Medical University of Graz

Role of TGF-b ligand signaling in DC-dependent immuno-regulation in lung cancer

Summary

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Supervisors:	Prof. Dr. Herbert Strobl Dr. Anna Birnhuber
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between March 24, 2021 00:00 and May 05, 2021 23:59 (Europe/Zurich)

Description

Background: The transforming growth factor beta (TGF-b) family comprises a group of structurally related proteins that include among others TGF-b1/2/3 and several bone morphogenetic proteins (BMPs). The expression of these proteins is tightly regulated during development and tissue homeostasis. Environment-exposed epithelial layers of barrier tissues such as skin and oral mucosa exhibit specific expression pattern of TGF-b1 and BMP7 in the steady-state. We recently showed that BMP7 expression is strongly upregulated within the epidermis in psoriatic lesions. Two separate signaling cascades involving a limited number of type 1 and type 2 receptors as well as intracellular SMAD proteins are known, i.e. canonical TGF-b versus BMP signaling. We recently observed in unpublished studies that BMP7 stimulation of human monocyte-derived DCs leads to the up-regulation of PDL1 and PDL2. These molecules have previously implicated in DC-dependent T cell regulation. Moreover, we observed the induction of AXL a TAM receptor involved in efferocytosis and negative regulation of microbial DC activation. Targeting of the PDL1/PD1 interaction proofed to be an efficient treatment strategy for non small cell lung cancer (NSCLC) patients. It was recently shown that BMP7 expression by NSCLC cells is negatively correlated with treatment outcome.

Hypothesis and Objectives: We hypothesize that (1) enhanced BMP signaling in NSCLC instructs tumor-infiltrating DCs to acquire PDL1, PDL2 and AXL resulting in an augmented immunoregulatory capacity of DCs; (2) ligands of BMP receptors expressed in the tumor microenvironment instruct cells of the monocyte/DC lineage to acquire a tolerogenic phenotype potentially leading to tumor immune escape; (3) differential expression of TGF-b ligands and their receptors within the NSCLC tumor microenvironment lead to altered signal strength via the classical TGF-b vs BMP signaling cascades in tumor-infiltrating leukocytes of the monocyte/DC lineage.

Methodology: The PhD student will perform immunohistology stainings of primary NSLC tumors for BMP7 and other TGF-b ligands, as well as downstream signaling proteins. Singe cell suspensions of tumor tissues versus non-affected lung tissue will be analyzed by FACS for DC associated molecules (PDL1, PDL2, AXL, others). Additionally available single cell RNA sequ data will be analyzed. In parallel, monocyte-derived DCs and progenitor cell-derived DCs will be stiumulated with TGF-b ligands and the signaling pathways leading to PDL1/2 and AXL induction will be dissected (**Year 1**). T cell assays (Treg, Th1/2/17) will be performed and the role of PDL1/PDL2 and AXL in these assays will be evaluated using inhibitor or knock-down strategies. Tumor infiltrating monocytic cells/DCs and T cells from NSLC patients expressing high and low levels of BMP7 and/or other TGF-b ligands and will be studied phenotypically and functionally (**Year 2**). Already available mice lacking BMPR1a in $CD11c^{+}$ cells will be analyzed, i.e. lung tumor model, steady-state lung, towards obtaining correlative in vivo data (**Year 3-4**).

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