Endothelial Progenitor Cells Co-cultured with Stromal Cells Undergo a Mesenchymal Transition Which Is NOTCH Signalling Dependent

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The discovery of endothelial progenitor cells (EPCs) and their isolation in clinically relevant quantities raises the prospect of neo-vessel formation to restore blood supply to ischemic tissues. However, their engraftment and vasculogenic potential on delivery have to date proved low. We report that mesenchymal stem/stromal cells (MSC), independent of source and age, improve the engraftment and vasculogenic potential of endothelial colony forming cells (ECFC) *in vivo*. This effect could be recapitulated *in vitro* with better survival of ECFC in the presence of MSC. MSC co-culture altered ECFC appearance to an elongated mesenchymal morphology and was associated with reduced proliferation which could only partially be reproduced in the absence of direct contact. ECFC primed via MSC contact had significantly reduced self-renewal potential but improved capacity to form tube structures *in vitro* and engraft *in vivo*. Primed ECFC displayed major differences in transcriptome compared to ECFC never exposed to MSC, with the expected modulation of genes involved in the cell cycle, but also upregulation of genes influencing mesenchymal transition, adhesion and extracellular matrix, and NOTCH signalling. Inhibiting NOTCH signalling, a potential upstream regulator of mesenchymal transition, in large part modulated this gene expression pattern, and functionally reversed the mesenchymal morphology of ECFC, profoundly reducing their tube forming ability. In conclusion, ECFC co-cultured with MSC survive better and undergo a mesenchymal transition that is dependent on NOTCH signalling resulting in significantly increased vasculogenic potential.

Biographic Details

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My name is Abbas Shafiee. I am postdoctoral research fellow specialized in stem cell biology, and tissue engineering. During my master's project I developed a new cartilage substitute by combining the nano-scale biomaterials and stem cells with potential application in human tissue regeneration. Thereafter, I joined The University of Queensland Centre for Clinical Research (UQCCR), to undertake my PhD. My PhD study at UQ focused on the *in vivo* definition of endothelial progenitor cells (EPCs) from the human term placenta tissues. As a result of this project, I established a new *in vivo* hierarchy amongst EPCs. In addition, we successfully isolated and delineated diverse fetal mesenchymal and endothelial populations directly from human tissue, which could have significant potential for clinical applications in the future. Since April 2016 I joined Queensland University of Technology and conducted a project on application of EPC for *in vivo* modelling of bone marrow tissue.