Universität Basel

Research Project

The clonal evolution of osteosarcoma in the course of time

Third-party funded project

Project title The clonal evolution of osteosarcoma in the course of time
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Osteosarcomas are primary malignant tumours of bone generally arising in children and adolescents with complex karyotypes and abundant structural and numerical aberrations. Long-term survival can currently be achieved in only 60% of patients despite of intense multimodal treatment protocols; a disappointing figure stagnating since more than three decades. A partial explanation for treatment failure might lie in the number and kind of mutations in osteosarcoma genomes that vary significantly between individual tumours and of which only few are targetable. Despite the genetic complexity, we have recently shown that >90% of osteosarcomas display mutation patterns similar to those seen in BRCA deficient breast and ovarian cancers (so-called BRCAness) rendering them likely susceptible to PARP inhibitor treatment.Since our findings captured BRCAness only in pre-therapeutic biopsies so far, the proposed project aims to follow its evolution over time using sequentially obtained material from 16 patients, including samples from the initial biopsy, the resection specimen as well as from recurrent disease. We shall integrate exome, genome and RNA sequencing supplemented by copy number and methylation analyses to explore the clonal diversity and hierarchy, thus building an evolutionary history of each tumour. Additionally, we shall assess the degree of BRCAness and therefore the likelihood of specific tumour cell populations to respond to PARP inhibition at different stages of the disease. An additional cohort of >220 osteosarcoma samples, all derived from an international osteosarcoma treatment trial (EURAMOS1), and with complete clinico-pathological data, is available for validation of the main findings from cohort 1 and further (epi-)genetic studies. Together with collaborators from other countries that have also collected samples of EURAMOS1 patients, we aim to assemble the yet largest series of osteosarcomas and attempt to correlate (epi-)genetic findings with clinico-pathological data. Specifically, we shall validate the prevalence of BRCAness and search for complementary / alternative vulnerabilites.We believe that only the complete integration of genomic and epigenomic data may identify subtle functional signatures of mutational processes with prognostic or even therapeutic impact. Hence the proposed project will provide a deeper understanding of osteosarcoma evolution in a time-dependent manner. Moreover, we will determine whether a BRCA-like phenotype is required for recurrence and/or metastatic progression and whether new signatures can be identified by integrating epigenetic data in a large cohort of clinically well characterized osteosarcomas.

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