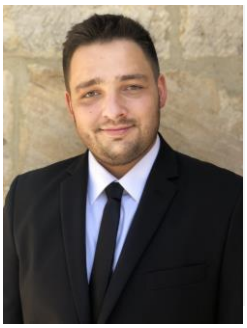
ImmunoTools *special* Award 2024



Lukas Amon, PhD-student

Supervisor: Prof. Dr. Diana Dudziak

Institute of Immunology, Jena University Hospital, Leutragraben 3, 07743 Jena, GERMANY

Department of Dermatology, Laboratory for Dendritic cell Biology, Forschungsmodul II, Uniklinik Erlangen, Hartmannstr. 14, 91052 Erlangen, GERMANY

Malignant melanoma hijacks Dendritic cells to modulate the induction of *de novo* T cell responses

Malignant melanoma is an aggressive tumour form that is characterized by a low survival of patients attributed to its predilection for forming metastasis in essential organs including the brain, liver and lung. Even though the rise of check-point inhibitors substantially improved current treatment options, the majority of patients does not respond to check-point inhibitor treatment regimens[1]. While check-point blockade frequently releases the brakes from pre-existing T cell responses, it is assumed that in non-responders the ability of the immune system to initiate *de novo* T cell responses is truncated[1]. This modulation of T cell responses is assumed to operate on two levels including the general dampening of priming (quantitative effect) and the polarization to primed T cells rather supporting tumour growth (TH2 responses; regulatory T cell generation) than tumour rejection (TH1/TH17 responses)[2]. Owing to their unique ability to prime and polarize naïve T cells, Dendritic cells (DCs) are in the spot light for the development of new cancer therapies[4].

In general, DCs regulate the induction of T cell responses via three distinct signals.[1,3] These consist of:

(1) the presentation of peptides in the context of MHC molecules to the T cell receptor determining T cell specificity

(2) contextual information transmitted via co-regulatory molecules to T cells determining the amplitude of T cell activation

(3) the secretion of cytokines driving T cell polarization directly impacting the effector functions of primed T cells.

In the course of multi-component co-culture systems containing murine B16F10 melanoma cells, DCs and T cells, we could demonstrate that surface-bound factors of the tumour reduce the capacity of DCs to initiate new $CD8^+$ and $CD4^+$ T cell responses in a tumour-dose dependent fashion. Mechanistically, the dampening of T cell priming was directly resulting from the tumour-dependent downregulation of co-regulatory molecules expressed on DCs, thereby diminishing the ability of DCs to provide a proper signal 2.

Therefore, we want to find avenues to overcome the negative regulation exerted by B16F10 melanoma on DCs and to understand the functional quality of T cells resulting from polarization of $CD4^+$ T cells into tumour-promoting (TH2, regulatory T cells) or tumour-rejecting (TH1, TH17) modules.

The reagents provided by the ImmunoTools *special* award will support us in tackling both research questions.

After creating a library of cytokine receptors expressed by DCs from available bulk RNA sequencing data, we want to harness prominent receptors on DCs to potentially over-turn the regulatory impact of B16F10 melanoma cells on the stimulatory capacity of DCs by stimulating them with select cytokines. These cytokines provided by ImmunoTools include IL-1alpha, IL-15 and IL-33 leading to direct DC activation and cytokines fostering DC homeostasis and survival including GM-CSF, FLT3-L and SCF.

To address the qualitative output of DC-dependent T cell priming in the presence of B16F10 cells, we will analyse the polarization of $CD4^+$ T cells under different priming conditions. Therefore, we will use the murine cytokines of ImmunoTools (1) IFN-lambda to stimulate DCs for fostering a TH1 response, (2) IL-1beta, IL-6 from ImmunoTools in combination with IL-23 and TGFbeta driving TH17 cell priming, (3) TGFbeta alone for regulatory T cell generation, and (4) IL-4 facilitating TH2 T cell generation.

The ImmunoTools *special* award would support us to understand how tumours regulate the qualitative outcome of DC-dependent T cell priming and how the dominant impact of tumours on the stimulatory capacity on DCs can be over-turned.

References:

1. Amon, L., Hatscher, L., Heger, L., Dudziak, D. & Lehmann, C. H. K. Harnessing the Complete Repertoire of Conventional Dendritic Cell Functions for Cancer Immunotherapy. Pharmaceutics 12, 663 (2020).
2. Amon, L. et al. Transcriptional control of dendritic cell development and functions. Int Rev Cell Mol Biol 349, 55-151, doi:10.1016/bs.ircmb.2019.10.001 (2019).

3. Coussens, L. M., Zitvogel, L. & Palucka, A. K. Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science 339, 286-291, doi:10.1126/science.1232227 (2013).
4. Roberti, M. et al. Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer. Nature Medicine 26(6):919-931, doi: 10.1038/s41591-020-0882-8 (2020).

ImmunoTools *special* AWARD for **Lukas Amon**

includes 10 reagents

recombinant mouse cytokines: rm IFN-lambda, rm IL-1alpha, rm IL-1beta, rm IL-2, rm IL-4, rm IL-6, rm IL-33, rm GM-CSF, rm M-CSF, rm SCF

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