Functional characterization of tumor-associated neutrophils (TANs) in lung cancer progression and metastasis

Summary

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Supervisor: Prof. Dr. Akos Heinemann
Availability: This position has been occupied.
Offered by: Medical University of Graz
Application deadline: Applications are accepted between August 02, 2017 00:00 and September 17, 2017 23:59 (CEST)

Description

Background:
The accumulation of genetic alterations and the loss of normal cellular regulatory processes will lead to the development of cancer, a heterogeneous disease characterized by histologic subtypes and mutational landscapes. More recently the field has realized that a large proportion of cells within the tumor microenvironment (TME) are non-cancerous cells, including fibroblasts and immune cells leading to the development of immune-based therapies. Lung cancer is the leading cause of cancer deaths worldwide and kills more patients each year than does breast, colon, prostate and pancreas cancer, combined. Non-small cell lung cancer (NSCLC), comprises mainly of lung adenocarcinoma (L-ADCA) and lung squamous cell carcinoma (L-SCCA), representing ~80% of all lung cancer cases. Although surgical intervention for early stage NSCLC can be curative, traditional chemo- and radiotherapy, when required, are of limited effectiveness. Given the limited treatment options it is not surprising that initial success of immune therapies for NSCLC has created enthusiasm for these novel therapeutics. Unfortunately, just ~20% of NSCLC patients benefit from novel therapies and underlying mechanisms for treatment failure are mostly unknown. Immune checkpoint inhibitor therapy, e.g anti-PD1/anti-PDL1 antibodies, likely fails for one of two fundamental reasons: (1) an antigen-driven immune response is not present or (2) an antigen-driven immune response is present, but one or more immune suppressive factors reside within the tumour microenvironment (TME) that function to derail an otherwise effective immune response. This highlights the need to identify additional immune suppressive factors located within the TME that when targeted, would improve the efficacy of immune checkpoint blockade.

Hypothesis and Objectives:
Several recent studies have shown the important role of neutrophils in cancer and our hypothesis that tumor-associated neutrophils (TANs) act as immune suppressive entity in the TME is largely based on two recent studies. (1) Gentles and colleagues showed that the neutrophil gene signature predicts mortality better than any other immune cell signature in a cohort of >18000 patients encompassing 25 different cancer types (Gentles et al., 2015). (2) Our group demonstrated in a cohort of 73 NSCLC patients that neutrophils are the most prevalent immune cell type present in NSCLC and have identified that neutrophils constrain antigen-driven immune responses in tumor, but not in non-adjacent lung tissue, strongly suggesting that this is a tumor-specific phenomenon (Kargl et al., 2017).

The purpose of this study is to (1) identify lymphocyte suppressive TAN subpopulations present in the TME in primary tumor and metastasis and (2) to elucidate the mechanism by which they get recruited into the TME, (3) inhibit lymphocyte function and limit immune checkpoint inhibitor efficacy. Further, we will analyze (4) the role of TAN subpopulations on tumor cells in the TME.

Methodology:
The PhD candidate will characterize TANs using flow cytometry, next-generation sequencing and multiplex fluorescence microscopy. Functional analysis of neutrophils will be investigated in assays of shape change, chemotaxis and Ca\(^{2+}\) signaling and levels of neutrophil specific enzymes will be assessed by ELISA and western blots. Lymphocyte/neutrophil and tumor cell/neutrophil interactions will be studied using co-culture systems. In this study, we will make use of established human non-small cell lung cancer cell lines, tumor tissue from consented patients and mouse models.

References:


Co-supervision and Cooperations:
Julia Kargl, Institute of Experimental and Clinical Pharmacology, Meduni Graz
Horst Olschewski, Division of Pulmonology, Meduni Graz
Grazyna Kwapiszewska & Andrea Olschewski, LBI for Lung Vascular Research, Graz

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