Universität Basel

Research Project

# Characterization of the Ewing's sarcoma protein's involvement in the maintenance of genomic stability

## Third-party funded project

**Project title** Characterization of the Ewing's sarcoma protein's involvement in the maintenance of genomic stability
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**Organisation / Research unit**
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Considering that a variety of genetic abnormalities typically occur in a given tumor, it is striking that some cancers exhibit highly characteristic genomic changes. They consist in chromosome fusions that occur at very specific chromosomal locations, one of which is always the locus of a FET protein. FET stands for the family of fused in sarcoma (FUS), Ewing sarcoma (EWS) and TATA box binding protein associated factor 15 (TAF15) proteins. The most common fusion proteins are EWS-FLI1 in Ewing sarcoma, FUS-CREB3L1 in low-grade fibromyxoid sarcoma and TAF15-NR4A3 in extraskeletal myxoid chondrosarcoma. Although normal FET proteins bind RNA, this activity is absent in the fusion proteins. Whether this loss is relevant for the development of the tumor is not known. In a previous study we mapped the RNA targets of EWS. To our surprise, we found that EWS binds RNAs that come from genomic loci that are prone to 'genomic instability'. We further obtained evidence that EWS helps the transcription of DNA into messenger RNAs, facilitating the progression of the RNA polymerization enzyme (RNAPII) through loci that are prone to form stable structures that impede transcription. In this project we would like to characterize the relationship between EWS and RNAPII-dependent transcription, and the consequences at the cellular level of the long-term reduction in EWS expression. We will employ cells and cell lines in which we can reduce EWS expression in a controlled manner. We will determine the rate at which the RNA polymerase II elongates transcripts genome-wide and the frequency with which lesions in the DNA that are known as DNA double-strand breaks occur when EWS is limiting. Furthermore, we will investigate the long-term consequences of reduced EWS expression on cell morphology, viability and functionality. Our study could thus contribute to an improved understanding of the pathogenic mechanisms of Ewing's sarcoma.

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