# Natural killer T (NKT) lymphocytes regulate intestinal tumor immunity

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i rum 2118 – Hälsovetarbacken, Hus 2, Arvid Wallgrens backe, Göteborg

*Fredagen den 22 september 2017, klockan 09.00*

av **Ying Wang**

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**Avhandlingen baseras på följande delarbeten**

I. Wang Y, Sedimbi S, Löfbom L, Singh A K, Porcelli S A, and Cardell S L. **Unique invariant natural killer T cells promote intestinal polyps by suppressing TH1 immunity and promoting regulatory T cells.** *Mucosal Immunology*. doi: 10.1038/mi.2017.34

II. Wang Y, Sedimbi S, Löfbom L, Porcelli S A, and Cardell S L. **Modulation of intestinal polyp development by natural killer (NK) T cell directed immunotherapy.** *Manuscript.*

III. Wang Y, Löfbom L, Porcelli S A, Yagita H, and Cardell S L. **Natural killer T cell agonist and PD-1 blockade cooperate to reduce intestinal tumor development**. *Manuscript.*

**SAHLGRENSKA AKADEMIN**
**INSTITUTIONEN FÖR BIOMEDICIN**

GÖTEBORGS UNIVERSITET

# Natural killer T (NKT) lymphocytes regulate intestinal tumor immunity

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**Abstract**

CD1d-restricted natural killer T (NKT) lymphocytes are known as potent early regulatory cells of immune responses, acting as a bridge between innate and adaptive immunity. While invariant NKT (iNKT) cells have a protective role in many tumor models, their ability to promote intestinal inflammation, known to enhance intestinal cancer, raised the question if they would be protective in intestinal tumor development. In this thesis we aimed to define the regulatory role of iNKT lymphocytes in the immune response to intestinal tumors, and explore iNKT cell directed immunotherapy in this disease. In the first section we have investigated the natural regulation by iNKT cells of intestinal tumor formation. *Apc*$^{Min/+}$ mice were used as a mouse model for colorectal cancer (CRC) in these studies. By crossing *Apc*$^{Min/+}$ mice with two different iNKT cell deficient mouse strains, we demonstrated that the absence of iNKT cells markedly decreased the total number of intestinal polyps in *Apc*$^{Min/+}$ mice. Results from mechanistic studies suggest that iNKT cells promote intestinal polyps by enhancing the activity of regulatory T cells specifically in polyps, promoting a switch to a suppressive (M2) macrophage phenotype, and suppressing antitumor TH1 immunity. In the second section we performed preclinical therapeutic studies with different iNKT cell ligands to determine whether this treatment could subvert the tumor enhancing function of iNKT cells and result in suppressed tumor development. We demonstrate that iNKT cell directed immunotherapy prevented the tumor enhancing function of NKT cells leading to a reduction of tumor growth. Further, a treatment combining the iNKT ligand α-GalCer with PD-1/PD-L1/2 immune checkpoint blockade succeeded to further reduce polyp development.

In summary, this thesis demonstrates that iNKT cells naturally promote intestinal tumor development, by enhancing immunoregulation and suppressing TH1 anti-tumor immunity. In contrast, iNKT cell directed immunotherapy combined with immune checkpoint blockade led to a reduction of tumors. This prompts further exploration of iNKT cell directed immunotherapy in intestinal cancer.

**Keywords:** NKT lymphocyte, CD1d, intestinal tumor, colorectal cancer, immunoregulation, α-galactosylceramide, PD-1

ISBN: 978-91-629-0272-8 (PRINT)
ISBN: 978-91-629-0273-5 (PDF)