Titolo progetto: Proteomic and miRnomic investigations of senescence-derived exosomes to identify circuits modulating cancer chemoresistance and tumor microenvironment

Codice Progetto: 2022LJTNCW

PRIN 2022 - Finanziato da MUR con riferimento all'intervento del PNRR a titolarità del Ministero dell'Università e della Ricerca - Missione 4 "Istruzione e Ricerca" - Componente C2 - Investimento 1.1 "Fondo per il Programma Nazionale di Ricerca e Progetti di Rilevante Interesse Nazionale (PRIN)" finanziato dall'Unione Europea – Next Generation EU

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Abstract: Senescence is a cellular defense mechanism consisting in a permanent cell cycle arrest as a consequence of stress, usually genotoxic. Conventional cancer treatments, such as chemo- or radiotherapy, induce either apoptosis or, in apoptosis-resistant tumor, senescence (TIS, therapy induced senescence). Cancer cells take advantage of this response to escape chemotherapy-induced apoptosis becoming un-targetable by conventional therapies. Senescent tumor cells are cell cycle arrested but remain viable and metabolically active. They acquire a senescence-associated secretory phenotype (SASP), an enhanced ability to produce and secrete pro-inflammatory cytokines, growth factors and extracellular matrix components. Although the SASP has been initially described as composed by soluble factors, recent evidences have shown that exosomes, one type of small extracellular vesicles (sEV), are critical components of the SASP. EVs can transmit proteins, nutrients and RNAs from one cell to another, thereby having an integral role in intercellular communication possibly propagating the chemoresistant phenotype in non-senescent tumor cells and contributing to establish metastatic niches.

Finalità: By using a lung cancer cellular model of chemotherapy induced-senescence, we will high-throughput investigate the proteomic and miRnomic content of early and late senescence-associated exosomes together with SASP in the modulation of cancer chemoresistance and tumor microenvironment. Through the combination of different unbiased screening and molecular approaches we aim to:
1. Identify exosomal proteins, directly involved in the modulation of DNA damage response (DDR) signaling activation, responsible for microenvironment inflammation associated with chemoresistance.
2. Identify exosome-contained miRNAs and their target genes associated with cancer chemoresistance and DDR/SASP activation.
3. Uncover the role of cytokines and chemokines secreted in media of chemotherapy-induced senescence to sustain cancer chemoresistance modulating the tumor microenvironment
4. Uncover cytokines and chemokines' dynamics and compartmentalization during senescence.
5. Unveil the role played by the RelA/p65 subunit of the NF-κB family of transcription factor in modulating these processes.

Risultati attesi:

Results will improve the understanding of the bystander effect of neighboring cancer cells. Specifically, by understanding how EVs and SASP may be involved in lung chemoresistance, novel targeted therapies may effectively replace current treatment options in the near future.

Risultati raggiunti: *in progress*

Partenariato:

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

Durata del progetto: 24 mesi

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Responsabile di Progetto per CNR-ISPAAM: Dott.ssa Arena Simona