Unravelling the role and anti-tumour potential of cDC2s expressing interferon-stimulated genes within intratumoural niches.

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L. Kelecom[I,II], L. Allonsius[I,II], P.M.R. Bardet[I,II], A. Debraekeleer[I,II], A.E.I. Hamouda[I,II], S. Deschoemaeker[I,II], D. Laoui[I,II]

[I]Laboratory of Dendritic Cell Biology and Cancer Immunotherapy, VIB Center for Inflammation Research, Brussels, Belgium, [II]Lab of Cellular and Molecular Immunology, Brussels Center for Immunology, Vrije Universiteit Brussel, Brussels, Belgium

The tumour microenvironment hosts a vastly heterogeneous landscape of immune cells, including dendritic cells, pivotal in initiating and sustaining anti-tumour responses. Yet, how these cells are spatially organized within tumours, and how this relates to their functionality and the establishment of anti-tumour responses remains elusive. Multiomics immune characterization of an in-house generated preclinical-relevant orthotopic lung adenocarcinoma (LUAD) mouse model, my lab revealed that several immune populations are restricted to specialized, local niches within the tumour-bearing lungs. As such, using spatial transcriptomics, previously unknown hubs enriched with several cell types exhibiting distinct interferon (IFN)-stimulated gene (ISG) signature, were uncovered within the intratumoural periphery.
Most prominently, ISG-cDC2s, which represent a recently uncovered activation state, were found to reside solely within these niches where they consistently co-localized with central memory T cells, suggesting that these niches may serve as central hubs for robust, local T-cell activation, mediated by these IFN-stimulated cDC2s. To understand how these niches wire effective antitumor biology, I will characterize these ISG hubs in mouse and human tumors at the molecular in depth using state-of-the-art technologies. Next, using *in vitro* functional assays and *in vivo* loss- and gain-off-function experiments, I will aim to elucidate the function of ISG-cDC2s within these hubs and how they influence tumor progression. Finally, I will provide proof-of-concept for the therapeutic potential of ISG-niche modulation in tumours.
Overall, we believe that by understanding the role of our recently discovered ISG-cDC2-niches, this project will advance our understanding on how cDC2 subsets modulate immune responses in cancer, and how DC-orchestrated anti-tumour responses are organized locally.