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Lotte de Winde, Postdoc

Lymph node stromal cells have the toolbox to control anti-tumor immunity

C.M. de Winde1, D. Panocha1, R. Nadafi1, A. Mikula1, L.G.M. van Baarsen2, T.D. de Gruijl3, R.E. Mebius1

1Molecular Cell Biology and Immunology, Amsterdam UMC location VU, Amsterdam.
2Rheumatology and Experimental Immunology, Amsterdam UMC location UvA, Amsterdam.
3Medical Oncology Laboratory, Amsterdam UMC location VU, Amsterdam.

Tumors have developed several strategies to evade anti-tumor immunity including impaired T cell responses. Tissue-draining lymph nodes (LN) are essential for initiation of efficient adaptive immune responses. LN stromal cells (LNSCs) organize and preserve the LN architecture and facilitate immune cell activation. Our lab has previously shown that LNSCs play an important role in peripheral tolerance (Baptista et al. 2014, Nadafi et al. 2020). LNSCs present self-antigens in MHC-I or MHC-II, which leads to the generation and maintenance of regulatory T cells (Tregs). As most tumor-antigens are unaltered or mutated self-antigens, we hypothesize that LNSCs present tumor-antigens as self-antigens in the context of key immune regulatory factors resulting in impaired anti-tumor immune responses. We find that primary human LNSCs stimulated with melanoma-conditioned media or after co-culture with melanoma tumor cells have increased tumor-antigen mRNA expression. This correlates with increased HLA-DR cell surface expression. Expression of other cell surface molecules involved in modulation of T-cell responses (CD80, CD86, CD54/ICAM-1, CD58/LFA-3, PD-L1) is also increased in melanoma-stimulated LNSCs, indicating that presence of melanoma results in an activated profile of LNSCs. Furthermore, mRNA levels of inhibitory T-cell regulators IDO1 and TGFB1 are increased in melanoma-stimulated LNSCs. These data indicate that LNSCs have the machinery to regulate T-cell responses. Their immunoregulatory toolbox is altered in cancer, which may result in evasion of anti-tumor immunity. Understanding tumor-derived changes in LNSCs at the molecular and cellular level will aid in unravelling the role of LNSCs in anti-tumor immunity and contribute to development of new immunotherapeutic strategies.

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Nikolina Bąbała, Postdoc

How to prevent T cells from getting tired of fighting cancer?

Bąbała N, Karrich J, Laurent A, Slot E, Anastasopoulos D, Bovens A, Amsen D

Department of Hematopoiesis, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Cytotoxic CD8+ T cells (CTLs) are essential for efficient anti-tumor immunity. Adoptive therapies using tumor-reactive CTLs have resulted in durable remission in human cancer patients. However, CTLs in the tumor microenvironment almost always lose their function in a process termed exhaustion, contributing to the failure of T cell based therapies in many patients with solid tumors. Understanding the mechanisms controlling exhaustion is, therefore, essential for rational design of new treatments against cancer. Exhaustion is generally believed to result from excessive and repeated stimulation of T cells. We have found an alternative explanation for the development of this dysfunctional state, namely the activation of CD8+ T cells in the absence of the full complement of signals required to license robust durable responses. In particular, our results show that signaling via Notch receptors operates already during priming of CD8+ T cells to prevent the development of exhaustion. This protective role of Notch can be harnessed to improve adoptive T cell therapies of cancer. Constitutive activation of Notch maintains functional properties, such as production of IFN□, TNF and Granzyme B, in adoptively transferred tumor-reactive T cells that infiltrated a model melanoma in mice. Single cell transcriptome analysis showed that Notch paradoxically promotes general progression through the 4 developmental stages of exhaustion that have been defined. Nonetheless, Notch maintains these cells in a functional and highly proliferative state. Notch therefore uncouples the acquisition of much of the signature exhaustion transcriptome from loss of function and proliferative capacity. Importantly, constitutive activation of Notch in adoptively transferred T cells results in better control of tumor growth in vivo. These results suggest that Notch can be used in the clinic. To avoid potential off-target toxicity, we designed a version of Notch, a Chimeric Notch Receptor (CNR), in which activity is strictly regulated by tumor antigen. Triggering of the CNR by heterologous ligand induces Notch signaling in vitro. Preliminary in vivo results indicate that the CNR is able to control T cell exhaustion in mouse intratumoral T cells. These proof of principle studies suggest novel possibilites to enhance CTL responses for the treatment of cancer in human patients.

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Cesar Oyarce, Postdoc

Targeting macrophages metabolism to prevent EMT: clues to reduce cancer therapy resistance

Cesar Oyarce1,2, Linde Veen1, Amber van der Zalm2, Mark Dings2, Paul Manoukian2, Tanja de Guijl1, Maarten Bijlsma2, Hanneke van Laarhoven1

1 Dep.t Medical Oncology
2 Center for Experimental and Molecular Medicine (CEMM).

Despite major advances the treatment of esophageal adenocarcinoma (EAC), the outcome remains poor. This is due to the development of therapy resistance mechanism such as the epithelial-mesenchymal transition (EMT). Tumor-associated macrophages promote EMT in several cancers; however, whether intratumoral macrophages promotes therapy resistance in EAC is still unknown. Here we show that targeting macrophage metabolism reduces macrophage-mediated EMT in EAC cells. Macrophages gene signature was increased in resections from EAC patients after neo-adjuvant chemoradiotherapy, as compared with biopsies samples. Moreover, EMT related genes strongly correlated with macrophages geneset expression in the same tissue. Particularly, pro-tumor macrophages CD163 gene expression strongly correlated with mesenchymal markers ZEB1, Vimentin (VIM) and N-cadherin, which was further confirm by IHC. To functionally demonstrate that macrophages promote EMT in EAC cells we performed in vitro coculture experiments. Macrophages and EAC cells were then brought to a single-cell suspension, mixed in a 5:1 macrophage:EAC cells ratio, and cultured in Matrigel for 5 days. Macrophage-induced EMT was determined by multicolor flow cytometry. Anti-tumor M1 macrophages promoted an epithelial phenotype (increased E-cadh and EpCAM expression in EAC cells) whereas pro-tumor M2 macrophages strongly induced a mesenchymal phenotype (increased N-cadh and CXCR4 expression in EAC cells). Furthermore, preventing lactate transport (using Syrosingopine and AZD3965) and glutaminolysis (with Telaglenastat) prevented pro-tumor macrophage-mediated reduction in E-cadherin in in EAC organoids. Combined, these data shows that inhibiting macrophage metabolism impairs macrophage-mediated EMT. This has the potential to enhance the effect of currently used treatments and improve the outcome of esophageal cancer therapy.