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Acute Lymphoblastic Leukemia Patients Carrying the t(4;11) Translocation: Pathophysiology, Epigenetic Mechanisms and Novel Treatment Strategies

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Chromosomal translocations affecting the human MLL gene are associated with high-risk Acute Leukemias with poor outcome. The most frequent chromosomal translocation is the t(4;11)(q21;q23) rearrangement leading to the creation of the two fusion gene MLL• AF4 and AF4• MLL, respectively. Both reciprocal fusion genes encode large fusion proteins that trigger the malignant transformation of hematopoietic precursor cells. In infants and early childhood Acute Lymphoblastic Leukemia (ALL) there is a high prevalence of up to 70% for carrying this specific translocation of the MLL gene. Moreover, MLL translocations can be exogeneously induced by treatment with Epipodophylotoxins (Topo II inhibitors), a situation that is frequently observed in therapy-induced leukemias.

The pathological disease mechanism provided by these fusion protein has been investigated. In vitro transfection experiments provided insights into the pathological disease mechanism(s) exerted by the two reciprocal MLL fusion proteins. Both fusion proteins change the biological properties of transfected cells, like e.g. activation of senescence, block of apoptosis, and growth transforming properties. Data obtained by biochemical experiments in combination with gene expression profiling experiments revealed functions of both MLL fusion proteins for epigenetic reprogramming. To this end, MLL-mediated leukemia is presumably based on a slow conversion of a given genetic program into the program of a cancer cell.

Based on our experimental data and the molecular functions(s) provided by these two MLL fusion proteins, we currently attempt to develop novel treatment strategies for t(4;11) leukemia patients by using a specific target protein necessarily involved in the oncogenic activation pathway.

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