MULTIFUNCTIONAL ROLE OF THE PAX5-JAK2 ONCOPROTEIN IN B CELL LEUKEMIA

B-cell acute lymphoblastic leukemia (B-ALL) is the most common tumor in children and also occurs in adolescents and adults. Despite good prognosis in pediatric patient outcome, at least 15% of patients will suffer from relapse. Hence, a deep understanding of the molecular mechanisms underlying the onset and progression of this disease is needed to improve current therapeutic approaches. During the last decade, world-wide genome sequencing effort have identified mutations in many genes that play an important role in the development of B cell leukemia. One of these genes codes for the transcription factor PAX5 that is essential for the generation of the immune cell type referred to as B cell, whose normal task is to generate specific antibodies to protect us from acute infections. In one third of all B-ALL cases, one of the two *PAX5* gene copies is lost, thus implicating PAX5 as a tumor suppressor in leukemia development. Another characteristic feature of B-ALL is the frequent occurrence of chromosomal translocations, which lead to gene fusions that code for novel chimeric transcription factors. A subset of B-ALL with poor prognosis is characterized by the *PAX5-JAK2* translocation that generates a fusion transcription factor consisting of the DNA-binding domain of PAX5 linked to the catalytically active domain of the JAK2 kinase. JAK2 can activate gene expression by phosphorylating members of the STAT transcription factor family or the nuclear protein histone H3, thus resulting in the local generation of active chromatin. The aim of this project is to elucidate how the PAX5-JAK2 protein controls leukemia development and/or maintenance. For this purpose, we have recently generated a mouse model expressing the PAX5-JAK2 protein from the endogenous *Pax5* gene. The PAX5-JAK2-expressing mice rapidly develop an aggressive B-ALL tumor, indicating that they mimic the role of PAX5-JAK2 in human leukemia. We will next investigate to what degree PAX5-JAK2 contributes to B-ALL development through activation of JAK-STAT signaling and/or activation of local chromatin at its target genes. We will identify and characterize PAX5-JAK2-regulated target genes by genome-wide gene expression, PAX5-JAK2 binding and chromatin profiling analyses of the mouse B-ALL tumor cells. CRISPR-Cas9-mediated mutagenesis will next be used to define the functional relevance of the top-ranked target genes for leukemia development. By analyzing the gene expression profile of human PAX5-JAK2^{+} B-ALLs, we will determine the degree to which the critical PAX5-JAK2 target genes identified in the mouse tumor model are also deregulated in the human disease. Collectively, these data will provide novel important insight into the molecular functions, by which the oncoprotein PAX5-JAK2 induces B cell leukemia, and may suggest improved therapeutic approaches for the treatment of this B-ALL tumor.