Internship Offer (M2) at Institut Curie

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Investigating and targeting intratumorheterogeneity in undifferentiated pleomorphic sarcomas

Project description

Sarcomas consist of a group of rare tumors of mesenchymal origin, characterized by their major clinical, pathological and biological heterogeneity. Among them, undifferentiated pleomorphic sarcoma (UPS) is one of the most frequent subtypes in adults. Primary UPS develop mainly from the limbs or parietal wall, and are frequently associated with incurable metastatic evolution. UPS belong to the group of sarcoma with complex genomics, characterized by multiple copy number alterations, genome instability, and frequent mutations in tumor suppressor genes. From a pathological point of view, UPS are composed of high-grade undifferentiated cells with marked pleomorphism and microscopic heterogeneity, suggesting the coexistence of multiple tumor cell subpopulations in these tumors. However, the precise identification of these tumor cell populations, as well as their role in tumor oncogenesis and interaction with the tumor microenvironment has never been documented. The SingleSARC project aims at investigating UPS heterogeneity and plasticity, identifying tumor cell populations associated to relapse and metastases and design new therapeutic strategies in this devastating disease.

Methodology : This project will primarily consist in perfoming the bioinformatics analyses of human and model UPS samples, to generate hypotheses that could be validated in vitro and in vivo. It will focus on the analyses of multiple primary UPS tumors coming from patients operated on in Institut Curie over the last two years, as well as already established patient-derived xenografts and UPS cell lines. Single-cell transcriptomic (scRNAseq) profiling as well as bulk genomic (Whole Exome Sequencing) and transcriptomic (RNAseq) sequencing data have already been generated and are ready for analysis.

The objectives of the project are :
- To characterize UPS cell populations and tumor microenvironment
- To identify the molecular mechanism driving UPS cell heterogeneity and understand the role of this heterogeneity in UPS oncogenesis

The candidate will be co-supervised by Sarah Watson, clinician scientist in Institut Curie, Head of the Sarcoma Clinical Group and expert in sarcoma genetics, and a member of Institut Curie Bioinformatic Unit. The project will primarily focus on performing and analysing scRNAseq data using various bioinformatics approaches to decipher tumor heterogeneity (Seurat, SingleR, Velocyto, Cell-PhoneDB, InferCNV), and integrate these data with bulk transcriptomic and genomic profiles. If the candidate is motivated for performing wet-lab experiments, the results will be confirmed in available cell lines and mice models. The candidate will work in close interaction with all the biologists and bioscientists of the team and of Institut Curie Bioinformatic Unit as well as with clinicians involved in sarcoma patients care in the hospital group.

Project references

1. COMPREHENSIVE AND INTEGRATED GENOMIC CHARACTERIZATION OF ADULT SOFT TISSUE SARCOMAS ; TCGA, Cell 2017

2. Biology and Management of Undifferentiated Pleomorphic Sarcoma, Myxofibrosarcoma, and Malignant Peripheral Nerve Sheath Tumors : State of the Art and Perspectives, Widemann, Journal of Clinical Oncology 2018

3. High throughput profiling of undifferentiated pleomorphic sarcomas identifies two main subgroups with distinct immune profile, clinical outcome and sensitivity to targeted therapies,Toulmonde, EBio Medicine 2021