

Over the last thirty years, the emergence of immunotherapies based on monoclonal antibodies (mAbs) has revolutionized the field of cancer treatment. mAbs target molecules that are overexpressed or exclusively present on malignant cells, thereby sparing healthy tissues and minimizing toxicity. One of the most successful advances in hematooncology is the development of anti-CD20 mAbs such as rituximab, which combined with chemotherapy leads to remission in 50-60% of patients with aggressive B-cell lymphomas. However, mAb-based immunotherapies often lead to the development of resistance characterized by poor prognosis and short survival time. So far, the phenomenon of resistance to rituximab and other mAbs has not been fully elucidated.

Efficient cancer eradication by mAbs is mediated by two complementary mechanisms – complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) involving natural killer (NK) cells. However, cancer cells repeatedly exposed to mAbs eventually become resistant to CDC. Our recent findings indicate that these cells as well acquire resistance to NK-cell mediated cytotoxicity, although they have never been in contact with these effector cells. Based on this observation, we hypothesize that mAbs induce phenotypic changes in malignant cells resulting in resistance not only to CDC, but also to NK cell-mediated ADCC. Interestingly, CDC and ADCC share a common feature – they both lead to cell death by inducing the formation of pores in the target cell membrane. In CDC, pore formation is mediated by membrane attack complex (MAC), whereas in ADCC by perforin. Since MAC and perforin belong to the same protein superfamily and play analogous roles in immune responses, we hypothesize that they may also interact with common inhibitors. Our preliminary data suggest that CD59 - a well-known inhibitor of MAC formation that is upregulated in CDC-resistant cells may also suppress the formation of perforin pores.

Therefore, the aim of this project is to elucidate the phenomenon of cross-resistance to both CDC and ADCC as this may help to enhance the understanding of the mechanisms responsible for the compromised activity of mAbs and consequently propose strategies to improve the efficacy of available immunotherapies or delineate novel treatment regimens for relapsed/refractory patients. Moreover, we will investigate the potential role of CD59 as a driver mediating CDC and ADCC to answer the question of its potential utility as a target for cancer immunotherapies.

In this project, using biological models reflecting the acquired resistance to mAbs widely used in hematooncology and novel models that will be generated in the course of this project, we intend to decipher the mechanisms of mutual impairment of complement- and NK cell-mediated cytotoxicity. By characterization of these models, we aim to identify common alterations responsible for the protection against CDC and ADCC.

Altogether, we believe that in this project we will unravel yet unknown mechanisms behind resistance to complement- and NK cell-mediated cytotoxicity, which will shed new light on the weaknesses of currently available therapeutic options and employ this knowledge for the benefit of devising more effective anti-tumor strategies.