Potential stem/progenitor cell approaches to repair the heart after infarction: Human cardiac progenitor cells and Smad3 inhibition

Dominique de Kleijn PhD
Associate Prof. Experimental Cardiology, UMC, Utrecht
Project Leader ICIN
Visiting Scientist Genome Institute Singapore

Myocardial infarction often leads to significant loss of cardiomyocytes and scarring putting the patient in a negative spiral leading to heart failure.
The formation of cardiomyocytes and other heart cell types is still very limited from bone marrow cells and embryonic stem cells. The transplantation of cells to the human heart is often confounded by arrhythmia and an immunological response.

Cardiac progenitor cells, resident in the heart, have the potential to differentiate into cardiomyocytes. We investigated the differentiation potential of human cardiac progenitor cells and studied expression of cardiac markers and contractile proteins in these cells. Next to this, we studied the electrophysiological phenotype of human cardiac progenitor derived cardiomyocytes.This revealed that cardiac progenitor cells form an interesting type of cell for therapy to repair the heart and studies in mouse and pig myocardial infarction models are ongoing.

Another approach is to prevent the scarring and stimulate the regenerative response of the heart. For this, we investigated the role of Smad3, a TGF-beta pathway signaling protein, in prevention of scarring and heart regeneration. This revealed that in a Smad3 null mouse infarction model, the mouse die of cardiac rupture. However, when mice can be rescued from the rupture by matrix metalloprotease inhibition, the heart recovers and the mice have an almost normal cardiac output. This identifies the potential role of Smad3 in cardiac recovery after infarction and opens the possibility to intervene using specific Smad3 inhibitors.

Derivation of clinically useful tissue cell lines from ES cells

Lim Sai Kiang, Group Leader, Stem and developmental cell biology, GIS

The pluripotency of embryonic stem cells (ESCs) to differentiate into cells from all three germ layers makes ESCs an ideal source of cells for regenerative therapy for many diseases and tissue injuries. However, this very property of ESCs also poses a unique challenge in therapeutic applications of ESC, namely the generation of the appropriate cell types for the treatment of a specific diseased or injured tissue in sufficient quantity and homogeneity to ensure therapeutic efficacy while inhibiting the generation of other cell types that may have a deleterious effect on the tissue repair and regeneration. At present, protocols that either enhance differentiation of ES cells towards specific lineages and/or enrich for specific tissue cell types are too inefficient and generally yield heterogeneous cell populations that might be tumorigenic. To resolve these problems, our approach has been to derive progenitor cell lines of limited potential from ESCs. This will allow for the expansion of a progenitor cell with a highly restricted differentiation potential that, upon differentiation, will generate a highly enriched population of a specific cell type with reduced or no tumorigenic potential. In this presentation, I will describe the derivation of human mesenchymal stem cell lines from human ESCs, and our strategy to derive insulin producing cell lines from human ESC using our experience in deriving an insulin-producing cell line from mouse embryo and a mouse ESC-derived progenitor insulin-expressing cell line.