Gene Function in Cell Growth, Differentiation & Development

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Introduction

Precision medicine (also referred to as personalised medicine) aims at tailoring medical therapy to the specific disease and needs of the individual patient. Stem cells are particularly well suited for precision medicine both for diagnosis and cell based therapy.

The institute studies various stem cell types and their differentiated progeny. A particular focus is on pluripotent stem cells, hematopoietic stem cells and mesenchymal stem cells. Additionally, engineered pluripotent stem cells are generated from normal body cells by reprogramming, referred to as induced pluripotent stem cells (iPS cells). Further to this we use precision genome editing by CRISPR/Cas technology for generating iPS cells with wanted properties for e.g. disease modelling.

Hematopoietic stem cells give raise to all cells of blood and we study blood cell composition based on DNA methylation signatures. Dendritic cells (DC) represent a highly specialized blood cell type required for immunity and immune tolerance. We investigate molecular mechanism of DC development from hematopoietic stem cells and DC migration. These studies also extend to general mechanism of cell-biomaterial interaction and their impact on cell motility and adhesion.

Finally, computational approaches are being widely used to study gene expression, chromatin architecture and gene networks in both normal physiological and pathological states. We would like to congratulate our computational expert Ivan Costa for accepting the position as Professor and founding head of the Institute for Computational Genomics, Joint Research Center for Computational Biomedicine, RWTH Aachen University, Aachen, Germany.

Fig 1: Hematopoietic stem cells develop into specific DC subsets cDC1, cDC2 and pDC by successive steps of lineage commitment and differentiation.

iPS Cells for Disease Modelling in vitro

Patient specific cells for studying human diseases are limited or not available. Here iPS cell technology provides a solution: iPS cells represent an inexhaustible cell source and can differentiate into cells of all three germ layers and thus a large array of cell types are readily obtained for disease modelling in vitro (Zenke, 2017; Zenke et al., 2017).
EMT Regulators as Switches in DC Development

DC originate from hematopoietic stem cells in bone marrow (Fig. 1) and exit the bone marrow niche as precursors to immigrate into peripheral tissues, such as skin (Fig. 4). Here DC become sessile and functionally embed to act as sentinels of the immune surveillance system. Following antigen uptake DC are activated, emigrate the peripheral tissue and travel via lymphatic vessels to lymphoid organs where they encounter T cells to present processed antigens (Fig. 4). We investigate signaling via TGF-β1 receptor and hepatocyte growth factor (HGF) receptor (also known as MET) in DC development, function and migration. We propose that mechanisms of mesenchymal-to-epithelial transition (MET) and epithelial-to-mesenchymal transition (EMT) are important for generating sessile and migratory DC, respectively (Hieronymus et al., Semin. Cell Dev. Biol., 2015; Sagi and Hieronymus, 2017, in press). In addition, a study in collaboration with Hovav et al., Hebrew University, Jerusalem, Israel revealed a differential and sequential role of BMP7 and TGF-β1 in differentiation of Langerhans cells (LC), the contingent of DC in the stratified squamous epithelia. Hence, we propose the concept that EMT and MET programs are regulated in DC/LC development by Met, and TGF-β1 and/or BMP7 signaling, respectively (Fig. 4).

Fig. 4: HGF/Met signaling induces LC and dermal DC emigration from skin in an EMT-like process, including matrix metalloproteinase (MMP) activation to facilitate arrival in lymph nodes and antigen presentation to naive T cells. In addition, HGF induces tolerogenic phenotypes by IL-10 and IL-27 secretion which results in enhanced numbers of regulatory T cells (Tregs).

Epi-Blood-Count: DNAm Based Leukocyte Subset Quantification

Analysis of the cellular composition of blood is a routinely requested laboratory test in hematological diagnostics. So far such measurements done with fresh blood samples and immunophenotypic analysis are labour intensive. Here we established an alternative approach based on DNA methylation (DNAm) measurements at individual CG dinucleotides (CpGs) that reflect the relative composition of leukocytes. The DNAm measurements, referred as “Epi-Blood-Count” show nearly the same precision as conventional hematocytological methods and are applicable also to frozen blood samples (in collaboration with Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation and Institute for Immunology, RWTH Aachen University Hospital, Aachen, Germany).

Predicted blood counts for granulocytes, lymphocytes and monocytes – based on our “Epi-Blood-Count” – correlate well with measurements on a hematology analyzer (Fig. 3A). In analogy, the method is also applicable to other leukocyte subsets, such as CD4 T cells, CD8 T cells, B cells and NK cells. Additionally, the calculated absolute cell numbers based on DNAm correlate nicely with absolute cell counts (Fig. 3B). Our Epi-Blood-Count approach allows determining white blood cell composition in frozen blood samples, improves the cost effectiveness and advances the standardization of white blood cell counts (Frobel et al., in press).

Fig. 5: Leukocyte subset Epi-Blood-Count and absolute quantification of cells based on DNA methylation (Frobel et al., in press).
Solution Blow Spinning Fibres for the Analysis of Cell Motility and Adhesion

New technologies have made possible the development of polymeric biomaterials with controlled geometry and physico-chemical properties. Solution blow spinning technique has the advantage of ease of use allowing the production of nano or microfibres and the direct fibre deposition on any surface in situ. Yet, very little is known about the influence of such fibres on biological functions such as immune response and cell migration. We engineered polymeric fibres composed of either pure poly(lactic acid) (PLA) or blends of PLA and polyethylene glycol (PEG) by solution blow spinning (SBS) and determined their impact on DC and on cell adhesion and motility (Paschoalin et al., 2017).

Cells readily interacted with fibres resulting in an intimate contact characterised by polymerisation of actin and the accumulation of focal adhesion components at sites of cell-fibre interactions (Fig. 6). Remarkably, fibres did not elicit any sizeable increase of activation markers and inflammatory cytokines in DC, which remained in their immature (inactive) state (Paschoalin et al., 2017). These findings will allow the development of new biomaterials for tissue engineering and regenerative medicine.

Computational Approaches for Personalized Medicine in Type II Diabetes

Type 2 diabetes (T2D) is a disease with an increasing prevalence in industrialized countries. T2D is currently treated with a combination of lifestyle changes and pharmacological therapies. However, there are no specific guidelines for how to use available anti-diabetic drugs to target the underlying genetic traits. In a collaborative work with Anders Rosengren (University of Gothenburg, Sweden), we have analysed genome-wide data from T2D patients to find novel biomarkers and evaluate therapeutic approaches targeting these genes.

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Selected References in 2017


Patent applications


On the Left: Poster Award to Kristin Seré, PhD at Medical Sciences Day 2017, Medical Faculty, RWTH Aachen University

Figure below: Lab Retreat in Antwerp, Belgium

Visiting the opencast coal mining area Weisweiler in the vicinity of Aachen, Germany