Unconventional T cells in colon adenocarcinomas

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13A, Göteborg

Fredagen den 2:e juni 2023, klockan 09:00

av **William Rodin**

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Avhandlingen baseras på följande delarbeten

I. Rodin, W. Szeponik, L. Rangelova, T. Sundström, P. Hogg, S. Wettergren, Y. Cosma, A. Bexe Lindskog, E. Quiding Järbrink, M. **Tumour-infiltrating non-Vδ1Vδ2 γδ T cells have tumour-promoting functions in humans.** *Manuscript*

II. Rodin, W. Sundström, P. Ahlmanner, F. Szeponik, L. Kajetan Zajt, K. Wettergren, Y. Bexe Lindskog, E. Quiding Järbrink, M. **Exhaustion in tumour-infiltrating Mucosal-Associated Invariant T (MAIT) cells from colon cancer patients.**
Cancer Immunology and Immunotherapy 2021; 70(12): 1-15.

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III. Rodin, W. Verveda, A. Sundström, P. Hogg, S. Kajetan Zajt, K. Rangelova, T. Trajanoski, Z. Kristenson, L. Bergh Thóren, F. Wettergren, Y. Bexe Lindskog, E. Quiding Järbrink, M. **Tumour-infiltrating MAIT cells kill target cells by a granzyme B dependent mechanism.** *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

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Abstract

Many factors influence the initiation and growth of tumours. The infiltration and activity of immune cells in the tumour microenvironment are widely recognised as key factors affecting the clinical outcome of cancer. In this context, conventional T cells have been studied thoroughly but much less is known about the enigmatic populations of unconventional T cells. Of particular interest are the γδ and mucosal-associated invariant T (MAIT) cells as they, among other things, are (relatively) abundant in humans, possess the ability to recognise transformed host cells, and secrete cytokines, as well as cytotoxic effector proteins. The aim of this thesis was to investigate the potential role of unconventional T cells in the immune response to tumours and specifically if they possess the ability to kill tumour cells. We used tissue from colon tumours, unaffected colon mucosa, and blood from patients undergoing curative resection surgery at the Sahlgrenska University Hospital, along with blood samples from healthy blood donors, to investigate the phenotype and effector functions of MAIT and γδ T cells. We demonstrated that MAIT cells accumulate in colon tumours while γδ T cell infiltration is reduced. The γδ T cells present in colon tumours contained a subset of $V\delta1^{-}V\delta2^{-}$ cells with potential tumour-promoting properties. Furthermore, we showed that a portion of the tumour-infiltrating MAIT cells were functionally impaired and characterised by expression of PD-1 and Tim3. The $PD\text{-}1^{+}Tim3^{high}$ MAIT cells had a reduced capacity to produce cytokines and effector proteins, compared to their $PD\text{-}1^{-}Tim3^{-}$ counterparts. We also showed that these functionally impaired, or exhausted, MAIT cells could be partially re-activated in the presence of monoclonal antibodies towards PD-1 (Pembrolizumab). In a third study, we demonstrated that circulating and tumour-infiltrating MAIT cells from patients and circulating MAIT cells from healthy donors can be readily expanded in vitro. Expanded MAIT cells regardless of tissue origin were highly cytotoxic and effectively killed both epithelial cancer cell lines as well as primary tumour cells derived from colon cancer patients. Lastly, we also showed that the cytotoxicity of expanded MAIT cells was partly dependent on the activity of one or more serine proteases, as blocking the activity of all serine protease activity reduced the cytotoxicity of expanded MAIT cells.

In conclusion, this thesis highlights some of the complexities of γδ and MAIT cell responses in tumour immunity, but also that specific subsets, such as MAIT cells, can be expanded and potentially used as future treatments against colon cancer.

Keywords: Unconventional T cells, MAIT cells, γδ T cells, colorectal cancer, tumour immunity

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