Project abstract

Name of DKFZ research division/group:	***Inflammatory Stress in Stem Cells (A011)***
Contact person:	***Dr. Marieke Essers, m.essers@dkfz.de 06221-423919***
Group homepage: Please visit our website for further information on our research and recent publications.	***https://www.dkfz.de/en/aktivierung-haematopoetische-stammzellen/index.php https://www.hi-stem.de/research-essers***

PROJECT PROPOSAL

Inflammation is a key component in a complex biological response of the body to harmful stimuli. In the context of the bone marrow, inflammation is an overarching process central to most if not all forms of stress, challenges and disease settings including leukemia and immunodeficiencies. In recent years, we have used the power of single-cell sequencing to investigate the heterogeneity and dynamics of the response of the whole HSPC and stromal bone marrow niche after treatment with the pro-inflammatory cytokine IFNa. We have discovered multiple time-dependent gene responses in different cell clusters within the HSPCs, with the strongest response in HSCs (Bouman et al, 2023). In addition, we have identified and described a novel bone-lining MSC sub-population, which unlike its stromal counterpart responded directly and dynamically to IFNα stimulation (iMSCs) (Sood et al, under review). Furthermore, we have described heterogeneity in IFN signaling in the hematopoietic system, which is already established early during hematopoietic development and stably inherited from stem cells to progeny (Werner et al, submitted).

Myeloproliferative neoplasms (MPN) are characterized by neoplastic proliferation of one or several hematopoietic lineages. The step-wise and variable progression from a usually indolent to an advanced or aggressive phenotype is linked to distinct mutations being more important for the primary phenotype, e.g. JAK2 V617F, while additional somatic mutations account for an aggressive phenotype and poor prognosis. In addition, recent experimental and clinical data has indicated the significant importance of inflammation related to the clinical characteristics and efficacy of treatment towards cytopenias, organ dysfunction and clinical symptoms in MPNs. We hypothesize that inflammation plays a pivotal role in clonal selection and therapy resistance during clonal evolution in patients with MPN. In the coming years we will focus on investigating the impact of IFN signaling heterogeneity and inflammation in the bone marrow on disease development and therapy response in MPN models. In collaboration with our clinical partners in Mannheim we will in addition investigate the impact of inflammation and IFN signaling heterogeneity in MPN patient samples. The combination of research models and patient material to study an important topic in hematological malignancies will make this an interesting topic for a clinician scientist project.