



Tailoring immunotherapy to organ specific metastasis

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Background

There is an increasing interest in defining immunotherapy efficacy according to the site of metastasis

1. Pts with different metastatic site respond differently to ICI. (Front Oncol 2020, Lung Cancer 2018)
2. Specific ICI efficacy in patients with bone metastases is not well understood
3. BM can impair immunotherapy efficacy in lung cancer (J Immunot Cancer, 2019)
4. Bone has a relevant role in modulating immune-response. Bone marrow contains high levels of multiple immune cells with relevant functions, affecting systemic immunity and therapeutic efficacy of conventional treatments and immunotherapy

HYPOTHESIS

In cancer patients local TIME plays crucial roles in modulating therapeutic responses.

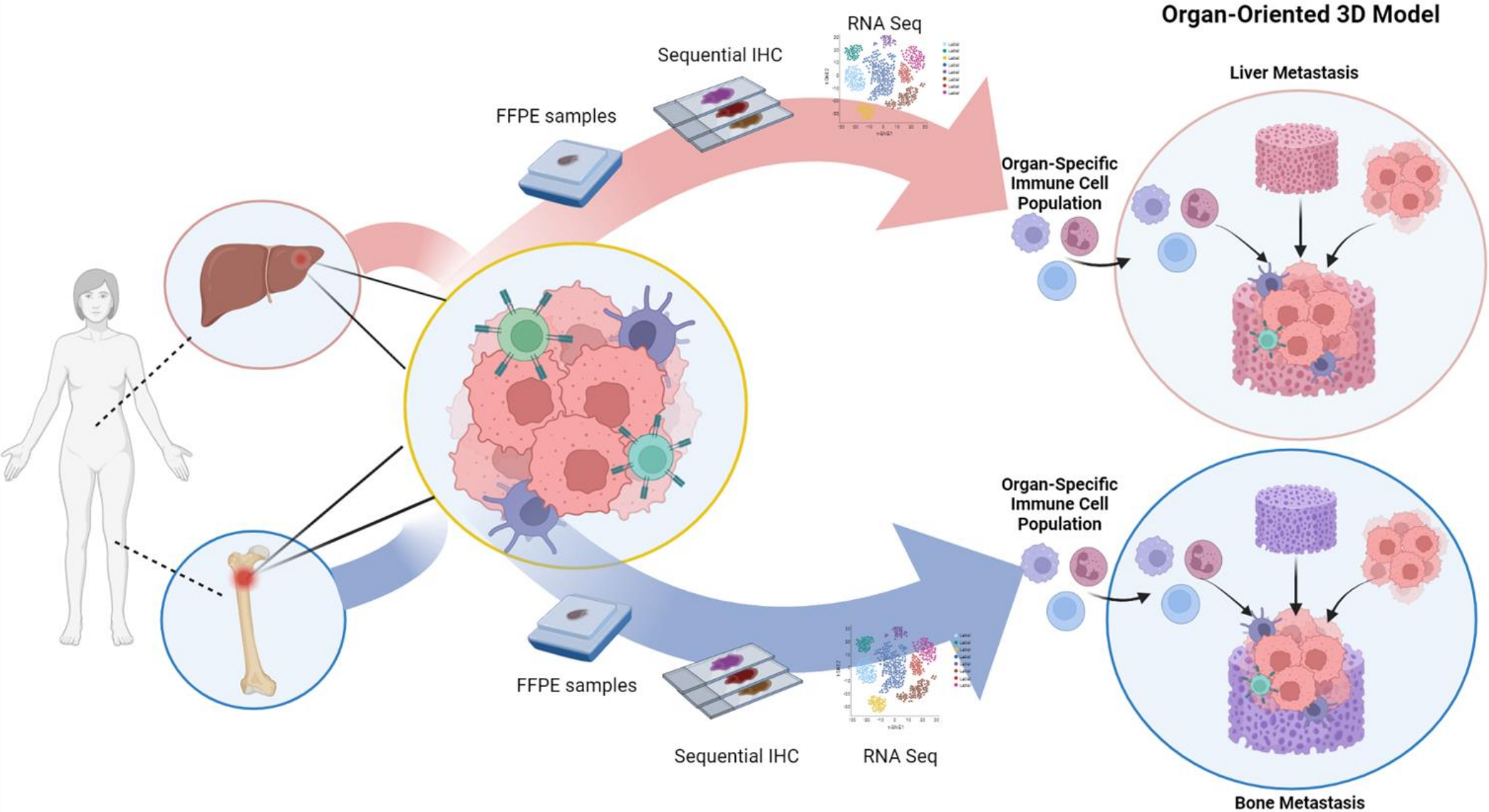
- Metastatic lesions may respond differently to ICI based on tissue-specific immune landscapes;
- The understanding of the tumor immune interactions in different metastatic organs will reveal organ-tailored therapeutic strategies and improve patient stratification;

AIMS:

We propose a metastatic based approach of personalized medicine.

- to define predictive markers/signature of response to ICIs, in the metastatic setting.
- to study metastatic specific TIME to compare bone and liver metastases in breast cancer patients
- to identify new targets for innovative therapeutic approaches

GRAPHICAL ABSTRACT



STUDY DESIGN

T1.1: A **retrospective/perspective study** will be performed to evaluate

T1.1.1: **TIME composition and tissue spatial organization** by seq IHC.

T1.1.2 RNA seq will be by NGS

T1.2: *In silico* study to obtain information on immune populations and RNAseq profile of organ Specific TIME. The complex relation between spatial organisation, molecular signatures of TIME and clinical data will be studied,

T1.3: The most relevant immune cell populations identified in T1.1-T1.2, for each specific organ will be chosen to set up 3D immunocompetent organ-oriented models that will be tested with ICI

EXPECTED OUTCOMES AND IMPACTS

- The project is designed to refine organ-tailored metastatic treatment and pave the way for subsequent studies on new immunotherapeutics targets, or clinical trials in which patients are stratified for immunotherapy according to biological integrated data.
- Determine whether metastatic organ-specificity affects immune-checkpoint blockade therapy compared to the tumor of origin.
- We expect to unveil how organ-specific immune landscapes in distinct metastatic sites impact the response to ICI therapy.



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