

Effect of CD1d on NKT Cell Maturation with



Dale Godfrey, Associate Professor Dept. Microbiology and Immunology, University of Melbourne Parkville, VIC 3010, Australia
godfrey@unimelb.edu.au

What is known about CD1d?

Dale Godfrey: CD1d is a beta-2-microglobulin associated, MHC class I like molecule, that has a hydrophobic antigen binding groove, well suited to the presentation of lipid and glycolipid antigens. CD1d acts as a restriction molecule for a specialised subset of T cells known as NKT cells. For a review of CD1d and other CD1 family members, see (1).

How can CD1d-dependent NKT cells be defined?

Dale Godfrey: This is an important question and the answer has changed with our understanding of these cells. Early studies defined NKT cells as T cells (CD3/T cell receptor-bearing cells) that co-expressed NK family molecules, such as NK1.1 (2,3). Over the last few years it has become increasingly clear that this definition is inaccurate, because not all NK receptor bearing T cells are CD1d-dependent/restricted NKT cells, and not all CD1d-dependent/restricted NKT cells express NK receptors (4). Currently, the best way to define NKT cells is based upon their TCR specificity, using soluble CD1d tetrameric molecules, loaded with a defined glycolipid antigen (typically α -galactosylceramide) thought to be recognised by all, or at least most, NKT cells. These reagents work well in mice and humans, and the fact that mouse CD1d tetramers can bind human NKT cells and vice versa says a lot about the evolutionary conservation of the TCR specificity of these cells. Another way to identify NKT cells in humans is to use a combination of V α 24 and V β 11 specific monoclonal antibodies. Most cells that co-express these TCR molecules are NKT cells, and most NKT cells co-express these TCR molecules, however there may be some exceptions to this (5). Antibodies specific for the mouse TCR- α chain do not exist, so the only reliable method in mice is to use CD1d tetramer. For a detailed review about how to detect NKT cells, see (6).

Did the lack of CD1d affect the long-term survival of NKT cells?

Dale Godfrey: NKT cell development involves early intrathymic selection steps where these cells branch away from the mainstream T cell development pathway. The earliest NKT cells do not yet express NK receptors such as NK1.1, but these molecules are subsequently acquired through a process we refer to as NKT cell maturation (7-9). This can occur both within, and outside of the thymus. It is well-established that CD1d expression in mice is essential for the initial selection stages of NKT cell development, but it was unclear if CD1d expression was also important for subsequent maturation and survival of NKT cells in and outside of the thymus. We therefore allowed NKT cells to develop in a CD1d sufficient thymus, and using a variety of approaches, we tested the ability of these

cells to mature and survive after transfer to CD1d-deficient thymus or peripheral environments (10). We found that CD1d is necessary for ongoing NKT cell maturation, both within, and outside of the thymus, because in the absence of CD1d, NKT cells failed to fully upregulate NK1.1 expression (the hallmark of mature NKT cells). However, even after several weeks in CD1d deficient environment, NKT cells maintained an activated (CD69⁺) phenotype, survived and proliferated to the same extent as they did in a CD1d sufficient environment. Similar findings were also reported in a separate study (11). These findings indicate that CD1d is necessary for NKT cell maturation, but is dispensable for NKT cell homeostasis. These findings are consistent with earlier observations from two studies (11, 12). Taken together, it seems that CD1d is necessary for NKT cell maturation, but is dispensable for NKT cell homeostasis.

The role of CD1d-independent pathways?

Dale Godfrey: It is very likely that CD1d-independent factors regulate NKT cell homeostasis, for example IL15 and to a lesser extent, IL7, may control NKT cell numbers (12). The influence of CD1d independent pathways on NKT cell development and function is an interesting and important question. It is clear that NKT cells can respond to cytokines such as IL7, IL12, IL15 (2), but some studies have suggested that these factors work in conjunction with TCR stimulation (13). The relative importance of CD1d dependent and independent factors in NKT cell function remains unclear, but in normal circumstances where both are present, it seems likely that both will shape the NKT cell response. CD1d independent factors may work to drive the NKT cell response to antigenic stimulation toward either a Th1 or a Th2 type direction (14). For example, IL12 can enhance IFN γ production whereas IL7 can enhance IL4 production associated with NKT cell activation (reviewed in (2)). The influence of CD1d-independent factors will likely be important considerations in the design of future, NKT cell based therapies where the NKT cell response needs to work in the desired direction (i.e. enhanced or suppressed immune response) depending on the disease being treated.

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