HUMAN CLONAL HEMATOPOIESIS AND ITS EFFECT ON HUMAN TUMOR GROWTH IN HUMANIZED MICE

HUMANE KLONALE HÄMATOPOESE UND IHRE AUSWIRKUNG AUF DAS TUMOR-WACHSTUM IN HUMANISIERTEN MÄUSEN

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SCHLAGWÖRTER – KLONALE HÄMATOPOESE, SOLIDE TUMORE, GENOMEDITIERUNG, HUMANE MAUSMODELLE, ENTZÜNDUNG

SUMMARY

Clonal hematopoiesis of indeterminate potential (CHIP) is provisionally defined as the presence of an expanded somatic blood cell clone carrying a mutation in genes that are drivers of hematologic malignancy (including *DNMT3A, TET2, ASXL1, TP53, PPM1D, JAK2 and SF3B1*) at a variant allele frequency of at least 2% in the absence of other hematologic abnormalities. CHIP is more frequent in aged individuals and associates with increased risk of cardiovascular disease and of hematologic cancer development. Recently, CHIP was detected in 25% of non-hematological cancer patients where it associates with shorter survival due to enhanced cancer progression. However, whether CHIP carrying cells contribute directly to tumor progression and what is the potential mechanism mediating this cross talk is unknown. In this project, we propose to dissect the contribution of hematopoietic cells carrying CHIP mutations to cancer progression, by combining the expertise of the Manz and Corn labs. Our goal is to establish non-hematological tumors (breast and melanoma) in humanized mouse models (MISTRG) carrying human hematopoietic stem cells genomically edited with CHIP mutations. Using this novel model, we will dissect whether CHIP carrying hematopoietic cells can accelerate tumor progression. We further aim to resolve the potential mechanism underlying CHIP-dependent tumor progression by testing the hypothesis that it is driven by the pro-inflammatory profile recently associated to *DNMT3A* and *TET2* mutant myeloid cells found in CHIP patients. Finally, we will test if therapeutic targeting of these pro-inflammatory pathways can effectively prevent the potential cross talk between CHIP mutant myeloid and non-hematological cancer cells, thus preventing CHIP-mediated tumor progression. In the long term, the data generated in this project might have a direct impact of the clinical management of non-hematological cancers patients, further opening new avenues for therapeutic intervention.