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Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
Consiglio Nazionale delle Ricerche

Titolo del Progetto: The new FKBP51s splice isoform in alternative macrophage polarization: multidimensional profiling of Tumor-associated macrophages and insights into extracellular vesicles as additional players in tumor progression

Codice Progetto: 20222N3X8L

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Abstract:

This proposal points to multidimensional profiling of tumor-associated macrophages (TAMs), the major components of non-tumor stromal cells that play an important role in promoting cancerogenesis and tumor progression. Targeting TAMs has recently emerged as a promising strategy for cancer defeat. Current approaches focus on reducing macrophage infiltration in tumor tissues and reprogramming TAMs from the M2 pro-tumoral to the M1 anti-tumoral phenotype to kill cancer cells. However, so far, these approaches have not produced benefits in terms of overall survival improvement. This project stems from the need for a deeper knowledge of TAMs biology and mechanisms, including their communication with surrounding cells, through extracellular vesicles. As alternative macrophage polarization is accompanied by alternative splicing of FKBP5, a gene constitutively expressed in immune cells, the present proposal is based on the central hypothesis that such splice isoform, FKBP51s, controls the signaling pathways of M2 macrophages and influences the cargo of EVs released by these “tumor-friendly” macrophages. Through this mechanism, FKBP51s supports an immune suppressive and pro-angiogenic tumor microenvironment. The project has a short-term goal to provide mechanistic insights into the TAMs biology by investigating the role of FKBP51s in the regulation of the intracellular signaling pathways and the proteome of M2 macrophages and by in-depth studying of M2 derived EVs (MDEVs). The long-term goal of this proposal is to study the MDEV-mediated communication of TAMs with surrounding cells such as endothelial cells that promote angiogenesis and T lymphocytes that become tolerogenic. The project also aims to investigate the efficacy of switching-splice oligonucleotides to target FKBP51s on melanoma organoids and evaluate tumor restraining in combination with immunotherapy. The results of this study will provide a set of information for a better comprehension of TAMs physio-pathology with possible translational applications in the field of cancer treatment and diagnosis.

Finalità:

Aim of the present project is to decipher TAMs language by providing mechanistic insights into the causative role of the alternative splicing of the FKBP5 gene in M2 polarization, and how it influences the proteome and secretome of M2 macrophages. Moreover, we will shed light on the molecular mechanism through which EVs released from TAMs exacerbate angiogenesis and immune tolerance. Results from our proposal will provide in-depth information on TAM biology along with tools for macrophage reprogramming that will impact cancer progression and IT response.

Risultati attesi:

- Dissect the signaling pathways involved in macrophage polarization and uncover the role of alternative splicing of the FKBP5 gene in the switch from M1 to M2 macrophages;
- Characterize M2-Derived extracellular vesicles MDEVs, and identify in their cargo a set of proteins and RNAs possibly regulated by FKBP51s;
- Assess the effect of FKBP51s on M2-macrophages and MDEVs cargo and their consequent effects on angiogenesis and immunoregulation;
- Study of the effect of splice-switching oligonucleotides (SSOs) targeting FKBP51s on melanoma organoids.

Risultati raggiunti: *In progress*

Partenariato:

- Università degli Studi di Napoli Federico II (coordinatore)
- LUM “Giuseppe Degennaro”
- Consiglio Nazionale delle Ricerche (CNR) Istituto per il Sistema Produzione Animale in Ambiente Mediterraneo (ISPAAM) Napoli

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Responsabile di Progetto per CNR-ISPAAM: Dott.ssa Chiara D’Ambrosio.