Karolinska Institutet

LUDWIG INSTITUTE FOR CANCER RESEARCH and DEPARTMENT OF CELL & MOLECULAR BIOLOGY

Integrating Extrinsic & Intrinsic Cues to Guide Cell Fate Decisions – Rational Approaches in Stem Cell Engineering

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssal Farmakologi, Nanna Svartz väg 2

Fredagen den 30 Augusti, 2013, kl 09.00

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Stockholm 2013

ABSTRACT

The long-term goal of stem cell engineering is to generate functional cells for cell replacement therapies, disease modelling and in drug development assays. It is evident that one of the major challenges in stem cell research is to develop reproducible methods to obtain well-defined and pure populations of clinically relevant cell types in a sustainable manner. Many studies have shown that appropriate signalling factors can specify desired cell types from stem cells, albeit in an inefficient manner. The heterogeneity seen in stem cell-derived cultures makes them unsafe and ineffective for use in the clinics and laboratories. In this thesis, we applied knowledge obtained from early developmental studies to develop rational approaches in stem cell engineering of a variety of clinically important cell types. In Paper I, we created mesendodermal progenitors by long-term activation of the Wnt pathway using a chemically defined inhibitor. These progenitors served as a renewable platform for more efficient stepwise derivation of cardiac, endothelial, osteogenic and chondrogenic cells. In Papers II and III, we integrated extrinsic and intrinsic cues by creating a permissive environment using appropriate growth factors, then forcing the expression of key transcription factors to achieve a highly efficient method to generate an array of neuronal cell types including dopamine, serotonin, motor and noradrenergic neurons. The purity of the cultures makes it possible to analyse subtype-specific genome-wide gene expression patterns and the discovery of novel markers provide insight into their transcriptional codes. We also showed, in a proof-of-concept experiment that the stem cell-derived neurons can be used in high throughput drug assays to analyse drug specificity.

ISBN 978-91-7549-231-5