SCIENCES & BIOENGINEERING SCIENCES

The Research Group

Cellular and Molecular Immunology

has the honor to invite you to the public defense of the PhD thesis of

ir. Xenia Geeraerts

to obtain the degree of Doctor of Bioengineering Sciences

Title of the PhD thesis:
Metabolic characterization of tumor-associated macrophage subsets

Promotor:
Prof. dr. ir. Jo Van Ginderachter (VUB)
Co-promotor:
Prof. dr. Sarah-Maria Fendt (KULeuven)

The defense will take place on
Monday, January 10, 2022 at 16h30 in auditorium D.0.03

Due to COVID-19measures, the capacity to physically assist the event at the Campus of Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2, 1050 Elsene, will be limited. The defense can also be followed through a live stream. Contact xenia.geeraerts@vub.be for more information.

Members of the jury

Prof. dr. ir. Jan Steyaert (VUB, chair)
Prof. dr. ir. Frederic Leroy (VUB, secretary)
Prof. dr. Cleo Goyvaerts (VUB)
Prof. dr. Massimiliano Mazzone (KULeuven)
Prof. dr. Olivier Feron (UCL)

Curriculum vitae

Xenia Geeraerts obtained her Master degree in Bioengineering Sciences: Cell and Gene Biotechnology in 2014 at the Vrije Universiteit Brussel. Immediately after she started her PhD within the lab of Prof. dr. ir. Jo Van Ginderachter (Cellular and Molecular Immunology, VUB), funded at first with the financial support of a VUB OZR grant and from October 2015 onward with a "For Women in Science" PhD Fellowship from the Research Foundation – Flanders (FWO-Vlaanderen) and L-Oréal-UNESCO. She participated and presented her work at different (inter)national conferences and symposia. Xenia Geeraerts is co-author of seven scientific papers published in peer-reviewed international journals, among which two times as a first author. She received the "VIrBr award for best master thesis – category Bioengineering Sciences" in 2014 and the "NSABS Best Oral Presentation" award in 2018. Finally, she guided and supervised one master and two bachelor thesis students.

Abstract of the PhD research

Cancer is a leading cause of death worldwide. Since years, cancer therapy has focused on methods which kill tumor cells. More recently, it has become clear that tumors are not a mass of transformed cells but also comprise a large portion of non-transformed cells, including immune cells, which can influence tumor development. Therefore, cancer research is currently putting the focus on strategies that boost or restore our immune system in their battle against cancer cells, known as immunotherapy.

Tumor-associated macrophages (TAMs) are amongst the most abundant immune cells in the tumor and are associated with poor prognosis in many cancer types. They can contribute to tumor initiation and progression by promoting angiogenesis, cancer cell proliferation, invasion, metastasis and therapy-resistance. However, the role of TAMs in tumorigenesis is more complex, as they can vary from a tumor-killing M1-like to a tumor-promoting M2 phenotype. This heterogeneity is a consequence of macrophage plasticity in response to the diversity of signals they can be exposed to, especially in the complex and dynamic environment of a tumor. In line with that, previous work from our lab has reported the co-existence of antitumoral MHC-II^{hi} M1-like TAMs and protumoral MHC-II^{lo} M2-like TAMs within mouse lung carcinoma tumors. Whether these TAM subsets are metabolically distinct is currently unknown. Since a close connection between macrophage metabolism and function has been elucidated, the study of TAM metabolism has become an attractive field which potentially paves the way for strategies to repolarize protumoral TAMs into antitumoral counterparts.

In this PhD thesis, we aimed to unravel the metabolism of MHC-II^{hi} and MHC-II^{lo} TAMs upon isolation from subcutaneous mouse 3LL-R lung tumors. We demonstrate that protumoral MHC-II^{lo} TAMs show a higher oxidative and glycolytic metabolism, suggesting these cells to be metabolically highly active. In contrast, antitumoral MHC-II^{hi} TAMs possess lower overall metabolic activity which is partially driven by a reduced carbon flow through the TCA cycle as a consequence of a hampered conversion of metabolites. Tumor-infiltrating immune cells are exposed to a specific tumor microenvironment, characterized by limited nutrient and oxygen availability and the presence of oncometabolites released, amongst others, by cancer cells. As we found the oncometabolite lactate to be highly represented in mouse 3LL-R lung tumors, we assessed to which extend lactate leaves its mark on the metabolism and function of the TAM subsets that infiltrate these tumors. We found that both TAM subsets rapidly exchange lactate in high lactate conditions, however, only MHC-II^{lo} TAMs use lactate as an additional carbon source to support their oxidative metabolism. Meanwhile, MHC-II^{hi} TAMs do not tolerate lactate as well as it drastically lowers their metabolic activity. Moreover, our investigation revealed lactate not only as a metabolic, but also functional regulator which enhances the T cell-suppressive capacity of protumoral TAMs.

Given the involvement of TAMs in tumor promotion, these cells are considered as promising therapeutic targets. We believe our description of the metabolic heterogeneity of TAM subsets in lung carcinoma tumors will prove to be an exciting addition to the field of immunometabolism. Moreover, this works indicates lactate as an important metabolic and functional regulator of TAMs, suggesting the potential of interference with lactate metabolism for future therapeutic use and the implementation of immunotherapy in the fight against cancer.