PROJECT

Supervisor:	Giovanni Tonon
Title:	Targeting mitophagy in metastatic cancer models
Curriculum:	Basic and Applied Immunology and Oncology
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/en/docenti/t/giovanni-tonon https://research.hsr.it/en/divisions/experimental-oncology/functional-genomics-of-cancer/giovanni-tonon.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

We have recently revealed a central role for mitochondria in determining resistance of cancer cells to therapy. To survive, cancer cells increase mitophagy, a process where mitochondria are continuously eliminated and rebuilt. Central to this process is a kinase, the PTEN Induced Kinase 1 gene (PINK1)[1], which present domains that could be targeted by small molecules. We hence propose that mitophagy exerts a central role in driving the survival of cells during cancer treatment, driving disease relapse[2,3]. Clinical trials are underway or completed to explore the potential of mitophagy-modulating drugs for treating various diseases, including neurodegenerative conditions and muscle decline during aging (https://clinicaltrials.gov/). However, there are no clinical trials testing mitophagy inhibition in cancer. Furthermore, most drugs targeting mitophagy show pleiotropic effects with unknown mechanisms[4].

Rationale and hypothesis

In this proposal, we aim to specifically target mitochondria by impairing their functional recycling. We propose to identify drugs that, by inhibiting mitophagy, may disrupt the survival of cancer cells and reduce disease recurrence. In parallel, we will elucidate the specific pathway leading to cell death to enhance the application in precision oncology of these compounds.

Objectives and specific aims

We found that the pervasive increase in mitophagy seen in cells withstanding therapy is mediated by the overexpression of PINK1: PINK1 sequesters in the cytoplasm the transcription factor Hepatocyte Nuclear Factor 4α (HNF4α)[1], a master regulator and a cell identity gene controlling mitochondrial biogenesis and DNA repair[5]. HNF4α can exert both oncogenic and tumor-suppressive functions, depending on the tumor type and context[6]. We will leverage multi-omic, bulk and single cell approaches[7,8] to define the role of PINK1-HNF4α axis in two deadly cancer types, metastatic colorectal cancer (mCRC) and metastatic pancreatic ductal adenocarcinoma (mPDAC).

By applying genetic approaches (transcriptomic and epigentic analysis), we will identify genes of the PINK1-HNF4α axis that can be targeted by available compounds. To increase clinical applicability, we will use both CRC and PDAC metastatic patient-derived organoids (PDOs), as advanced preclinical models for drug screening that closely mimic the patient response[9]. The most promising compounds will be finally tested in ad-hoc mouse models.

Expected outcomes

We propose a comprehensive strategy aimed to validate novel enticing adjuvant therapies, supported by extensive mechanistic validation and thorough pre-clinical testing, to finally tackle metastatic disease centered on targeting a pathway so far not considered crucial for cancer survival, mitochondria metabolism. Furthermore, this study will provide insights into the characterization of the pathway for an early selection of the patients that could benefit of therapy targeting mitochondrial dysfunction, thus increasing the success of clinical application.

Skills that the student should acquire (max. 600 characters including spaces):

The student will apply novel molecular and cell biology approaches that allow the comprehensive definition of the (epi)genetic and transcriptomic landscapes. We will exploit engineered in vitro models[10], fluorescent-labeled[11] and barcoded tumor cells[1]. Especially, she/he will learn to handle patient derived organoids and perform large scale base-compounds screening. In addition, the student will acquire the expertise to manage a broad range of computational and genomics data.

References (max. 15)

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