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-IIlo M1-like TAMs and protumoral MHC-IIhi 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-IIlo and MHC-IIhi TAMs upon isolation from subcutaneous mouse 3LL-R lung tumors. We demonstrate that protumoral MHC-IIlo TAMs show a higher oxidative and glycolytic metabolism, suggesting these cells to be metabolically highly active. In contrast, antitumoral MHC-IIhi 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 extent 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 protumoral counterparts express a higher lactate transport 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 work 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.