RESEARCH TOPIC-MEM14
DECODING THE IMMUNE HETEROGENEITY OF INTRAHEPATIC CHOLANGIOCARCINOMA

Curriculum MEM Standard

Laboratory name: Hepatobiliary Immunopathology Lab, Humanitas Clinical and Research Center - IRCCS

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Abstract

Background
Cholangiocarcinoma (CCA) is a deadly cancer of the biliary epithelium. With incidence and mortality rates currently increasing, it is now the second most common type of primary liver cancer and represents up to 3% of all gastrointestinal malignancies. CCA is anatomically classified as intrahepatic (iCCA), perihilar, and distal. Recent evidences suggest that iCCA and extrahepatic CCA are biologically different cancers; iCCA is a highly chemoresistant tumour, and pharmacological therapies are generally unsuccessful. Thus, there is an obvious need for better understanding of tumor characteristics and pathogenesis and eventually for effective therapies.

Hypothesis
Preliminary data produced by our group suggest that the T cell intratumoral infiltrate in iCCA patients impacts prognosis after complete resection. T cells infiltrating tumors are largely dysfunctional, but whether a subset maintains superior functionality remains ill defined. It is therefore vital to dissect the main characteristics of the tumor microenvironment (TME) and identify involved pathways and key players.

Aims
We propose a project aiming to define the cellular and molecular mechanisms involved in the TME of iCCA

Experimental Design
We will prospectively collect liver tissue and peripheral blood from iCCA (n=30) patients undergoing resective surgery at the Hepatobiliary Surgery Unit in Humanitas. From each single patient we will isolate the CD45+ infiltrate from (i) cancer sample, (ii) cancer-free sample, and (iii) the intrahepatic circulation. Further neoplastic and non-tumoral cholangiocytes will be isolated. We will:
1. perform a detailed study of the transcriptome (single cell RNA sequencing) and

metabolome of the tumor infiltrate of subjects with iCCA.
2. define those cell subsets that are enriched in tumors compared with cancer-free tissues and blood, using high-dimensional single cell phenotypic analysis.
3. investigate subgroups of patients with iCCA with different TNM stage and define if they have different infiltrate distributions, by computational analysis of high-content data.

Expected Results
We aim to define major characteristics of the TME of iCCA and to identify those cell subsets that are enriched in iCCA. This characterization, matched with clinical follow-up of the enrolled patients, will allow to stratify patients into different risk groups.

Impact on cancer
CCA is characterized by a grim prognosis with a 5-year survival of less than 20%. Response to chemotherapy is very low and diagnosis if commonly performed in advanced stages of disease. We believe this project will provide important insight into the molecular pathogenesis of iCCA, and potentially identify novel therapeutic targets.

Main technical approaches
Transcriptomic analysis (single cell RNA sequencing)
- Metabolomic
- high-dimensional single cell FACS phenotypic analysis

Scientific references

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Type of contract

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