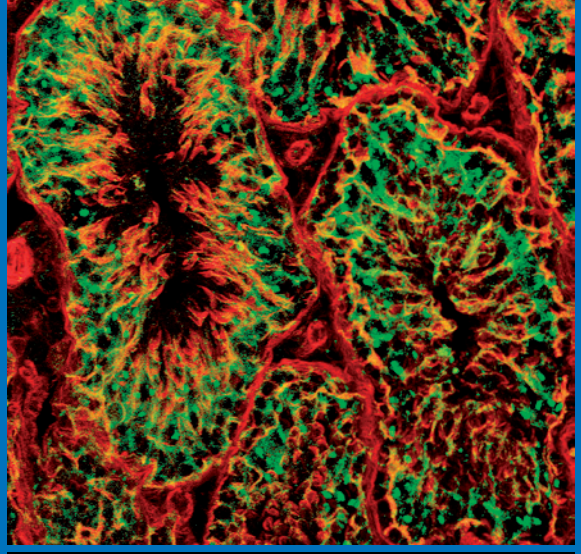
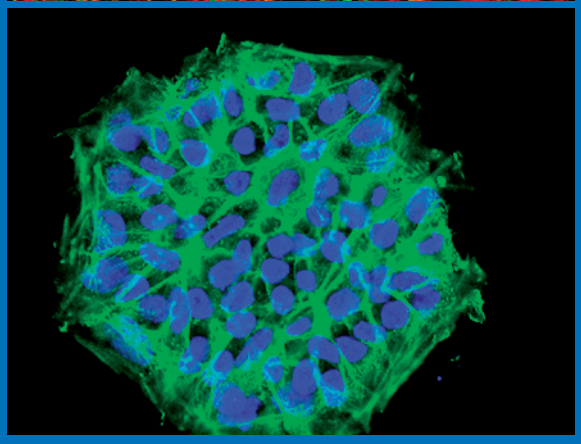
Gene Function in Cell Growth, Differentiation & Development





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Introduction

The institute is working on different types of stem cells: (i) somatic stem cells isolated from tissues of mice and man, which are primed to differentiate towards specific lineages (Fig. 1). Examples for somatic stem cells are hematopoietic stem cells (HSC) that give rise to all types of blood cells, and mesenchymal stem cells (MSC) that differentiate towards cells from bone, cartilage and adipose tissue. (ii) Embryonic stem cells (ES cells) are pluripotent and can be differentiated towards all cell types of the three germ layers. (iii) It is also possible to reprogram terminally differentiated cells into induced pluripotent stem cells (iPS cells), which closely resemble ES cells (Fig. 1). Various conditions are modified to regulate self-renewal and lineage-specific differentiation of these stem cell types. For example the impact of specific biomaterials and surface topography on stem cell growth and differentiation is investigated. Furthermore, the laboratory is using genome precision engineering with CRISPR/Cas to generate cells with wanted properties. Many of these studies build on a strong expertise in bioinformatics and computational biology for data analysis and prediction.

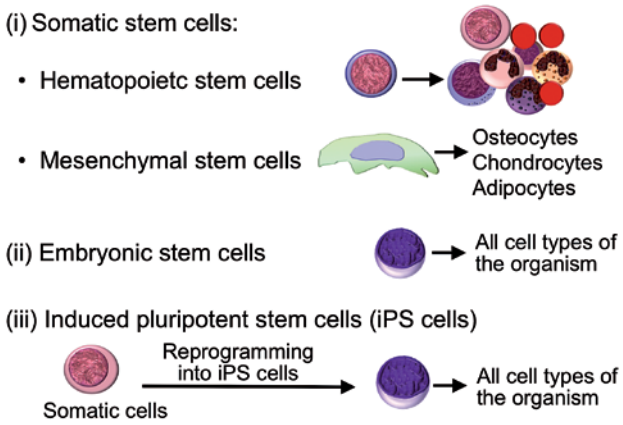

Fig. 1: Schematic presentation of different types of stem cells used in the laboratory.

Epigenetic Definition of Cells in Culture – a Quality Check

Quality control of cell preparations is important – particularly for cells to be used in clinical applications and regenerative medicine. To this end, we designed new assays based on epigenetic modifications (Lenz et al., 2015; de Almeida et. al., 2016). The genetic information of our DNA is not only encoded by the sequence of the four bases, but also in epigenetic modifications that govern activity of genomic regions. There are different types of epigenetic modifications – for example DNA can be methylated in the context of cytosine-guanine dinucleotides (CpG sites). These DNA methylation (DNAm) patterns are modified in the course of development, aging and disease. Deep sequencing and microarray technology facilitate genome wide analysis of DNAm profiles to identify cell type specific epigenetic characteristics. A large set of genome wide DNAm profiles of iPS cells, ES cells and various more differentiated cells has been used to identify a simple epigenetic signature that is indicative for pluripotent differentiation potential (Fig. 2). This Epi-Pluri-Score is based on DNAm levels at only two CpG sites (associated with the genes *ANKRD46* and *C14orf155*) and provides a cost-effective and reliable method for quality control of iPS cells and ES cells (Lenz et al., 2015).

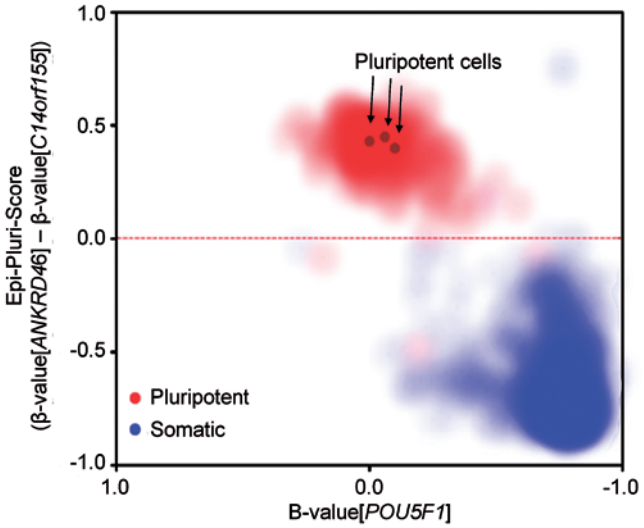

Fig. 2: Quality control of three iPS cell lines with Epi-Pluri-Score demonstrates association with pluripotent cells. Red cloud: DNA methylation profiles of 264 pluripotent cell samples; blue cloud: DNA methylation profiles of 1,951 non-pluripotent cell samples (Lenz et al., 2015).

StemCellFactory

Cell culture of pluripotent cells is particularly labour intensive. Reprogramming of somatic cells into iPS cells, culture expansion and differentiation towards specific lineages require culture over several months. On the other hand, drug testing in personalized medicine necessitates simultaneous handling of many patient specific iPS cell lines in parallel. To address this challenge the *StemCellFactory* consortium (www.stemcellfactory.de) is currently testing and further developing the prototype of an automatic production facility for patient-specific iPS cells (Fig. 3). The *StemCellFactory* consortium combines leading experts in stem cell research and engineering sciences in North Rhine Westphalia, based in Aachen, Bonn, Münster and Herzogenrath. This platform enables automated generation of iPS cells and their differentiation towards hematopoietic, cardiogenic and neuronal lineages for high throughput drug testing.

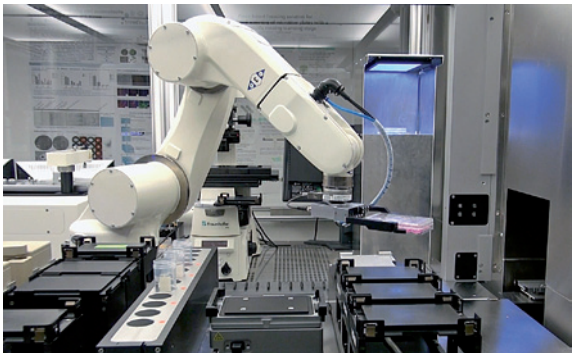

Fig. 3: StemCellFactory, an automatic production facility for patient-specific iPS cells.

Transcription Factor Circuitry of Dendritic Cell Development

Dendritic cells (DC) are professional antigen presenting cells that develop from HSC in bone marrow through successive steps of lineage commitment and differentiation. Multipotent progenitors (MPP) are committed to DC restricted common DC progenitors (CDP), which differentiate into specific DC subsets: classical DC (cDC) and plasmacytoid DC (pDC) (Fig. 4A). To determine epigenetic states and regulatory circuitries during DC differentiation, we measured consecutive changes of genome-wide gene expression, histone modification and transcription factor occupancy during the sequel MPP-CDP-cDC/pDC (Fig. 4B; Lin et al., 2015a).

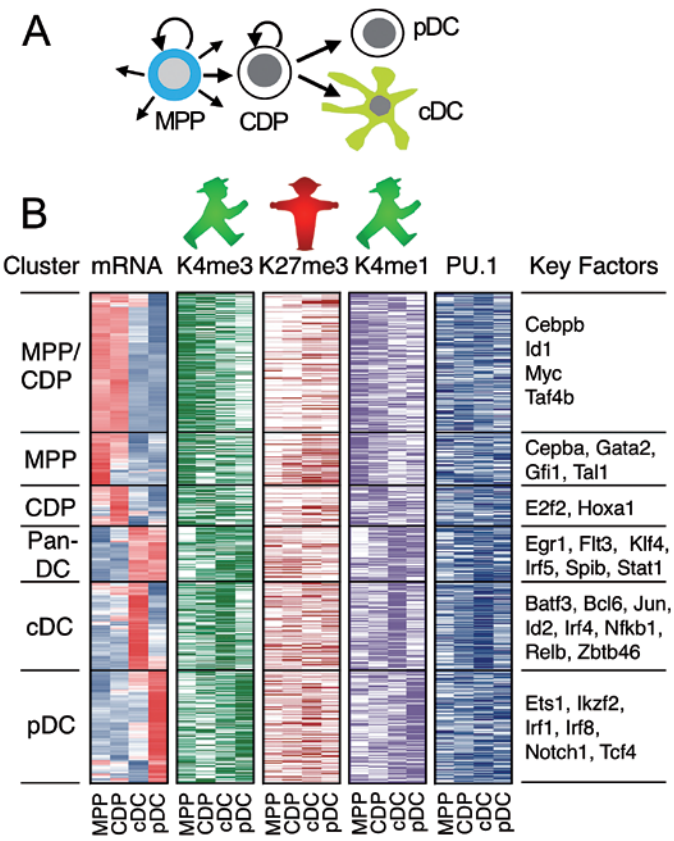

Fig. 4: (A) The sequel MPP-CDP-cDC/pDC of DC development. (B) Changes in gene expression (mRNA) and histone H3 methylation (H3K4me1, H3K4me3 and H3K27me3) and transcription factor PU.1 occupancy during DC development. The H3K4me1 and H3K4me3 marks are associated with gene activation and the H3K27me3 mark is associated with gene silencing.

Information of these different levels of molecular information was subsequently integrated into a computational network to devise a transcription factor circuitry for DC commitment and subset specification (Fig. 5). This circuitry reflects the transcription factor hierarchy that drives the sequel MPP-CDP-cDC/pDC, including feedback loops inferred for individual or multiple factors. These mechanisms stabilize distinct stages of DC development and DC subsets (Lin et al., 2015a).

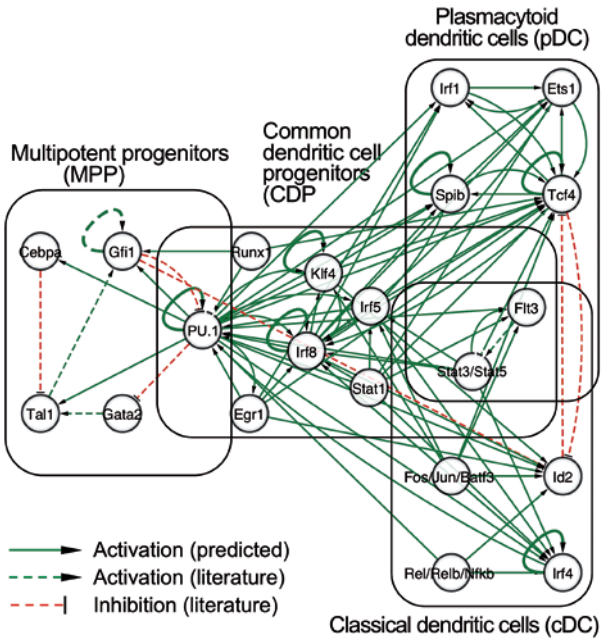

Fig. 5: Network illustration of the transcription factor circuitry that drives DC development from MPP towards CDP and DC subsets (cDC/pDC).

Magnetic Nanoparticles for Bimodal Tracking of Cells by Optical and MR Imaging

Cell-based therapies have high potential for treatment of a wide range of diseases, including cancer, immunological or neurodegenerative disorders. However, frequently

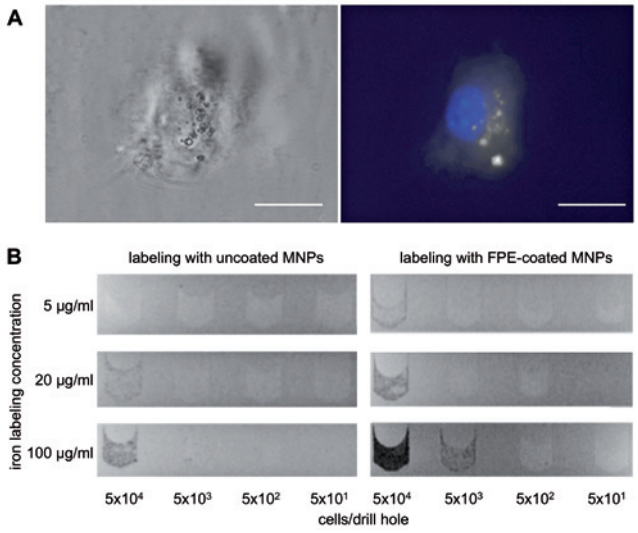

Fig. 6: Optical imaging and MRI of DC labelled with fluorochrome-tagged polyelectrolyte (FPE)-coated MNP. (A) Phase contrast and fluorescence images of DC labelled with FPE-coated MNP (left and right, respectively). Scale bars, 10 µm. (B) T2-weighted multiple gradient echo images in coronal direction of agarose phantoms filled with DC labelled with uncoated MNP (left) and FPE-coated MNP (right). Note, that PE-coating improved MRI contrast properties of MNP.*

translation to clinical applications is hampered due to the lack of adequate tools for cell tracing after transplantation. It is possible to label cells with magnetic iron-oxide nanoparticles (MNP) and then monitor their distribution and functional integration upon transplantation *in vivo* by magnetic resonance imaging (MRI).

For effective labelling of hematopoietic stem and progenitor cells or DC, the magnetic iron-oxide nanoparticles were further optimized by using layer-by-layer assembly of polyelectrolytes (PE) (Schwarz et al., Nanomedicine, 2012; Celikkin et al., 2015; in collaboration with W. Richtering and J. E. Wong, Institute of Physical Chemistry, RWTH Aachen University, Aachen, Germany and M. Hoehn, In vivo NMR Research Group, MPI for Metabolism Research, Cologne, Germany). To further improve on cellular labelling and tracking we currently employ fluorescently tagged PE to add optical imaging modalities onto MRI contrast agents (Jakubcová et al.; manuscript in preparation; Fig. 6). This will also enable histological analysis of cells upon functional integration in tissues.

GAR22β is Important for Cytoskeleton Dynamics and Cell Motility

Spatio-temporal cytoskeleton dynamics is pivotal for many biological functions, including cell adhesion and migration. Gas2-related protein on chromosome 22 (GAR22β) is a gene induced by thyroid hormone in human red blood cells (Gamper et al., Exp. Hematol., 2009). We have generated GAR22β knockout mice (GAR22β-/-) and found that cells lacking GAR22β moved faster than cells of wild type controls. Loss of GAR22β increased the turnover of focal adhesions (FA) (Gamper et al., 2015).

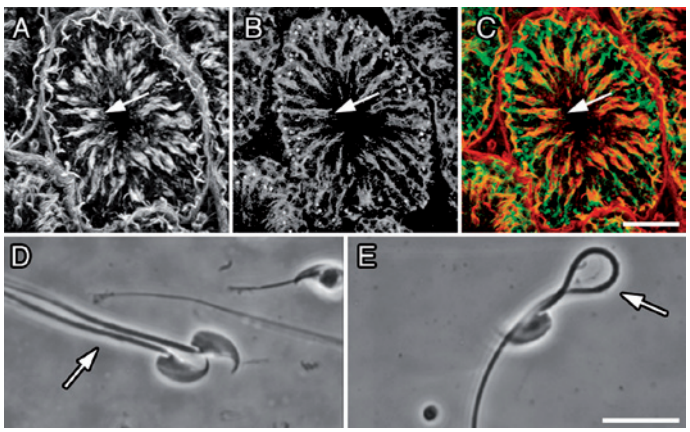

Fig. 7: (A-C) GAR22β co-localises with actin in seminiferous tubules. Cryosections of wild type testes were stained with fluorescent phalloidin and GAR22β antibodies and analysed by confocal microscopy. Actin distribution throughout the seminiferous tubuli and its co-localisation with GAR22β (arrows) is indicated. In the merged image, actin is shown in red, GAR22β in green. Scale bar: 50 µm. (D-E) Deletion of GAR22β gene alters spermatozoa morphology. Wild type spermatozoa (D) were characterised by a relatively straight shape (arrow), whereas GAR22β-/- spermatozoa (E) showed a prominent 180° bend at approximately the end of the mid piece (arrow). Scale bar: 10 µm.

In contrast over-expression of GAR22β (or its re-expression in GAR22β-/- cells) reduced cell motility and FA turnover. Mechanistically, GAR22β-actin interaction was stronger than GAR22β-microtubules interaction resulting in GAR22β localisation and dynamics that mirrored those of the actin cytoskeleton. Furthermore, a proteomic approach demonstrated that GAR22β interacts with the regulator of microtubule dynamics end-binding protein 1 (EB1). This GAR22β-EB1 interaction was required for the ability of GAR22β to modulate cell motility. Notably, GAR22β is highly expressed in mouse testes where it co-localises with actin (Fig. 7) and its absence resulted in reduced spermatozoa generation, lower actin levels in testes and impaired spermatozoa motility (Gamper et al., 2015). These findings identify GAR22β as a novel regulator of cell adhesion and migration that impacts on spermatogenesis.

Computational Biology of Cell Differentiation, Diseases and Gene Regulation

Epigenetic mechanisms, such as DNA methylation and histone modification, remodel chromatin architecture on a genome-wide scale. To better understand these processes, we develop innovative bioinformatics approaches for the integrated analysis of genome-wide gene expression data, histone modifications (chromatin immunoprecipitation followed by next generation sequencing, ChIP-Seq; Fig. 8), open chromatin assay (DNase-Seq) and DNA sequencing data.

For example, bioinformatics was applied for integrating the epigenetic and regulatory changes occuring during DC development based on gene expression, ChIP-Seq and DNA sequencing data. In short, we first detected cell specific PU.1 peaks close to genes with cell specific expression by ChIP-seq. Then, we analyzed the sequence around these PU.1 peaks for detection of transcription factors potentially co-binding with PU.1 in a cell specific manner. Third, we devised a PU.1 centred regulatory network based on PU.1 occupancy and gene expression (Fig. 5). This approach identified targets of known and novel transcription factors that impact on DC development (Lin et al., 2015a).

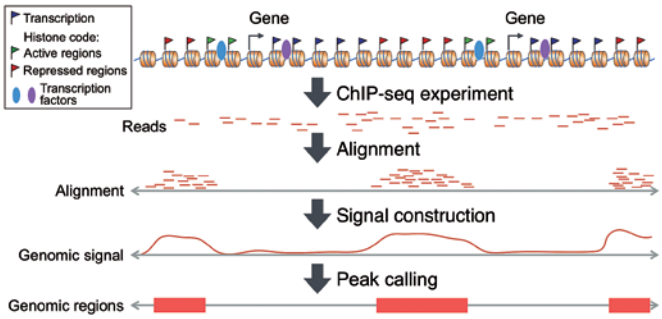

Fig. 8: Work flow of analysing ChIP-seq data and identifying peaks from genome-wide next generation sequencing data.

Another study focused on the association between DNA methylation changes (MethylCap-Seq), histone modification (ChIP-Seq), gene expression (RNA-Seq) and nuclear lamina contacts during replicative senescence of fibroblasts and mesenchymal stem cells (Hänzelmann et al., 2015). This analysis demonstrated that genomic regions that lose methylation during culture expansion are closely associated with the nuclear lamina. In contrast, genomic regions that become more methylated in senescence are close to genes that are also differentially expressed during senescence.

In collaboration with the Department of Hematology, Oncology and Stem Cell Transplantation, RWTH Aachen University Hospital, Aachen, Germany we investigated epigenetic and regulatory mechanisms underlying regulation of the tumor suppressor gene MTSS1 in chronic myeloid leukemia (Schemionek et al., 2015).

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[2] Verfahren zur Verbesserung der Diagnose von Telomererkrankungen (PRDM8); 2015; DE 10 2015 121 969.7 (Wagner W, Weidner C, Beier F, Brümmendorf TH).

[3] Epigenetic Classification of Human Mesenchymal Stromal Cells; 2016; EP16152198.4 (Wagner W, de Almeida DC).

Team

Lab retreat at European Parliament (Brussels), Belgium