ImaBiotech
Revealing Biological Secrets

Whitepaper #6a: Immuno-Oncology

T cell metabolic adaptation: crucial checkpoint for antitumor immunity

Introduction

Tumor micro-environment is characterized by a consistent reduction in oxygen and blood-borne nutrients that significantly affect the metabolism of distinct cell subsets. Immune cells populating malignant lesions need to activate alternative pathways to overcome tumor-prolonged nutrient deprivation. In particular, the metabolic switch occurring in transforming tissues dramatically impacts on tumor-infiltrating T cell biology.

Immunotherapies that block inhibitory checkpoint receptors on T cells have transformed the clinical care of cancer patients. However, for a significant number of patients, these therapies have proven ineffective.

- How do metabolites regulate T cell infiltration during disease progression?
- How to optimize your immune-oncology drug activity with metabolism reprogramming?

Tailoring immune responses by manipulating cellular metabolic pathways provide new options for cancer immunotherapy.

In this paper, we describe in the context of the tissue microenvironment and more specifically according to tumor infiltrating lymphocytes (TILs), the metabolic patterns of a stage II colorectal cancer sample and discuss how immunomodulatory strategies could synergize with immunotherapy to circumvent its current limitations with the use of innovative imaging capabilities and data analysis workflows.

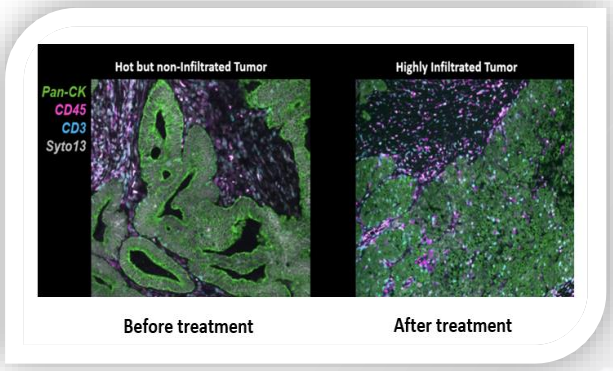


Fig 1. Example of immunomodulatory metabolic strategies to increase anti-tumor immunity (Nanostring courtesy).

T cell exhaustion in tumor microenvironment

We combined standard microscopy Imaging and Quantitative Mass Spectrometry Imaging (QMSI) from stage II colorectal cancer tissue sample in order to map up to 5,000 metabolites and small molecules and track metabolic phenotypes (Ait-Belkacem *et al.,* 2017) as well analysis the tissue structure and TILs (Tumor Infiltrated Lymphocytes). In order to decipher the complexity of the highly multiplex Mass Spectrometry imaging data, we used image segmentation with Uniform Manifold Approximation and Projection (UMAP) for Dimension Reduction and analysed the content of each sub-structure of the image/tissue as reported in a previous White paper #8.

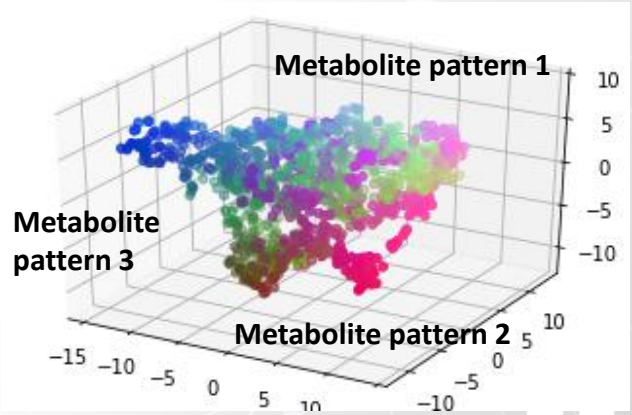


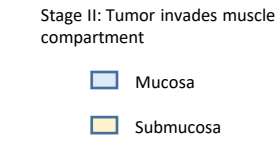
Fig 2. UMAP of metabolite clusters present in the colorectal cancer tissue

WP6a - T cell metabolic adaptation: crucial checkpoint for antitumor immunity

Once the clusters are transposed and colorized on the tissue section, the density of Tumor Infiltrated Lymphocytes (TILs) is assessed in each metabolite cluster by measuring the area occupied by mononuclear cells over the stromal area on hematoxylin and eosin (H-E)-stained sections. Tumor content is also assessed in each defined metabolite cluster.

Clusters	TILs %
0	80
1	0
2	50
3	0

Table 1. Percentage of TILs according to tissue type/metabolite clusters



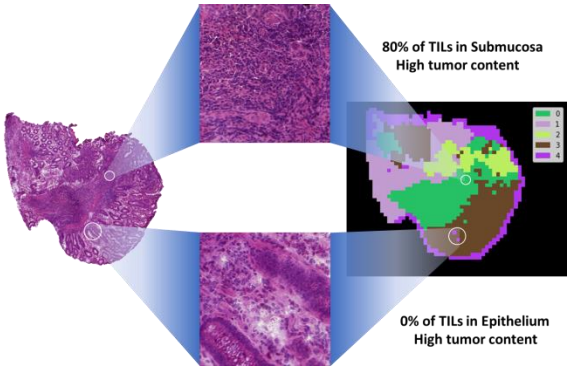


Fig 3. Tissue annotations according to metabolite clusters

The table 1 beside describes the result of the cluster annotations for the stage II colorectal cancer sample used in this study. As previously reported, with disease extent, TILs are more and more excluded from the location of the origin of tumor cells. As the tumor progresses within the tissue, tumor immunity strongly impacts on tumor-infiltrating T cell biology.

Tumor metabolism reprogramming regulates tumor microenvironment T cell infiltration

The four (4) metabolite patterns identified in our study clustered with tumor content indicating a tumor specific metabolic reprogramming. In these highly tumor content environments, lymphocyte infiltration is also modulated indicating that the metabolic signatures shape the inclusion/exclusion of T cells in the tumor microenvironment.

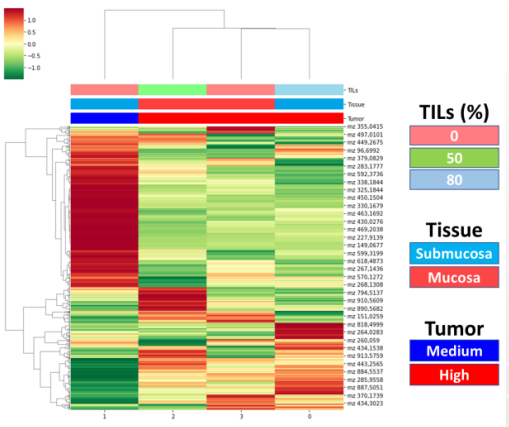


Fig 4. Heatmap showing the metabolite expression of the stage II colorectal case. Rows represent metabolites. Columns represent individual metabolite pattern in the cluster identified by UMAP from 0 to 3.

Metabolic interplay between tumor cells and immune cells

The competitive uptake of glucose under TME conditions is responsible for the damage to T cell function and the ensuing low pH of the TME has been shown to be beneficial for the selection of more aggressive tumor cells and suppress tumor immunity to promote tumor progression. Using Metlin database, peaks in the high resolution MSI datasets have been annotated and significant upregulation of lactic acid and glucose were found in clusters with impaired immune cell response, 2 and 3 respectively (table 2). This demonstrates that the **Metabolic interplay between tumor cells and immune cells can contribute to the exhaustion of TILs and therefore immunosuppression**

	Mass	Formula	Upregulated	Detected
Lactic acid	90.0779	C3H6O3	Cluster 2	
Glutamine	146.1445	C5H10N2O3	-	Yes
Pyruvic acid	88.0621	C3H4O3	-	Yes
Glucose	180.1559	C6H12O6	Cluster 3	

Table 2. Potential targets from the annotation process

Conclusion

We made a QMSI data exploration study on a stage II colorectal cancer tissue in order to reveal the role of metabolic signatures in anti-tumor immunity. Based on the founded metabolic clusters, predictive metabolic signatures can be identified that monitor the status of the TME and therefore the infiltration levels of immune cells. This can be a powerful tool for the prediction of response to immunotherapies or to the exploration of novel therapeutic strategies.

Nowadays, current pathological staging present limitations in prognosis and response to therapies. Patients could have totally different final outcomes although they might possess similar clinical and pathological types. The development of metabolic signatures which could comprehensively combine the metabolic profile with the clinical parameters could improve the accuracy of the prediction. In conclusion, the metabolic signature could indicate the status of the tumor microenvironment to provide more clues in the exploration of immunomodulatory strategies.

References

1. Ait-Belkacem *et al*. Microenvironment Tumor Metabolic Interactions Highlighted by qMSI: Application to the Tryptophan-Kynurenine Pathway in Immuno-Oncology. *SAGE Journals* 2017, 22(10), 1182–1192.

For more information visit ImaBiotech website

or contact us at contacts@imabiotech.com

ImaBiotech Lille

152 rue Dr Yersin Loos 59120
FRANCE

ImaBiotech Boston

44 Manning road Billerica MA 01821
USA

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