UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi Biomolecolari – XL CICLO

Research Topic ID: XL – 1.23

Proponent: Dr. Elena Sacco

Project Title: Targeting metabolism to identify novel pharmaceutical interventions in cancer models

Scientific background and 'open issues'

Metabolic reprogramming is one of the hallmarks of cancer[1], playing an important role in tumorigenesis, metastasis, drug resistance, and cancer stem cells [2,3]. Indeed, cancer cells adapt their metabolism to sustain an increased requirement of energy and building blocks for supporting their abnormal proliferation. Metabolic alterations are the result of cell-intrinsic factors (genetic mutations[4,5] and epigenetic alterations[6]) and cell-extrinsic factors, comprising aberrant vascularization that determines reduced nutrient availability and hypoxia. The absence of oxygen triggers a hyper-glycolytic phenotype via HIF1α signaling, leading to acidosis and extracellular matrix (ECM) modification, promoting invasion and metastasis metastasization[7]. Moreover, the role of the tumor microenvironment (TME) in metabolic rewiring is emerging as essential [8,9]: it is a complex and dynamic niche including surrounding blood vessels (endothelial cells), immune cells (e.g., macrophages, lymphocytes), fibroblasts, and the ECM. Among TME elements, Cancer associated fibroblasts (CAFs) secrete signaling molecules that support cancer growth and invasion through multiple mechanisms, including metabolic crosstalk [10,11]. For instance, Caveolin 1 (Cav-1) deficient CAFs display enhanced catabolism and produce metabolites that are used by neighboring cancer cells to fuel oxidative energy production, a phenomenon called reverse Warburg effect [12,13]. Moreover, there is evidence that CAFs can perform mitochondrial transfer toward cancer cells [14][15]. Therefore, understanding the metabolic interactions between cancer cells, CAFs and ECM may help to identify potential metabolic vulnerabilities that can be targeted for novel anti-cancer therapies.

To this aim, advanced in vitro models are necessary: 3D cultures with increasing levels of complexity (e.g. spheroids including different cell types, in presence of ECM components) can better recapitulate the tumor architecture and heterogeneity than 2D cultures[16,17], and so can be used to mimic the TME and its role in cancer metabolic rewiring. 3D models provide a more realistic representation of cancer cell growth rate, direction, exposure to nutrients, drugs, and oxygen gradients. Moreover, selective pressures in 3D cultures can enrich cancer stem cells (CSCs), providing a reliable platform to study cancer metabolism and identify novel treatment strategies.

Objectives

Understanding the role of CAFs and ECM in modifying cancer metabolism in the TME for developing more efficient cancer therapies.
To this end, the objectives of the project are:

- Develop reliable and reproducible 3D cancer models from tumor cell lines including increasing grades of complexity
- Characterize the metabolic phenotype of the developed 3D models using different methodologies (see the next section)
- Integrate different approaches to identify potential new metabolic targets in cancer

Methodologies

- Development of advanced preclinical 3D cancer models
- Quantitative imaging by confocal and multi-photon microscopy on live and fixed samples employing fluorescent dyes and antibodies
- Study of bioenergetic parameters by mean of Seahorse technology
- Evaluate metabolic parameters using specific fluorescent probes and biosensors detectable by flow cytometry and fluorescence microscopy
- Omics data collection and integration with computational models

Collaboration / Co-tutoring opportunities

- Prof. Daniela Elena Costea (Bergen, Norway) – can share her expertise on co-cultures of CAFs and cancer cells.
- Prof. Laura Russo (Unimib) – can be a valid collaborator for her expertise on the biopolymers useful for the development of 3D models of cancer and bioprinting.
- Prof. Rocco Piazza (Unimib) – can collaborate to perform transcriptomic analysis.
- SYSBIO (Doc. Daniela Gaglio) – can collaborate for metabolomics analysis.
- Prof. Chiara Damiani – can collaborate for computational modelling and omics data integration.

Project's Sustainability & Mobility

- Our laboratory has been involved in different projects aiming to identify novel targets of cancer, and in the last years it has acquired expertise in developing three-dimensional cancer models for this purpose, such as spheroids and organoids from patients with bladder cancer and from patient derived xenografts of breast cancer. The methodologies that our laboratory has applied to the study of cancer metabolism include Seahorse technology, confocal microscopy, and flow cytometry. Moreover, our laboratory has recently received fundings for the PNRR project Elixir, that includes the purchase of a multi-photon microscope for advanced imaging analysis.

- Pertinent research articles published by the proposers: Campioni et. al 2022[18], Pasquale et al. 2020[19], Proietto et al. 2023[20], Di Filippo et.al 2022[21], Damiani et. al 2020[22]

- Putative foreign institutions for achieving the required ordinary mobility (at least 3 months are mandatory for regular fellowships):

(A) Gade Laboratory for Pathology, Department of Clinical Medicine and Centre for Cancer Biomarkers CCBio, Haukeland University Hospital, University of Bergen, N-5021 Bergen (Norway), Prof. Daniela Elena Costea.
(B) Sbarro Institute of Cancer Research and Molecular Medicine and Center for Biotechnology, Temple University, Philadelphia (PA, USA), Prof. Andrea Morrione / Prof. Antonio Giordano.

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