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Immune Cell Profiling of Colorectal Cancers:

Unravelling the Connection to Treatment Responses

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal, Å Göransson, Medicinaregatan 11, den 14:e December, kl. 9.00.

av **Azar Rezapour**

Fakultetsopponent:
Professor Karin Leandersson
Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Liang, F. **Rezapour, A**. Szeponik, L. Alsén, S. Wettergren, Y. Bexe Lindskog, E. Quiding-Järbrink, M. Yrlid, U. Antigen Presenting Cells from Tumor and Colon of Colorectal Cancer Patients Are Distinct in Activation and Functional Status, but Comparably Responsive to Activated T Cells. *Cancers* 2021, 13, 5247. DOI:10.3390/ cancers13205247

II. **Rezapour, A.** Rydbeck, D. Byvald, F. Tasselius, V. Danielsson, G. Angenete, E. Yrlid, U. A Type I Interferon Footprint in Pre-Operative Biopsies Is an Independent Biomarker That in Combination with $CD8^+$ T Cell Quantification Can Improve the Prediction of Response to Neoadjuvant Treatment of Rectal Adenocarcinoma. *OncoImmunology* 2023; May10;12(1):2209473

III. **Rezapour, A.** Tasselius, V. Danielsson, G. Falk, P. Angenete, E. Yrlid, U. PD-1 levels and CD103+CD39- proportions among CD8 T cells as predictors of non-responders to neoadjuvant treatment of rectal cancer. (*Manuscript*)

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

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Unravelling the Connection to Treatment Responses

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Abstract

Understanding the interplay between tumor cells and the immune system holds the key to the development of more effective treatments for cancer patients. Therefore, we have emphasized our efforts on deciphering the intricacies of these interactions to pave for more effective therapeutic strategies. We observed that different microenvironments in tumor and adjacent colon tissues influence immune cell behavior differently. Notably, cells known as antigen-presenting cells within the tumor show different activation and functional status compared to those in the colon. Despite this, they react similarly when exposed to signals from activated T cells, immune cells responsible for attacking cancer cells.

The challenge remains in predicting how patients with rectal cancer will respond to treatments. Several studies have highlighted the potential of using tumor-infiltrating lymphocytes (TILs) as markers to predict treatment outcomes. An emerging predictive tool, the biopsy-adapted Immunoscore (IS_B), assesses TILs to forecast tumor regression. To enhance its accuracy, we used a method incorporating multiplex immunofluorescence. By focusing on certain T cell subsets and the expression of Myxovirus resistance protein A (MxA), a component indicative of anti-tumoral inflammation, this refined method provided a better predictive framework. Specifically, the presence of MxA^+ cells in the tumor stroma, combined with the density of $CD8^+$ T cells, offered improved predictions regarding patient with a complete response to neoadjuvant treatment i.e., no detectable rectal cancer after the chemoradiotherapy.

However, while TIL density and the presence of MxA-expressing cells provided insights regarding complete responders, our approach did not distinguish non-responders from treatment responders. A more nuanced approach revealed that non-responders had a higher proportion of a particular T-cell subset, $CD8^+CD103^+39^-$ present in the tumor but not in in paired rectal tissue prior to treatment. In addition, the non-responders exhibited a lower expression of PD-1 on TILs compared to responders, indicating an inadequate tumor microenvironment for immune cell activation. However, when T cells were stimulated *in vitro*, their responses were overall similar, regardless of how the tumor responded to the neoadjuvant treatment in the patient.

In conclusion, while tools like the IS_B offer predictive insights, refining these with multiparametric immune activity screens of the pre-operative biopsy can provide a more accurate picture of the patient's ensuing responses to neoadjuvant treatment. This has significant implications for patient stratification and could possibly lead to the development of more personalized treatment regimens of rectal cancers.

Keywords: Rectal cancer, tumor infiltrating T cells, MxA, Interferon type I, CD39, CD103, PD-1, cytokines, response to the treatment.

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