Switching Invariant Natural Killer T (iNKT) Cell Response from Anticancerous to Anti-Inflammatory Effect: Molecular Bases

Miniperspective

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Supporting Information

ABSTRACT: Since the discovery in 1995 of α-galactosylceramide 1 (α-GalCer), also known as KRN7000,1 hundreds of compounds have been synthesized in order to activate invariant natural killer T (iNKT) cells. Such keen interest for this lymphocyte cell type is due to its ability to produce different cytokines that bias the immune response toward a Th1 or Th2 profile. Thus, an understanding of the immune polarization mechanism via iNKT activation may pave the way toward new therapeutics in various domains including cancer and infectious and autoimmune diseases. In this review, we propose an up-to-date analysis of iNKT activators associated with a structure−activity relationship (SAR) study aimed at complementing available reviews by highlighting molecular bases for a selective immune response.

WHAT ARE iNKT CELLS?

Natural killer T cells (NKT) are a very versatile lymphocyte type able to influence both innate and adaptive immunity implicated in a broad range of pathological conditions, such as infections, autoimmunity, and cancer.2,3 NKT cells are roughly defined as lymphocytes that display properties of both T cells and NK cells, sharing surface markers of these two cell types, such as the T-cell antigen receptor (TCR) and NK cell receptors (NK1.1 in C57Bl/6 mice, CD161 in humans), and able to secrete large amounts of various cytokines or exert direct cytotoxic activities.4 Most importantly, NKT cells are sensitive to lipid antigens presented to their TCR in the context of major histocompatibility complex (MHC) class-I-like glycoproteins (for instance, CD1 molecules) expressed by antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells. NKT cells have been extensively characterized in humans and mice but have also been identified in other mammals.3

Mainly depending on the type of TCR they express, the nature of the MHC-presenting molecule and the lipid(s) they recognize, NKT cells can be divided into at least three groups. The most frequently studied group is made up of invariant NKT cells (iNKT, also referred to as type I NKT).5 While conventional T lymphocytes normally express a highly variable TCR responsible for recognition of the antigenic diversity of peptides, the main characteristic of iNKT cells is that they express a semi-invariant TCR recognizing lipid antigens.4 The common TCR is a heterodimer composed of two polypeptide chains, named α and β. Each chain is divided into a constant (C) domain and a variable (V) domain. The V domain, which harbors all TCR diversity, is generated from the somatic random rearrangement of various gene segments. V domains of the TCR α-chains arise from the random association of one Vα