Myeloid hypoxia in tumor progression
Miloš Gojković, Pedro Veliça, Gabriella Darmasaputra, Helene Rundqvist, Randall Johnson
Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden

Introduction
The cells of the immune system have to be able to exert their functions in areas of low oxygen tension. In macrophages, functions such as phagocytosis, migration and antigen presentation has been shown to be partly dependent on HIF-1 activation. Knocking out HIF-1 in macrophages leads to decreased infiltration, activation and bacterial killing, as well as decreased cancer progression and growth in the MMTV-PyMT mouse model of breast cancer. However, the effects of increased HIF-1 expression and activity in myeloid cells is not fully understood.

Our aim
To understand the role of overexpressed HIF in myeloid cells and how it affects tumor biology.

Methods
In this study, we used LysM driven Cre to delete VHL gene in myeloid cells, in order to remove the regulation of HIFs. The tumor growth was then studied using the MMTV-PyMT mouse model of breast cancer. Our results show that:
- Knocking out VHL under the LysM promoter increases the lung permeability.
- Increased presence of CD45+ cells in alveolar compartment and expression of CD11b.
- The primary tumor growth is not affected by the KO.
- Metastatic establishment shows conflicting results in different models.

Our results show that:
- Increased permeability of lung endothelium to the alveolar compartment.
- Increased number of alveolar CD45+ positive cells.

Conclusions
Deletion of VHL under the LysM promoter resulted in increased pulmonary permeability and signs of inflammation.
Loss of myeloid VHL does not affect primary tumor growth.
Different results were found in different models of metastatic establishment.
A spontaneous model of metastasis is needed to conclude the nature of myeloid hypoxia in metastatic establishment.

Future studies
Determination of metastatic burden VHL LysM + PyMT mice.
Studying the role of myeloid hypoxia in different cancer treatments:
- Exploring how observed phenotypes may effect efficiency of chemotherapy, adaptive T-cell transfer and checkpoint blockade.
- Finding the route of permeability:
The vessel permeability could be both para-cellular or trans-cellular, which is not distinguished by the Evans blue assay.

VHL is essential in Oxygen Dependent regulations of Hypoxia Induced Factors

Myeloid VHL Deletion results in a VEGF independent increase in lung permeability
Evans blue assay showed increased permeability of lung endothelium to the alveolar compartment.
The permeability is specific for the lung

Myeloid VHL Deletion does not affect primary tumor growth
No difference in growth of spontaneous mammary carcinoma...

Myeloid VHL Deletion results in increased level of Arginase-1 expression and activity
Arg-1 is increased in macrophages

Arg-1 positive cells are present within metastatic fold of VHL LysM mice

©2020 Milos Gojkovic
Milos Gojkovic
PhD Student • CMB
Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden
Phone: 0468 5248 7313
milos.gojkovic@ki.se