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# The Yin and Yang of Invariant Natural Killer T Cells in Tumor Immunity—Suppression of Tumor Immunity in the Intestine

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CD1d-restricted invariant natural killer T (iNKT) cells are known as early responding, potent regulatory cells of immune responses. Besides their established role in the regulation of inflammation and autoimmune disease, numerous studies have shown that iNKT cells have important functions in tumor immunosurveillance and control of tumor metastasis. Tumor-infiltrating T helper 1 (TH1)/cytotoxic T lymphocytes have been associated with a positive prognosis. However, inflammation has a dual role in cancer and chronic inflammation is believed to be a driving force in many cancers as exemplified in patients with inflammatory bowel disease that have an increased risk of colorectal cancer. Indeed, NKT cells promote intestinal inflammation in human ulcerative colitis, and the associated animal model, indicating that NKT cells may favor tumor development in intestinal tissue. In contrast to other cancers, recent data from animal models suggest that iNKT cells promote tumor formation in the intestine by supporting an immunoregulatory tumor microenvironment and suppressing TH1 antitumor immunity. Here, we review the role of iNKT cells in suppression of tumor immunity in light of iNKT-cell regulation of intestinal inflammation. We also discuss suppression of immunity in other situations as well as factors that may influence whether iNKT cells have a protective or an immunosuppressive and tumor-promoting role in tumor immunity.

**Keywords: natural killer T cells, CD1d, tumor immunity, immunosuppression, intestinal inflammation, intestinal polyposis**

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## INTRODUCTION

CD1d-restricted natural killer T (NKT) lymphocytes belong to a diverse group of non-conventional T cells that recognize non-peptide antigens. These T cells have some general features that distinguish them from conventional T cells that are activated by foreign peptides presented on MHC class-I and -II molecules (1, 2). Non-conventional T cells often have a memory/pre-activated phenotype and respond more rapidly to stimulation and can be activated in the absence of T-cell receptor (TCR) signals. They are generally not recirculating but preferentially localize to particular tissues and have a reduced TCR diversity compared with conventional T cells. These characteristics make

**Abbreviations:** AOM, azoxymethane; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; NKT, natural killer T; dNKT, NKT cell with diverse TCR; iNKT, NKT cell with invariant TCR; TCR, T-cell receptor; TH, T helper; TLR, toll-like receptor; Treg, regulatory T.

non-conventional T cells rapid responders to infection, inflammatory signals, and tissue damage and enable them to regulate the quality and quantity of immune responses. Recent progress in our understanding of the activation and function of these cells has led to an increased appreciation of their role in health and disease. The evolutionary conservation of CD1d and NKT cells between mouse and humans, and the essentially non-polymorphic nature of CD1d, has made the CD1d-NKT-cell system attractive to explore for the development of targeted immunomodulation.

Natural killer T cells recognize lipid and glycolipid antigens of self or microbial origin presented on the MHC class-I-like CD1d molecule. The term "NKT cells" is now generally used synonymously with CD1d-restricted T cells that carry TCRαβ (3). This definition will be used here. NKT cells can be divided into two subsets based on the TCR expressed. The first is type I or invariant NKT (iNKT) cells. These display an invariant TCR α-chain (Vα14-Jα18 in the mouse, Vα24-Jα18 in humans) paired with TCR β-chains using a limited set of Vβ segments but diverse CDR3 (4–6). In contrast, type II or diverse NKT (dNKT) cells have diverse TCR (7–9). The relative roles of these NKT-cell subsets have been explored in mice lacking all NKT cells (*CD1d*$^{-/-}$ mice) and mice lacking only iNKT cells (*Jα18*$^{-/-}$ mice). Studies of iNKT cells have also been greatly facilitated by the use of CD1d multimers loaded with the iNKT-cell ligand α-galactosylceramide (αGalCer) (10) which detects essentially all iNKT cells with high specificity. In contrast, while the role of dNKT cells can be studied in TCR transgenic mice (11) and deduced from comparisons of *CD1d*$^{-/-}$ and *Jα18*$^{-/-}$ mice, there are no specific reagents that detect all dNKT cells. Thus, studies of dNKT cells are more challenging. From studies of animal models and humans, both subsets of NKT cells have been suggested to play a role in diverse immune settings including autoimmunity, immunity to infections, and tumor immunity. Sometimes the two subsets have a similar function, while in other immune responses they counteract each other (12, 13). Besides the division of NKT cells based on their TCR, different functional programs have been identified in iNKT cells (14). For example, the iNKT1, iNKT2, and iNKT17 subsets express distinct sets of transcription factors. This makes them poised for the production of certain cytokines analogous to the T helper (TH) 1, TH2, and TH17 conventional T-cell subsets and corresponding subsets of innate lymphoid cells. More recently, iNKT cells with immunosuppressive function have been described that do not fit into this classification, as discussed below (15–17).

The majority or data from animal models and inferred from studies of human cancers show that iNKT cells enhance TH1 tumor immunity and combat tumors. However, in some situations, iNKT cells have surprisingly have demonstrated the opposite effect and promoted tumor development (**Figure 1**) (17–19). A recent example of iNKT-cell promotion of tumors is from a spontaneous mouse model for human colon cancer (17). We recently demonstrated that deletion of iNKT cells in this model reduces spontaneous intestinal polyp formation by 75%. Here, we will discuss our findings in light of the role of iNKT cells in intestinal immunity and compare tumor models that demonstrate tumor suppressive and tumor-promoting effects of iNKT cells.

## NKT CELLS ENHANCING TUMOR IMMUNITY IN MANY MODELS

The potent role of iNKT cells in tumor immunosurveillance and suppression of tumor metastasis was demonstrated many years ago. The enhancement of tumor immunity by iNKT cells has been

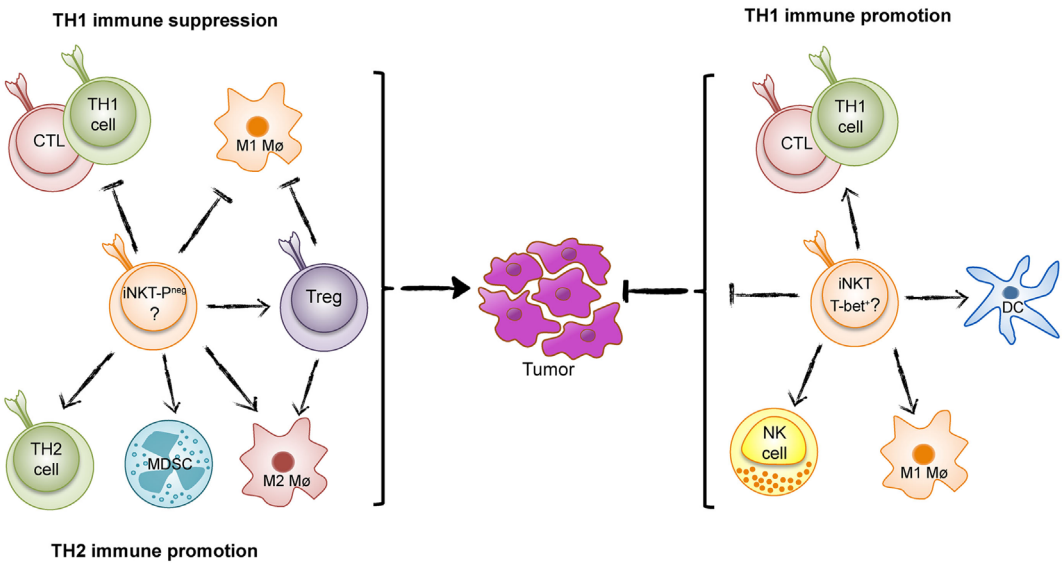


**FIGURE 1** | The Yin and Yang of invariant natural killer T (iNKT) cells in tumor immunity. iNKT cells can either suppress T helper 1 (TH1) tumor immunity and promote an immunosurveillance environment as found in intestinal polyposis (Yin, left) (PLZF-neg; PLZF-negative), or enhance TH1 immunity to tumors as found in many tumor models and inferred from studies of human cancer (Yang, right).

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