PROJECT 1

DoS: Riccardo Vago

Title: Analysis of extracellular vesicle-carried factors leading to cancer occurrence and progression

Curriculum: Basic and Applied Immunology and Oncology

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

Tumors depend on a crosstalk with the surroundings to guarantee their survival (angiogenesis, immune escape), to support phenotypic changes (epithelial-to-mesenchymal transition) required to leave the primary tumor mass and to prepare the bone marrow and pre-metastatic organs allowing migrating tumor cells to settle and grow. Extracellular vesicles (EVs) are emerging as important vehicles for tumor-derived factors to sustain tumor development, prepare pre-metastatic sites and reduce immune surveillance (1,2).
The proposed project envisages the study of the mechanisms that lead to tumor occurrence and progression like stromal reorganization, neo-angiogenesis promotion and cell migration through the analysis of selected bioactive molecules such as enzymes and transcripts carried by cancer EVs. They will be isolated from a plethora of cancer model cell lines (breast, bladder, kidney, lung, etc) resembling different stages, grade and phenotype of the diseases and the content will be analyzed to highlight unique features linked to tumor progression, such as proteins, non-coding RNAs, and metabolites, since preliminary data suggest an involvement of such molecules in tumor development. The EV-mediated transfer of key molecules, their impact on healthy cell physiology and their role in malignant transformation will be studied. In particular, the evaluation of a subgroup of lncRNA including UCA1, H19 and MALAT1 will be performed in terms of regulation of cellular processes leading to EMT transition, increased proliferation, migration and invasion and apoptosis escape, as well as drug resistance in receiving cells. A thorough dissection of the molecular and cellular pathways emerged as involved in these processes will be pursued, seeking possible therapeutic targets. The lncRNA-miRNA-mRNA axis will be investigated not only in the tumor cells of origin, but also in those that received the EVs undergoing malignant transformation. These findings will be compared with databases such as The Cancer Genome Atlas, which includes genomic, epigenomic, transcriptomic, and proteomic data derived from cancer patients. The dual role of EVs as cancer effectors and potential biomarkers to detect and monitor tumor development will be assessed. In addition, the possibility to exploit EVs as to convey therapeutic molecules will be explored.

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

The student will use the most common molecular, cell biology and biochemistry techniques. He/she will acquire skills in isolating extracellular vesicles; in analyzing vesicular content; in defining the effect of the delivery of specific cargoes to recipient cells and in validating the results obtained in vitro by comparing with databases.

References (max. 15)

(1) Peinado *et al.* (2012) *Nature Med.* **18,** 883–891
(2) Hoshino et al. (2015) Nature 19;527(7578):329-35