LABORATORY OF

HAEMATOONCOLOGY

Haematopoietic stem cell, self-renewal, myeloid differentiation, leukaemia, inflammation

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In our research group we investigate the regulation of haematopoietic stem cell (HSC) maintenance and fate by transcription factors and their target genes, determine whether these elements are altered in human leukaemias (in particular acute myeloid leukaemia, AML), and elucidate their contribution to leukaemogenesis. In addition, we investigate how cell extrinsic factors regulate HSC self-renewal and how they impact myeloid commitment. Our three main research lines are:

1. To determine the function of C/EBPα target genes in normal and malignant haematopoiesis;
2. To define the role of the β-catenin-TCF/LEF transcription-mediating complex in normal and aberrant haematopoiesis;
3. To assess the effects of chronic inflammation in HSC fitness and leukaemogenesis.

To reach these goals we employ murine and human primary cells, as well as murine models. We perform a variety of *in vitro* assays to assess cell proliferation, apoptosis, colony-forming potential, replating ability, differentiation, and migration. Further, we carry out murine bone marrow cell transplantation assays, challenge mice with infectious agents, and perform HSC mobilization assays *in vivo*. Using primary cells from patients suffering from AML, we generate PDX models. To get novel insights into the molecular mechanism of stem cell regulation and transformation, we employ molecular biology approaches including CRISPR technology, RNAseq, and ChIP-seq/qPCR.

Together, we aim at understanding the mechanisms that control HSC maintenance and fate, and determine cell intrinsic and extrinsic factors that contribute to the development of leukaemia. Ultimately, our work will contribute to establishing the knowledge for the development of better AML therapies.

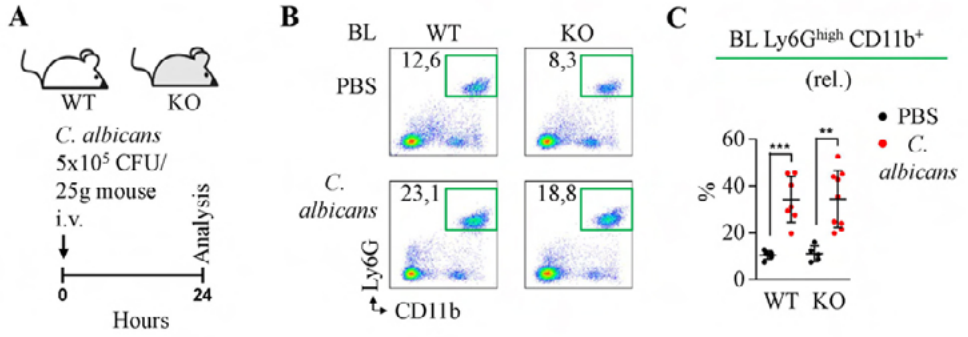

Figure 1. Candida albicans infection in WT and Cebpg KO mice. (A) Graphical representation of the infection protocol. (B) Representative flow cytometry plots from WT and Cebpg KO blood from mice treated with PBS or C. albicans. Green boxes indicate percentage of CD11b+Ly6G+ neutrophils. (C) Quantification of panel B.

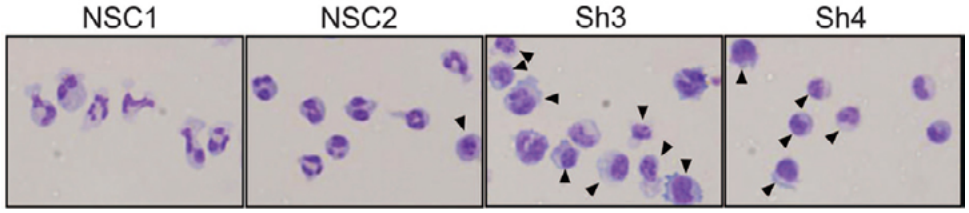

Figure 2. Evi2b knockdown blocks granulocytic differentiation of 32D/G-CSF-R cells. 32D/G-CSF-R cells were infected with shRNAs targeting and downregulating expression of the transmembrane protein Evi2b (sh3 and sh4) or non silencing control shRNA (NSC1 and NSC2). Cell morphological analysis was assessed on May-Grunwald Giemsa stained cytospins.

Selected publications:

1. Zjablovskaja P, Kardosova M, Danek P, Angelisova P, Benoukraf T, Wurm AA, Kalina T, Sian S, Balastik M, Delwel R, Brdicka T, Tenen DG, Behre G, Fiore F, Malissen B, Horejsi V, Alberich-Jorda M* *(2017)* EVI2B is a C/EBPα target gene required for granulocytic differentiation and functionality of hematopoietic progenitors. ***Cell Death Differ*, 24**:705-716.
2. Wurm AA, Zjablovskaja P, Kardosova M, Gerloff D, Bräuer-Hartmann D, Katzerke C, Hartmann JU, Benoukraf T, Fricke S, Hilger N, Müller AM, Bill M, Schwind S, Tenen DG, Niederwieser D, Alberich-Jorda M, Behre G* (2017) Disruption of the C/EBPα-miR-182 balance impairs granulocytic differentiation. ***Nat Commun*, 8**:46.
3. Gonzalez D, Luyten A, Bartholdy B, Zhou Q, Kardosova M, Ebralidze A, Swanson KD, Radomska H, Zhang P, Kobayashi SS, Welner RS, Levantini E, Steidl U, Chong G, Collombet S, Choi MH, Friedman AD, Scott LM, Alberich-Jorda M*, Tenen DG* (2017) ZNF143 is an important regulator of the myeloid transcription factor C/EBPα. ***J Biol Chem*, 292**:18924-18936.
4. Zjablovskaja P, Danek P, Kardosova M, Alberich-Jorda M* (2018) Proliferation and differentiation of murine myeloid precursor 32D/G-CSF-R cells. ***J Vis Exp*, (132).**
5. Kardosova M, Zjablovskaja P, Danek P, Angelisova P, Lobo de Figueiredo-Pontes L, Welner RS, Brdicka T, Lee S, Tenen DG, Alberich-Jorda M* (2018): C/EBPγ is dispensable for steady-state and emergency granulopoiesis. ***Haematologica*, 103**: e331-e335 .

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