSCs. CD-expression was also augmented in extracellular vesicles (EVs) derived 3D cultures, relative to 2D cultures. Remarkable anti-tumor effects of the CD-expressing iPSC-MSCs and EVs from 3D cultures were observed *in vitro* as well as in a human breast cancer xenograft model with and without 5-FC treatment. Importantly, activation of the prodrug also resulted in elimination of the modified iPSC-MSCs thus providing a safeguard against wayward stem cell progeny. Taken together, the results here provide evidence that iPSC-MSCs from 3D cultures have immense translational potential as cellular carriers of therapeutic transgenes and in precision medicine.

Biography

Thomas Bartosh has completed his PhD degree in Cell Biology and Genetics from The University of North Texas Health Science Center, USA. He has joined the Institute for Regenerative Medicine (IRM) at Texas A&M University in 2008 to develop therapies with mesenchymal stem cells (MSCs). He is currently an Assistant Professor of Medical Physiology in the College of Medicine at Texas A&M University. He studies the advantages of using three-dimensional (3D) culture methods to activate MSCs and exploit their inherent therapeutic potential.

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