



## RESEARCH TOPIC DASME1

### Deciphering the molecular and architectural tumor immune microenvironment of iCCA under chemoimmunotherapy

#### Curriculum DASME Standard

#### Research Area

Gastro-Onco

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#### Abstract

Intrahepatic cholangiocarcinoma (iCCA) is a rare, yet aggressive biliary tract cancer (BTC) with limited therapeutic options and a dismal prognosis. Systemic chemotherapy has represented the mainstay treatment for unresectable disease for over a decade. More recently, first-line treatment with immune checkpoint inhibitors plus standard chemotherapy with cisplatin and gemcitabine has demonstrated a survival improvement in two phase 3 trials (TOPAZ-1 and KEYNOTE-966), setting a new standard of care. However, predictive biomarkers of response to chemoimmunotherapy are yet to be identified. BTC harbors a poorly immunogenic tumor immune microenvironment (TIME) with limited infiltration of anti-tumor lymphocytes and massive infiltration of highly activated immunosuppressive cells, such as CD4<sup>+</sup>FoxP3<sup>+</sup> regulatory T cells (Tregs), as supported by our lab preliminary data. Therefore, understanding the underlying mechanisms driving response to chemoimmunotherapy remains a highly unmet need.

We hypothesize that specific cellular networks sustain the anti-tumor activity of CD8<sup>+</sup>/CD4<sup>+</sup> T cells while blocking immunosuppressive T-reg/M2 macrophages in iCCA, influencing tumor response and dictating patients' prognosis. We also postulate that chemoimmunotherapy would induce the early expansion of Ki-67<sup>+</sup> CD4<sup>+</sup> and CD8<sup>+</sup> T cells with characteristics of immune activation (HLA-DR<sup>high</sup>, CD38<sup>high</sup>) in peripheral blood (PBMC), and specific molecular and metabolic features would influence tumor regression.

### Main technical approaches

- high-dimensional mass cytometry
- spatial transcriptomics
- longitudinal analysis of the molecular and metabolic pathways in peripheral activated T cells
- high-dimensional flow cytometry

### Scientific references

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