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ICGEB International SEMINAR PROGRAMME 2017

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The pathogenesis of chronic lymphocytic leukemia (CLL) is determined by a complex profile of genetic lesions, and by a characteristic dependence on extracellular stimuli coming from the microenvironment for survival and proliferation. Among others, NOTCH1 signaling is halfway between the genetic and the microenvironment-dependent pathogenic mechanisms. In fact, NOTCH1 is one of the most recurrently mutated genes in CLL at diagnosis and is associated with aggressive/progressive disease, poorly responsive to therapies. Mutations cluster in exon 34 of the gene and are represented most frequently by a frameshift deletion resulting in protein truncation and PEST domain loss. It was demonstrated that mutations impact on protein stability and prolong signaling, as the PEST domain is critical for protein degradation upon phosphorylation and ubiquitination of specific residues in this region. For this reason, they are considered stabilizing, rather than activating mutations, as the resulting protein is predicted to remain transcriptionally active in the nucleus for longer time. However, microenvironmental stimuli are critical to activate the pathway, as binding to the NOTCH1 ligands, belonging to the Jagged or the DLL families, and expressed by the neighboring stromal cells, is required to trigger signaling even in the presence of mutations. Activated NOTCH1 contributes to remodeling of gene expression of leukemic cells through direct (transcription-mediated) or indirect (epigenetic) mechanisms. Functionally, we found that mutated NOTCH1 promotes growth and migration of leukemic cells by switching off expression of the tumor suppressor gene DUSP22 through promoter methylation. In particular, mutated cells exhibit increased chemotactic responses toward CCL19, an important chemokine regulating trafficking of CLL cells to lymphoid niches. The relevance for the disease is that NOTCH1 mutations may contribute to an unfavorable prognosis by promoting the migration of leukemic cells to the lymphoid organs, where the protective microenvironment provides stimulatory signals favoring a more aggressive behavior.

"Tumor-host interactions in chronic lymphocytic leukemia: moving up a NOTCH?"

Host: D. Efremov

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