Cancer Immunotherapy

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Improving cancer immunotherapy

Our main goal is to improve immunotherapy for cancer patients by using translational *in vitro* and *in vivo* tumor models, performing correlative analysis of patients treated with immunotherapy and conducting early clinical interventional trials (also see link to Medical Oncology).
One of our research foci is on the role of glycans and glycan-binding receptors in anti-cancer immunity. Glycans can mediate important interactions with immune cells and manipulation of glycans and glycan-binding receptors (lectins) bear a great potential to improve anti-tumor immune reactions. Glycan-mediated interactions in cancer immunology are significantly underexplored and could be used to improve anti-cancer immunity. Our group has studied the interaction between glycans that contain sialic acids (siaologlycans) and their interaction with Siglec receptors on immune cells and have demonstrated that this pathway can be targeted to augment T cell stimulation and tumor control. Current goals include improvement of cancer immunotherapy by modifying glycans in the tumor microenvironment and glycans of cellular products for adoptive cell therapies including genetically modified T cells.
An additional focus of our group is the improvement of immune checkpoint blockade and adoptive cellular therapies by investigating mechanisms and patterns of resistance to these therapies. To this end, we are investigating the tumor microenvironment as well as circulating immune cells in patients undergoing immune checkpoint blockade or adoptive T cell transfer. Identified pathways are further studied in the laboratory for their potential as new targets to improve antitumor immune responses.

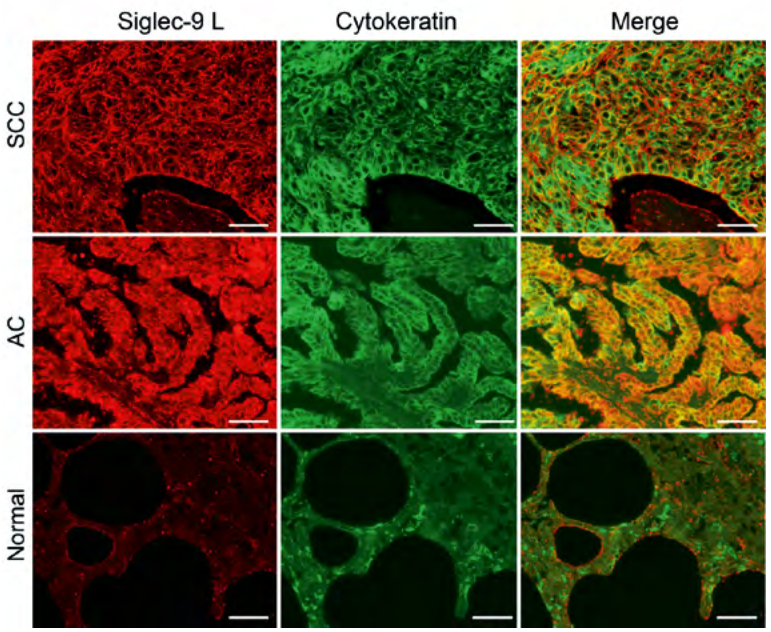

Fig. 1: Upregulation of Siglec-9 ligands in non-small cell lung cancer.
Squamous cell carcinoma (SCC), adenocarcinoma (AC) or normal lung tissue was stained with Siglec-9-Fc proteins (red) to detect Siglec-9 ligands and merged with cytokeratin staining to identify carcinoma cells. Siglec-9 ligands were found to be more often found in tumor tissue compared to normal tissue (from Stanczak *et al.,* J Clin Invest 2018).

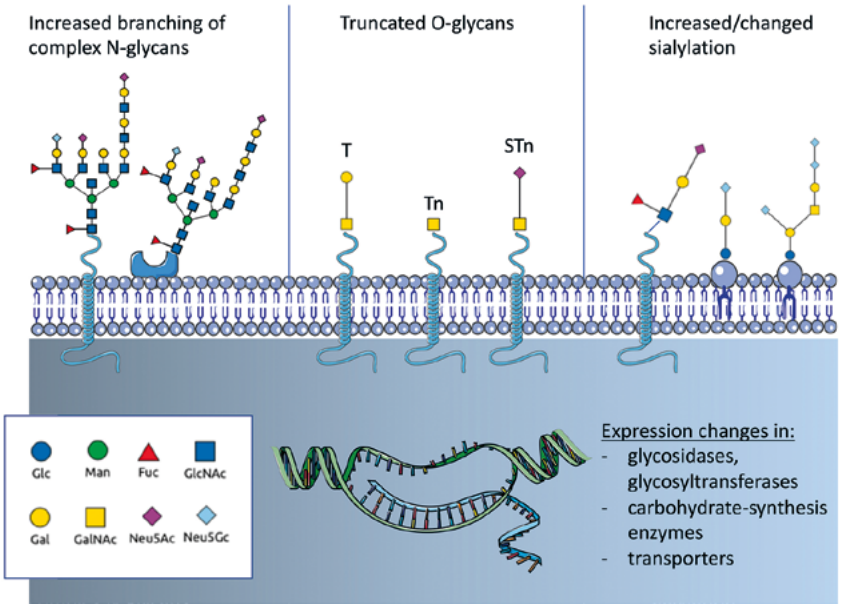

Fig. 3: Changes occurring in cancer-associated glycans.
Three main changes can be found in cancer that are regulated by genetic or epigenetic alterations in genes of glycan-modifying enzymes or enzymes involved in carbohydrate biosynthesis. N-glycans show often an increased branching due to increased MGAT5 expression. Another often observed change is the truncation of O-glycans and the exposure of new TACA including the T antigen, Tn antigen and the sialyl-Tn antigen (STn). In addition, changes of sialylation of both glycoproteins and glycolipids can be observed. Increased sialylation (hypersialylation) is often observed. The introduction of the non-human sialic acid Neu5Gc can also be observed. Glc, glucose; Man, mannose; Fuc, fucose; GlcNAc, N-acetyl-glucosamine; Gal, galactose; GalNAc, N-acetyl-galactosamine; N-acetyl-neuraminic acid; Neu5Gc, N-glycosyl-neuraminic acid (from Mantuano *et al.,* J Immunother Cancer 2020).

Selected Publications

Mantuano NR, Stanczak MA, de Araújo Oliveira I, Kirchhammer N, Filardy A, Monaco G, Christian Santos R, Carlos Fonseca A, Fontes M, de Souza Bastos Jr C, *et al.* (2020). Hyperglycemia enhances cancer immune evasion by inducing alternative macrophage polarization through increased O-GlcNAcylation. Cancer Immunol Res, 8, 1262–1272.

Gray MA, Stanczak MA, Mantuano NR, Xiao H, Pijnenborg JFA, Malaker SA, Weidenbacher PA, Tanzo JT, Ahn G, Woods EC, *et al.* (2020). Targeted desialylation overcomes glyco-immune checkpoints and potentiates the anticancer immune response *in vivo*. Nat Chem Biol, online ahead of print.

Trefny MP, Rothschild SI, Uhlenbrock F, Rieder D, Kasenda B, Stanczak MA, Berner F, Kashyap AS, Kaiser M, Herzig P, *et al.* (2019). A Variant of a Killer Cell Immunoglobulin-like Receptor Is Associated with Resistance to PD-1 Blockade in Lung Cancer. Clin Cancer Res 25, 3026–3034.

Adams OJ, Stanczak MA, von Gunten S and Läubli H (2018). Targeting sialic acid-Siglec interactions to reverse immune suppression in cancer. Glycobiology 28, 640–647.

Stanczak MA, Siddiqui SS, Trefny MP, Thommen DS, Boligan KF, von Gunten S, Tzankov A, Tietze L, Lardinois D, Heinzelmann-Schwarz V *et al.* (2018). Self-associated molecular patterns mediate cancer immune evasion by engaging Siglecs on T cells. J Clin Invest.

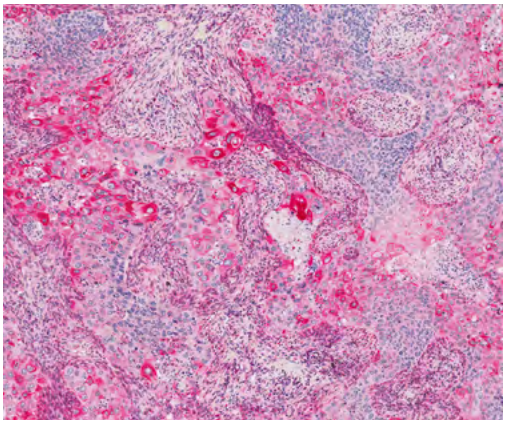

Fig. 2: HLA-F as a ligand for KIR3DS is present in lung cancer patients resistant to PD-1 blockade.
Immunohistochemical staining of lung adenocarcinoma tissue (form Trefny *et al.,* Clin Cancer Res 2019).compared to normal tissue (from Trefny *et al.,* Clin Cancer Res 2019).

Connection to Clinical Practice

Alfred Zippelius, Frank Stenner, Jakob Passweg
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Adoptive cell therapy for solid cancers

Adoptive cell therapy with TILs (tumor-infiltrating lymphocytes) for melanoma patients have been developed several years ago at the NIH. Clinical trials have shown high and very encouraging response rates depending on the stage and selection of patients. We have established and expansion protocol for the treatment of melanoma patient refractory to standard immune therapy with checkpoint inhibitors (and BRAF/MEK inhibition in BRAF mutated patients).

Our first planned clinical trial just recently started and will recruit patients. It includes an adapted classical expansion protocol and the application of IL-2 after the adoptive TIL transfer. In addition, we will perform a PD-1 blockade after stopping IL-2 treatment to render the tumor microenvironment more permissive for tumor-attacking T cells.

Our program will enable us to expand this treatment option to other tumor types. In addition, we are working to improve the expansion protocols and the specific expansion of tumor- recognizing T cells. Finally, the program will also allow for a direct translation of new genitically- modified T cell therapies into early clincical trials.