Medical University of Graz

The role of neutrophil-derived myeloperoxidase (MPO) in non-small cell lung cancer metastasis

Summary

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Supervisors:	Julia Kargl Dr. Luka Brcic
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: We have previously demonstrated that neutrophils are a prevalent immune cell type present in non-small cell lung cancer (NSCLC). Myeloperoxidase (MPO) is a peroxidase enzyme that generates reactive oxygen/nitrogen species and is most abundantly expressed in neutrophils. Upon neutrophil activation, during acute inflammation or in the tumor microenvironment (TME), MPO is secreted into the extracellular milieu during degranulation and utilizes H_2O_2 to hypochlorous acid that reacts with surrounding proteins and cell surface molecules and thereby can alter signaling pathways and cell function.

Epithelial-mesenchymal transition (EMT) is a fundamental event for primary tumors to metastasize to distant sites. Altered gene and protein expression causes changes in cell morphology and behavior, resulting in the loss of attachment to neighboring cells, intravasation, and migration into distant tissue. However, the entities residing within the TME that drive EMT are poorly understood.

Hypothesis and Objectives: The aim of this study is to identify neutrophil-derived molecules in the TME that affect tumor cell dissemination. We hypothesize that MPO, expressed and released by tumor-associated neutrophils, is such a molecule. Preliminary data in our lab suggest that MPO is capable of entering tumor cells and can alter tumor cell signaling and phenotype. Preliminary mouse experiments revealed reduced primary tumor burden and altered metastatic burden in the absence of MPO. Taken together, these preliminary data suggest a novel aspect of MPO in primary tumor growth and metastasis formation and form the rational to study MPO as a driver of EMT in NSCLC. Understanding the role of neutrophils and MPO in the TME and its role in metastasis may be a crucial step towards the potential clinical use of MPO inhibitors in lung cancer patients.

Methodology: The PhD candidate will investigate the mechanism by which MPO affects EMT using lung cancer cell lines *in vitro* (cell signaling, proliferation, migration, invasion and EMT marker expression and phenotype). Further, transplantable tumor models and a LSL-K-ras model of lung adenocarcinoma in the setting of p53 deficiency, a well-established lung cancer mouse model to study metastasis ($Kras^{LSL\text{-}G12D}/Trp53^{fl/fl}/MPO^{-/-}$) will be used (Years 1-2). Mouse tumor tissue analysis includes immunohistochemistry, multiplex fluorescence microscopy, flow cytometry, and gene and protein expression analysis (Year 2-3). Furthermore, we will make use of NSCLC primary tumor and metastasis tissue from consented patients to validate our *in vitro* and *in vivo* findings (Year 4).

References:

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