PROJECT 2

DoS: Giovanni Tonon

Title: Dissolving chromatin scars to restore cancer sensitivity to therapy

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:
https://research.hsr.it/en/divisions/experimental-oncology/functional-genomics-of-cancer/giovanni-tonon.html;
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Project description

Understanding, and targeting, cancer resistance remain the most important challenge faced by oncologists and cancer scientists [1]. While targeted and immune therapies have entered the clinical arena, providing important inroads towards more effective treatments for patients, the baseline treatment for many cancers remains chemotherapy[2]. As for the much-sought after identification of the mechanism underlying resistance to cancer treatment, genomic analyses have revealed how resistance to targeted and immune therapies oftentimes stems from the selection of subclones, endowed with specific genetic lesions which allow cancer cells to withstand treatment. This knowledge is imperative, since it provides key clues towards the design of ad-hoc strategies to screen and identify novel drugs effective in refractory patients, as it has been demonstrated several times for these specific treatments. Conversely, despite enormous efforts by the community, the analysis of samples obtained from patients developing resistance to chemotherapy have failed so far to elucidate the underlying strategy deployed by cancer cells to overcome chemotherapy [3]. No genetic clones seem to emerge in the resistant population [4,5] and only a handful of somatic mutations have been proposed as potential culprits, with no pervasive genetic mechanism identified[3].

We posit that resistance to chemotherapy stems from epigenetic modifications, triggered by chemotherapy, which stably imprint the cancer epigenome and drive resistance. In fact, the pivotal role of epigenetic changes in carcinogenesis is increasingly apparent, even in the early stages of tumorigenesis before genetic lesions ensue [6]. Several lines of evidence, from the literature, as well as our own preliminary data, support the notion that epigenetic mechanisms may also underscore cancer resistance to chemotherapeutic drugs.

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Skills to be acquired by the student

This project is rooted in an international grant that engages various groups in Italy, and leading groups in the most prestigious cancer centers in the UK and the USA, with the active engagement of scientists from different venues, from cell biologists and molecular biologists, to mathematicians, engineers and clinicians. The student will be explosed to a a broad range of molecular biology, cell biology, biochemistry and genomics approaches. We will exploit engineered in vitro models, namely labeled and barcoded tumor cells and patient derived organoids, as well as in vivo models.

References

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