PROGETTO

Supervisore: Raffaella Di Micco_____

Titolo/*Title*: __Studying the interplay between senescent cancer cells and the immune micronvironment in acute myeloid leukemia_____

Curriculum: ___GCT_____

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: _____https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy/senescence-in-stem-cell-aging-differentiation-and-cancer/raffaella-di-micco.html_____

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Increasing evidence indicates that therapy-evoked stresses drive tumor cells into senescence, beneficial as an arrest, but potentially detrimental due to other senescence-associated (SA) effects such as the largely pro-inflammatory secretory phenotype (SASP) or stemness-like and plasticity-conferring reprogramming. These processes may account for therapy resistance in both cell-autonomous and non-cell-

autonomous manner, highlighting persistent senescent cells an important target principle to enhance anticancer treatment efficacy. Recent findings in solid tumors have also uncovered that senescent cells act as antigen presenting cells and activate adaptive immunity for efficient cancer eradication. However, the role of senescent cells in acute myeloid leukemia response to therapy and within the complex bone marrow micronvironment remains unexplored.

Rationale and hypothesis

Our project is based on the hypothesis that senescent leukemic cells interact with non-neoplastic cells of the tumor microenvironment thus providing opportunities to be harnessed by innovative senescence-based strategies that will profoundly improve the long-term outcome of AML patients. This hypothesis also lays on our recent discovery that in human primary AML samples the adaptive immune system triggers senescence immune-surveillance in AML via activation of a strong Interferon gamma response (Gilioli et al. Biorxiv 2022).

Objectives and specific aims

The objective of this proposal is to identify critical access points in the tumor microenvironment for therapeutic intervention and demonstrate their durable beneficial impact on outcome in immune-competent animal models. We propose the following distinct but inter-related aims:

Aim 1: Uncover specific niches for senescent leukemic cells and gain molecular insights into senescence-associated Immune microenvironment (IME) remodeling in MLL-AF9 driven AML models using high throughput immunophenotyping, transcriptome analyses, and spatial proteomic techniques.

Aim 2: Functionally interrogate and modulate interactions at the interface between therapy-induced senescent (TIS) AML and the IME. Utilize genetically engineered mouse models for senescence elimination (p16-3MR mouse model) and CRISPR-mediated genetic inhibition to identify potential therapeutic targets.

Aim 3: Assess the efficacy of Immune Checkpoint Blockers in combination with senescence-inducing therapies to enhance immune stimulation against AML in preclinical models.

Expected outcomes

This work will provide insights into the mediators of TIS AML-IME interactions, delineate functional properties of immune niches, and identify senescent-associated niches poised for immune-mediated tumor eradication. Preclinical studies using checkpoint inhibitors will evaluate their efficacy in combination with senescence-inducing therapies, providing rationale for immune-mediated therapies in AML treatment.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The student will acquire a unique molecular expertise in the field of DNA damage, senescence and leukemia biology and combine it with cutting-edge immune-oncology approaches. He/she will become proficient with cellular and molecular assays to test leukemia response to treatment and its interplay with immune cells in vitro and in murine models in vivo. Moreover she/he will become familiar with genomic approaches such as scRNA seq and spatial analyses to identify senescent cells within the leukemic micronevironment. The student will be trained to become an independent thinker and will have the unique opportunity to interact with internal and international collaborators leaders in the field.

Bibliografia (max. 15)

Gilioli D, Fusco S, Tavella T, Giannetti K, Conti A, ..., Di Micco R§. Therapy-induced senescence upregulates antigen presentation machinery and triggers anti-tumor immunity in Acute Myeloid Leukemia (BioRxiv 2022 doi: https://doi.org/10.1101/2022.11.17.515658). § corresponding author

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