PROJECT 1

DoS: Emilie Venereau

Title: Targeting of HMGB1 recycling as an innovative therapeutic strategy to fight cancer

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/genetics-and-cell-biology/units/tissue-regeneration-and-homeostasis.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

State of the art

Tumor microenvironment is a complex and dynamic ecosystem surrounding tumoral cells and composed of numerous cell types, such as blood vessels and immune cells, and non-cellular components of extracellular matrix. Tumor cells control the functions of the cellular and non-cellular components in the microenvironment through complex signaling networks redirecting the non-malignant cells to sustain their own benefit (1). It is essential to deepen our knowledge on the crosstalk between tumor cells and their microenvironment to identify new targets for therapeutic intervention. In our laboratory, we study a protein, called High Mobility Group Box 1 (HMGB1), that appears to be a promising therapeutic target in cancer. HMGB1 is a highly conserved non-histone nuclear protein that binds to DNA and participates in stabilizing nucleosomes, regulating gene expression and DNA repair (2). In the extracellular medium, HMGB1 acts as a danger signal and triggers "sterile" inflammation and tissue regeneration (3-7). In the context of cancer, the role of HMGB1 remains controversial as it can act as a tumor suppressor or an oncogenic factor depending on the context (8, 9). Most importantly, HMGB1 released by dying tumor cells contributes to the activation of the immune response against malignant cells (10, 11).

Scientific Objectives

The fate of HMGB1 after its release in the tumor microenvironment remains completely unknown. We recently uncovered the swapping and recycling of HMGB1 protein between tumor cells and their microenvironment. The objective of the project is to investigate whether this protein-saving process contributes to tumor progression, by favoring the escape from the immune system, in a mouse model of lung cancer. To address this issue, we will combine the use of novel tools generated in the laboratory (e.g. fluorescent recombinant proteins, transgenic mice) with cutting edge imaging procedures such as Image Stream, the first commercially available imaging flow cytometer combining the advantages of flow cytometry with those of microscopy analysis. We generated designer HMGB1 proteins as potential drugs to unleash the immune response against the tumor and the second objective of the project is to conduct a preclinical evaluation of these novel molecules to assess their therapeutic properties on tumor progression in a mouse model of lung cancer.

Impact of the expected results in the field of research

Our project will bring a quantum leap in the knowledge of HMGB1 contribution to cancer progression, by delivering a novel paradigm by which HMGB1 can be recycled in the tumor microenvironment to support tumor progression. These findings might pave the way for the targeting of HMGB1 recycling as an innovative therapeutic strategy for patients affected by lung cancer and harbor the potential to be extended to a variety of cancer types in the future.

Skills to be acquired by the student (*Number of characters*, *including spaces*: max 600):

- Technical skills: cell culture, molecular biology, imaging, flow cytometry, histology, mouse model of cancer and transgenic mice.
- IT skills: Microsoft Office, GraphPad Prism software, online resources and tools (NCBI), Flow Cytometry Analysis software, ImageJ, Photoshop, Inkscape software.

- Communication skills: oral/poster presentations (lab meetings, internal seminars, national and international conferences), article writing (research articles and reviews).

References (max. 15)

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