Medical University of Graz

LipoIMMUNE, Impact of Monoglyceride Lipase on the tumor microenvironment

Summary

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Supervisors:	Prof. Dr. Gerald Höfler Dr. Paul Vesely
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:

Monoglyceride lipase (MGL) is the rate-limiting enzyme for monoglyceride (MG) hydrolysis. 2-arachidonylglycerol (2-AG), one of the most prominent MGs, acts as an endocannabinoid receptor (CBR) agonist, systemically inhibiting pain- and inflammation. MGL, however, hydrolyzes 2-AG yielding glycerol and arachidonic acid (AA). Thereby, MGL limits the anti-inflammatory capacity of the endocannabinoid (EC)-system and at the same time, provides AA the precursor for eicosanoid- inflammation mediators [1]. In mice, systemic knockout (KO) of MGL increases the incidence of lung adenocarcinoma. Similarly, MGL deficiency impairs anti tumorigenic functions of the tumor microenvironment (TME): CBR-2 dependent activation of tumor associated macrophages (TAMs) promotes tumor growth through suppression of tumor cell toxic CD8+ T-cells. Conversely, in tumor cells, MGL promotes a fatty acid network of signaling lipids. These include lysophospholipids, ether lipids, phosphatidic acid and prostaglandin E2, favoring cell migration, invasion, survival, and tumor growth [2-8]. Focusing on lipolytic enzymes in cancer biology, we observed that tumor cell specific MGL-KO reduced lung tumor load and density of TAM infiltrates.

Hypothesis and Objectives:

MGL shows context dependent pro- or anti- cancerogenic activities. (i) It promotes oncogenic lipid signaling in tumor cells. (ii) It regulates the anti-tumor immune response via the EC system, and (iii) provides AA for production of immune modulatory eicosanoids. Hence, we hypothesize that **MGL shows tumor promoting or suppressive functions, depending on its interaction with the TME.**

Methodology:

The conditional pRb/p53 knockout (Rbp53)[9] and conditional KRASG12D (LSL-KRAS)[10] lung cancer mouse models will be applied. Mice with pulmonary activated LSL-KRAS show substantially denser TAM infiltrates than those with Rbp53[9]. Comparison of these two models should enable us to understand if the diverse roles of MGL in cancer biology can be explained by tumor specific TME. The prospective PhD student will (i) establish Rbp53 and LSL-KRAS mouse lines with conditional or complete lack of MGL (ii) analyze tumors and TMEs of each tumor model (iii) perform mechanistical studies to understand interaction of tumor cells and their TME. In the **year 1**, the PhD student will establish experimental cancer models. An MGL-ko line and a conditional MGL-ko (MGL-flox) line are crossbred with either Rbp53 or LSL-KRAS mice. The resulting lines will allow us to test the impact of tumor cell specific or systemic MGL-KO in the two different tumor models. In the **year 2-3**, the student will induce experimental lung cancer through inhalation of CRE expressing adenoviruses in each of the established lines. Additionally, diverse patient derived lung cancer samples (tumor and TME) will be assessed by immunohistochemistry and by flow cytometry analyses. The student will also apply standard techniques including qRT-PCR, in situ RNA hybridization, western immunoblotting and lipase activity measurements with 14C labeled lipid substrates. Mass spectrometric lipid analyses will be performed at the lipid core of the Medical University of Graz. Cytokine and chemokine analyses will be performed using ELISA assays and, using the Bio-Plex 200 at the MUG cytometric flow core. In the **year 3-4**, the student will test if pharmacological interventions in MGL metabolism can ameliorate tumor growth and aggressiveness.

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Collaborations within the RESPImmun programme: H.Olschewski will provide patient derived BAL samples, J. Kargl and K. Leithner will train the student in fluorescence aided cell sorting techniques and collaborate with us assessing the immunological TME and its interactions with the tumor cells. L. Marsh will support the project with his immune cell expertise.

References:

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