Universität Basel

Research Project

Modulation of sialoglycans for cancer immunotherapy

Third-party funded project

Project title Modulation of sialoglycans for cancer immunotherapy
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Department
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The introduction of immune checkpoint inhibitors (ICI) into routine cancer therapy has changed the prognosis of cancer patients. Current ICI are blocking antibodies that target immune checkpoints including PD-1 and CTLA-4. ICI are the proof of principle that a dysfunctional immune system can be re-activated against an established tumor. However, only a minority of patients responds to the currently available ICI. New strategies to target additional pathways to reverse cancer-associated immune suppression are therefore needed.Others and my group within the Cancer Immunology Laboratory in Basel have defined a new adaptive, immunosuppressive pathway, the sialoglycan-Siglec-9 pathway that involves sialic-acid binding immunoglobulin-like lectin (Siglec) receptor 9 and upregulation of sialic acid-containing Siglec ligands (sialoglycans) in the tumor microenvironment. We have also recently described and upregulation of the inhibitory Siglec-9 receptor on tumor-infiltrating T cells.The general objective of this project is to delineate the role of Siglec receptors and Siglec ligands in adaptive anti-tumor immunity and to generate tools to target Siglec receptors and their ligands for cancer immunotherapy. First, we will elucidate Siglec signalling in tumor-infiltrating T cells. We will generate a defined Jurkat cell line overexpressing different Siglec receptor variants to elucidate their downstream signaling. To further understand signaling and pathways influenced by inhibitory Siglec receptors on tumor-infiltrating T cells, we will use these defined cell lines to perform an unbiased proteomic analysis. These findings will help to understand how Siglec-9 inhibits T cell function in cancer. Second, we will study the role of Siglecs on dendritic cells in anti-tumor immunity and also autoimmunity with new mouse models. We will perform multicolor flow cytometric analysis on non-small cell lung cancer, colorectal cancer, and epithelial ovarian cancer samples as well as tumor-draining lymph nodes to characterize Siglec expression on human dendritic cells in cancer patients. In addition, we will use genetic mouse models to study the function of Siglecs on dendritic cells in cancer and autoimmunity. Finally, in collaboration with Carolyn Bertozzi at Stanford, agents that target Siglec receptors and their ligands in cancer will be developed. Already established preclinical models will be used for combination immunotherapy regimens together with established ICI and mechanisms of anti-tumor immune activation will be studied in vivo.With the proposed research project, we will improve our understanding for the role of the Siglec-sialoglycan immunosuppressive pathway in cancer patients. We have produced a set of tools for in vitro and in vivo studies of the sialoglycan-Siglec pathway that will significantly move potential compounds further in the preclinical and hopefully into future clinical development. Our findings will be highly relevant to translate the basic scientific findings into clinically active drugs that will help cancer patients, synergize with ICI and improve current cancer immunotherapies.

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