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Innate Lymphocyte Effectors (Natural Killer, Natural Killer T and γδ T Cells) in Infection and Myocarditis

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1. Introduction

Myocarditis is defined as an inflammation of myocardium where the infiltrating leukocytes are intimately associated with cardiomyocyte necrosis or drop-out (Liu, 2005; Woodruff, 1980). Cardiac damage may be minimal and self-limiting or may result in chronic fibrosis and cardiac dysfunction leading to death in children and young adults (Eckart et al., 2004; Fabre, 2006; Solberg et al., 2010). As discussed in other chapters of this book, infections with a highly diverse group of viruses, bacteria, fungi, and worms have been implicated in infectious myocarditis (Friman et al., 1995). Enteroviruses and adenoviruses are usually considered as the predominant viral etiological agents, and are associated with approximately 80% of clinical myocarditis where a viral infection is documented. However, virtually any virus infection may initiate myocarditis (Bowles et al., 2003; Woodruff, 1980). While seasonal influenza virus is only a minor etiological agent in myocarditis, evidence from the most recent influenza H1N1 pandemic (Vila de Muga et al., 2010; Wiegand et al., 2010; Zheng et al., 2010) suggests a higher incidence of both mortality and morbidity, and accounts for 5% of complications in infected children (Zheng et al., 2010).

Myocardial injury results either directly from replication and induction of death or dysfunction in infected cardiocytes, or from host responses to infection (Huber, 2010). Although anti-viral host responses (innate or adaptive) are intended to control and eliminate the infection, cytokines and by-products such as nitric oxide or oxygen free radicals may also damage adjacent uninfected cells (Szalay et al., 2006). Innate immunity is the initial host response to infection and usually occurs within hours or days of virus introduction. The major characteristic of the innate response, besides its rapidity, is that it is broadly reactive to multiple infectious agents. While it is highly unlikely that innate immunity can completely eliminate the infection, it can suppress microbial replication until the far more potent and highly specific adaptive immune response kicks in. The reason for this is quite simple, viruses replicate rapidly with, for example, one picornavirus infected cell in tissue culture producing up to a million progeny virions within 18-24 hrs. In vivo, such rapid and uncontrolled growth could result in extensive tissue injury or death of the organism prior to a useful adaptive immune response being established since during a primary immune response, production of meaningful numbers of virus-specific T cells could

take 7-10 days after virus inoculation. The best known innate immunity results from microbial products binding to and activating Toll-Like Receptors (TLR) or RNA helicases (RIG-I and MDA-5) which activate transcription factors (NFkB) leading to expression of cytokines (TNFα, IL-1β and IL-6) and nitric oxide (Hosoi et al., 2004; Michelsen et al., 2004); or interferon response factors (IRF3/7) leading to expression of type 1 interferons (IFNα/β) RANTES and IP-10 (O'Neill, 2004; Vogel et al., 2003). These roles for TLR are discussed elsewhere. This review will concentrate on lymphocytes belonging to the innate immune response and discuss their role in myocarditis. These lymphocytes include natural killer (NK), natural killer T (NKT) and γδ T cells.

2. Natural killer cells

Natural killer (NK) cells are capable of distinguishing between infected/transformed cells and uninfected/non-transformed cells and are able to kill the former using perforin or granzyme dependent mechanism (Topham & Hewitt, 2009). The best recognized mechanism for NK cell activation is through Type 1 interferons (IFNα/β). Type 1 interferons upregulate multiple interferon response factors (IRFs) and two of these IRFs are strongly implicated in NK cell proliferation and activation (Taniguchi et al., 2001). NK cell numbers are dramatically reduced in IRF2-/- mice (Lohoff et al., 2000). NK cell numbers are also reduced in IRF1-/- mice but in this case, the defect is not inherent in the NK cell progenitor since adoptive transfer of IRF1-/- bone marrow into wild-type mice results in NK cell proliferation (Ogasawara et al., 1998). Rather, IRF-1 appears to control IL-15 expression in bone marrow stromal cells and IL-15 promotes NK cell generation. Similarly, other cytokines including IL-2, IL-12 and IL-18 promote NK cell responses (Agaugue et al., 2008). In contrast to IRF1, IRF2 is inherently important in the NK cell progenitor since adoptive transfer of IRF2-/- bone marrow into wild-type recipients fails to generate NK cells. How NK cells recognize aberrant cells has received substantial study since these effectors are non-T cells, lack the T cell receptor and CD3, and do not undergo genetic recombination of recognition receptors (Biron et al., 1999; Orange et al., 2002). NK cells express substantial numbers of both activating and inhibiting receptors (reviewed in (Lanier, 2008)), and despite lacking classical T cell receptors, NK cells can recognize microbial molecules. Examples include NKp46 recognition of the influenza hemagglutinin protein (Mandelboim et al., 2001), Ly49H recognition of m157 (mCMV) (Arase et al., 2002), NKp44/NKp46 recognition of NDV hemagglutinin-neuraminidase (Jarahian et al., 2009), and Ly49P recognition of m04 (mCMV) (Kielczewska et al., 2009). NK activation receptors pair with ITAM-bearing DAP12, FcεRI-γ and CD3-ζ signaling molecules. Stimulation of the NK activating receptors leads to phosphorylation of the ITAM components and recruitment of Syk and ZAP-70. This results in actin cytoskeletal reorganization, which promotes secretion of preformed cytokines. The cytokines primarily produced by NK cells are IFNγ/TNFα, or perforin/granzyme. Activation also increases transcription of cytokine genes. In contrast, inhibitory NK receptors are either monomeric type 1 glycoproteins of the immunoglobulin superfamily [examples include: killer cell immunoglobulin-like receptors (KIRs) and leukocyte immunoglobulin-like receptors (LILRs)] or type II glycoproteins containing a C-type lectin—like scaffold [examples include: Ly49 and CD94-NKG2A]. Both types of receptor contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their intracellular domains which, when activated, recruit tyrosine phosphatases that block the phosphorylation steps initiated by the NK activating receptors and thus inhibit NK cell functions (Lanier, 2008).

NK inhibitory receptors recognize major histocompatibility complex class I (MHC I) molecules which represents one mechanism by which NK cells distinguish between infected and normal cells, as many viruses attempt to evade the immune system through down-regulation of MHC molecules (Hewitt, 2003).

Evidence for a major role of NK cells in clinical myocarditis is rather weak. NK cells were not observed in heart tissue from 18 cases of biopsy proven myocarditis (Chow et al., 1989). Other studies have found either increased numbers of NK like cells in peripheral blood of dilated cardiomyopathy patients (Yokoyama, 1988) or diminution of NK cell activity in such patients (Maisch et al., 1985). Studies in patients with Chagas' disease find no alteration in NK cells early in the disease but an increase in these innate effectors occurs at later stages (Sathler-Avelar et al., 2003). One potential problem with clinical studies is that diagnosis of myocarditis or dilated cardiomyopathy is a relatively late event in the disease process and may be quite removed from the initiating acute infection (Woodruff, 1980). In fact, while viral genomic sequences can be detected in clinical heart biopsies for months and possibly for years, it is rare for infectious virus to be isolated from the hearts of myocarditis patients. Any role for NK cells may be over by the time human tissue is studied. The best evidence that NK cells might participate in viral myocarditis comes from mouse models. These studies indicate that NK cells are important in controlling coxsackievirus B infections in vivo (Gauntt et al., 1988; Gauntt et al., 1989; Vella & Festenstein, 1992) as depletion of these cells substantially increases virus titers in the heart or pancreas. The ability of NK cells to suppress virus infection may relate to their cytolytic activity to infected cardiocytes. Rapid elimination of infected cells before virus replication is complete would restrict the number of progeny virions produced and therefore limit the next cycle of infection. The second mechanism by which NK cells may help control virus infection is through either augmenting or accelerating the adaptive immune response to the virus. NK cells directly interact with both dendritic cells and activated T cells causing maturation of the dendritic cells and increased activation of the T cells (Zingoni et al., 2005). Interactions occur through up-regulation of OX40L on the NK cells and OX40 on activate CD4+ lymphocytes. Also, NK cells contain high concentration of pre-formed cytokines which can be rapidly released upon NK receptor engagement and these cytokines provide the environment necessary for optimal adaptive immunity development. As with the mouse model of CVB3 myocarditis, NK cells also control spread of Trypanosoma cruzi in the mouse model of Chagas' disease (Brener & Gazzinelli, 1997).

3. Natural killer T and γδ T cells

The other two major innate lymphocyte populations are natural killer T (NKT) and γδ T cells. NKT cells primarily recognize lipid antigens presented by CD1d molecules. The γδ T cells represent a more diverse population and in many cases, the antigen specificity of these cells is not known. However, as discussed below, the γδ T cells known to be involved in experimental viral myocarditis are also CD1d restricted. For this reason, description of the CD1 family of molecules is provided followed by discussion of the NKT and γδ T cells in innate immunity.

3.1 CD1 molecules and regulation of their expression

There are five distinct CD1 molecules, CD1a, CD1b, CD1c, CD1d and CD1e (Figure 1). Although these different molecules most likely arose from a single common ancestral gene

and are located as a cluster of genes on the same chromosome (De Libero & Mori, 2003), they share only approximately 30% homology and have distinct expression patterns and functional characteristics (Blumberg et al., 1995; Calabi et al., 1989; Kasmar et al., 2009). These proteins belong to a family of non-polymorphic, class I-like major histocompatibility complex (MHC) molecules (Boes et al., 2009). Humans express CD1a, CD1b, CD1c, CD1e (Group 1 CD1 molecules) and CD1d (Group 2 CD1 molecule). Mice express two isoforms of CD1d but lack any of the Group 1 CD1 molecules (Bradbury et al., 1990; Sugita et al., 1999). Other mammals express varying combinations of the different CD1 isoforms. For example, ruminants, such as cattle, express CD1a, three isoforms of CD1b and CD1e but lack either homologues of CD1c or CD1d (Van Rhijn et al., 2006). To date, all mammals have at least one CD1 molecule and a similar CD1-like molecule has been recently found in birds (Dvir et al., 2010). The wide distribution of CD1 expression among species underlines the importance of these molecules in immunity. A major difference between the non-classical CD1 molecules and the classical MHC I and MHC II molecules is that the latter molecules primarily present peptide antigens while CD1 molecules present amphipathic glycolipid (Kasmar et al., 2009; Kulkarni, 2010) and possibly hydrophobic peptide (Van Rhijn et al., 2009) antigens to T cells which provides a more comprehensive sampling of microbial products than the classical MHC molecules alone could provide. There are few CD1 genes (maximum of 12 but not all are present in all species) compared to the classical MHC molecules (>200), and CD1 proteins are highly conserved with few if any allelic variations. However, crystal structure analysis suggests that CD1 proteins have substantial flexibility and can conformationally change to present diverse microbial and self glycolipids (Zajonc et al., 2008).

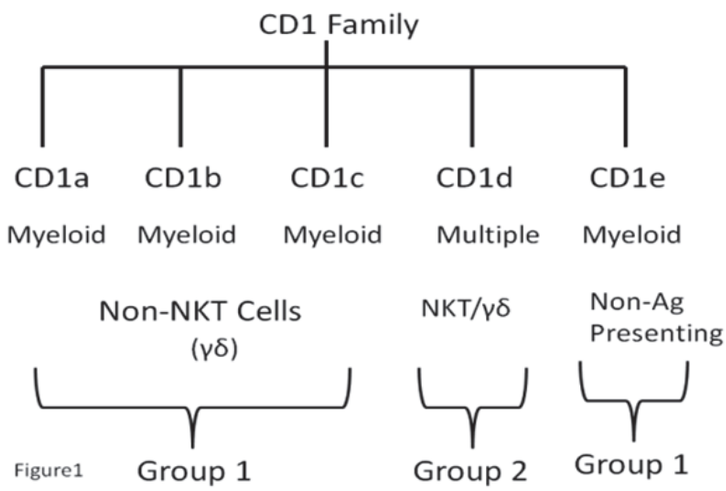

Fig. 1. CD1 family of non-classical MHC class I-like molecules.

There are five known members of the CD1 family divided into Group 1 and Group 2 molecules. All CD1 molecules present lipid antigens, unlike classical MHC molecules which primarily present peptide antigens. All CD1 genes derive from a common ancestral gene.
Unlike the other four members of the CD1 family, CD1e is only found as a soluble form in endosomes where it aids in trimming phosphatidylinositol for presentation by CD1b (de la Salle et al., 2005). CD1a, b, and c molecules are expressed on myeloid cells while CD1d is

expressed on these cells and additionally on non-hemopoietic cells including cardiac myocytes and endothelial cells (Blumberg et al., 1995; Exley et al., 2001; Huber et al., 2003) . CD1 molecules structurally resemble class I MHC molecules since they consist of a single polypeptide chain coded by the CD1 gene and are associated with β2 microglobulin. However, antigen presentation more closely resembles class II MHC molecules since antigen loading occurs in the endosome pathway and is TAP independent (Boes et al. , 2009; Brutkiewicz et al., 1995; Odyniec et al., 2004). The CD1 extracellular domain has a deep antigen binding groove containing two to four hydrophobic pockets into which the alkyl lipid tails of antigens are inserted leaving the glycosylated portion available for T cell recognition (Cheng et al., 2006; Zajonc et al., 2003; Zajonc et al., 2008). The cytoplasmic tails of CD1b, CD1c and CD1d contain a tyrosine motif which directs these molecules to the late endosome while the CD1a cytoplasmic tail lacks this motif and directs this molecule to the early endosome. The difference in trafficking of the CD1 molecules may reflect an evolutionary process since bacteria localize to different cellular organelles and expression of CD1 isoforms to distinct endosome compartments should promote maximal capture and presentation of microbial antigens to host immunity (De Libero & Mori, 2003). CD1b presents bacterial lipids including mycobacterial mycolic acids (Beckman et al., 1994), lipoarabinomannan (Sieling et al., 1995), glucose monomycolate (Moody, 2001), and self-glycosphingolipids such as GM1 ganglioside (Shamshiev et al., 2000). CD1a and CD1c present bacterial phospholipids (Beckman et al., 1996). CD1d presents a bacterial sphingolipid from *Sphingomonas* (Kinjo et al., 2005), alphaproteobacterium from *N. aromaticivorans* (Mattner et al., 2008), glycolipids from *B. burgdorferi* (Kinjo et al., 2006), and a self-sphingolipid isogloboside (Mattner et al., 2005). The sphingolipid α-galactosylceramide (αGalCer) isolated from marine sponges, is the classical CD1d ligand (Kawano et al., 1997), but CD1d has also been shown to present an α-galactosyl-diacylglycerol of *B. burgdorferi* (BbGL-II) (Kinjo et al., 2008; Kinjo et al., 2006). Evidence for CD1 presentation of viral antigens is sparse despite the fact that CD1-restricted T cells have been shown to respond in various viral infections including HIV, HSV, influenza and picornavirus (De Santo et al., 2008; Exley et al., 2001; Li & Xu, 2008; Yuan et al., 2006). Indeed, it would be highly unlikely that CD1 could directly present picornavirus molecules since these are non-enveloped viruses and should therefore lack any potential for glycolipid or lipopeptide antigens. Possible explanations for CD1-restricted immune responses to viruses exist. For example, infection may promote cellular lipidation of virus proteins (Van Rhijn et al., 2005) or infection may cause increased expression of endogenous glycolipid antigens (De Libero et al., 2005; Paget et al., 2007). Lysosomal α-galactosidase A is an enzyme which degrades endogenous lipid antigens (Darmoise et al., 2010). However, subsequent to many infections, α-galactosidase A activity can be severely curtailed leading to endogenous lipid accumulation. This means that CD1d dependent innate immunity may be directed to both exogenous and endogenous antigens during infections.

Endogenous glycosphingolipids binding to CD1 include GM1 ganglioside, sulfatide, galactosylceramide, and sphingomyelin (Darmoise et al., 2010; De Libero & Mori, 2003; Franchini et al., 2007; Hegde et al., 2010; Roy et al., 2008). The self-glycosphingolipids are not only important as self-antigens for T cell activation, but their presence may stabilize and promote CD1 expression on the cell surface (De Libero & Mori, 2003). Unlike microbial glycolipids which require processing in the endosomes, glycosphingolipids can directly bind to CD1 molecules expressed on the cell surface and can displace glycolipids already in these surface CD1 molecules (De Libero & Mori, 2003). Although endogenous

glycosphingolipids have been primarily viewed as the probable self antigen in CD1-dependent immunity, recent studies by Pei et al (Pei et al., 2010) demonstrated that cell lines incapable of glycosphingolipid biosynthesis were nonetheless capable of activating CD1-restricted cells. Thus, the types of self antigen capable of activating the CD1-dependent innate immune response are likely to be broader than originally thought.

Group 1 CD1 molecules are not expressed on monocytes in the blood and recent studies have shown that serum immunoglobulin and lipids suppress expression of these molecules (Leslie et al., 2008; Smed-Sorensen et al., 2008). However, once monocytes leave the circulation, Group 1 CD1 molecules can be induced by signaling through TLR2 (Roura-Mir et al., 2005), TLR2/TLR5 agonists, or cytokines (GM-CSF and IL-4) (Moody, 2006). CD1d is not up-regulated by GM-CSF and IL-4 (Exley et al., 2001; Sallusto & Lanzavecchia, 1994). CD1d is constitutively expressed in dendritic cells, monocytes and macrophage, but levels can be further increased subsequent to infection (Dougan et al. , 2007; Durante-Mangoni et al., 2004; Huber et al., 2003; Skold & Behar, 2003). Such up-regulation depends upon signaling through TLR and cytokines (IFNγ, IFNβ, TNFα) (Raghuraman et al., 2006; Skold et al., 2005). While microbial infections can up-regulate CD1 expression, they can also result in CD1 down-regulation (Donovan et al., 2007; Raftery et al., 2006). Viruses are well-known for their ability to evade immunity through multiple different mechanisms (Alcami & Koszinowski, 2000; Antoniou & Powis, 2008; Vossen et al., 2002). While most investigations of immune evasion by viruses center on the adaptive immune response, viruses also interfere with innate immunity. The HIV Nef protein binds to CD1d decreasing CD1d transport to the cell surface (Hage et al., 2005). Similarly, HSV, suppresses CD1 expression by interrupting the CD1 recycling pathway (Yuan et al., 2006). Karposi sarcoma-associated herpesvirus (KSHV) uses its modulator of immune recognition (MIR) proteins to ubiquitinize the cytoplastic tail of the CD1d molecule leading to its endocytosis (Sanchez et al., 2005). Activation of TLR7/8 blocks CD1 expression at the protein and mRNA levels (Assier et al., 2007). Finally, infection can change the endosomal processing of glycolipids which could restrict antigen availability to CD1 molecules.

Unlike Group 1 CD1 molecules, CD1d can be expressed on non-hemopoeitic cells (Huber et al., 2003; Monzon-Casanova et al. ; Sikder et al., 2009) CVB3 infection augments CD1d expression on macrophage, dendritic cells and T cells (Huber, 2006). The virus also causes de novo CD1d expression on non-hemopoietic cells (cardiac endothelial cells and myocytes), but only in non-hemopoietic cells actively replicating virus. Uninfected myocytes/endothelial cells immediately adjacent to infected cells remain CD1d negative (Huber et al., 2003). The requirement for active virus replication strongly suggests that TLR signal pathways such as TLR3 (recognizing single stranded RNA) or TLR7/8 (recognizing double stranded RNA) are necessary. However, virus replication alone is insufficient. Mice or cells infected with a non-pathogenic variant of CVB3, H310A1 (Knowlton et al., 1996), fail to up-regulate CD1d either on hemopoeitic or non-hemopoeitic cells (Huber et al., 2003; Huber & Sartini, 2005b). A major difference between the non-pathogenic and pathogenic (H3) variants of CVB3 is that the pathogenic virus is a potent inducer of TNFα. Further studies showed that TNFα and H310A1 infection up-regulated CD1d expression whereas either TNFα or H310A1 infection alone did not. In the mouse model of CVB3 induced myocarditis, CD1d is required for cardiac inflammation and injury. Mice lacking CD1d fail to develop myocarditis despite high levels of virus replication in the heart (Huber et al., 2003). Since CD1d is up-regulated on both hemopoeitic and non-hemopoeitic cells subsequent to CVB3 infection, a major question is where expression of this molecule is most

important in pathogenesis. CD1d-restricted effectors are cytolytic to CVB3 infected cardiocytes in vitro and expression of CD1d on infected cardiocytes in vivo may contribute directly to their death through cytolytic T lymphocyte activity. To address this question, bone marrow transplantation was performed between wild-type (CD1d+/+) and CD1d-/- mice where either the hemopoeitic cells were CD1d+ and the non-hemopoeitic cells (heart) was CD1d- or the opposite (Huber, 2006). These studies showed that CD1d expression on both hemopoeitic and non-hemopoeitic cells contributed to heart disease, although CD1d expression on hemopoeitic cells was of primary importance. There are no published studies showing the importance of CD1in clinical myocarditis. It is therefore not possible to evaluate the significance of CD1-dependent innate immunity in the human disease. However, based on the tight control of CD1 for pathogenesis in the experimental disease, the strong association between various microbial infections and clinical myocarditis, and the importance of CD1-restricted immunity in many different microbial infections; future investigation into a role for CD1 in this disease would be warranted.

3.2 Natural killer T cells and CD1-restricted γδ T cells

Many T cells respond to CD1 molecules (Barral & Brenner, 2007; Kaufmann, 1996) and express either T cell receptors (TCR) consisting of α/β or γ/δ polypeptide chains. Group 1 CD1-restricted αβ T cells are clonally diverse with fine antigen specificity, recognition of both self and foreign lipid antigens and either double negative (CD4-CD8-) or single positive (CD4+ or CD8+) (Barral & Brenner, 2007; Kaufmann, 1996; Vincent et al., 2005). The αβ T cell response is slow, similar to classical MHC αβ T cell responses indicating that these CD1-restricted effectors probably do not belong to the innate immune system. There are two major populations of γδ T cells in humans (Vδ1 and Vδ2) with Vδ2 cells primarily present in the circulation and Vδ1 cells primarily found in tissues and intestine (Das et al., 2004). Subsets of both γδ populations recognize antigens in context of non-classical MHC class I-like molecules including group 1 CD1(Rincon-Orozco et al., 2005; Russano et al., 2007). Activation of the group 1 CD1 restricted effectors requires IL-12, NKG2D activation on the effector and adhesion molecule interactions (LFA3/CD2, LFA1/ICAM1) in addition to TCR engagement. Since mice lack Group 1 CD1 molecules, this species does not have Group 1 CD1-restricted immunity. However, these effectors may function in humans.

T cells reacting to CD1d (Group 2 CD1) are also diverse. CD1d-restricted natural killer T (NKT) cells are designated as either invariant NKT (iNKT, also known as Type 1) or diverse NKT (also known as Type 2) cells (Barral & Brenner, 2007; Kronenberg, 2005; Ronchi & Falcone, 2008; Taniguchi et al., 2010). Type 1 iNKT cells have a TCR comprised of a single type of TCRα chain (Vα14Jα18 for mice and Vα24Jα18 for humans) and one of a limited number of distinct TCRβ chains resulting in limited clonal diversity. In contrast, Type 2 NKT cells use TCR comprised of diverse α and β chains. iNKT cells comprise between 2-40% of CD3+ cells in various tissues (Bendelac et al., 2007; Terabe & Berzofsky, 2008), have a constitutively activated phenotype, and rapidly secret large amounts of cytokines (IFN-γ, IL-4, IL-17, IL-5, and IL-13) upon activation due to the presence of pre-formed cytokine mRNA in the cells (Kronenberg, 2005; Michel, 2007; Olson et al., 2009; Stetson et al., 2003). Three mechanisms of iNKT cell activation have been described (Figure 2). Direct activation involves recognition of microbial antigens presented by CD1d on antigen presenting cells (TCR-mediated). In contrast, indirect activation either involves microbial stimulation of antigen presenting cells to release cytokines (IL-12 and Type 1 IFN) and presentation of

self/altered self lipid antigens on CD1d; or cytokines (IL-12 and IL-18) in the absence of CD1d antigen presentation (Brigl et al., 2003). Both inflammation and TLR activation can affect expression of enzymes involved in lipid metabolism (Khovidhunkit et al., 2004; Salio et al., 2007) and this may either increase total self lipid in endosomes or alter self lipids making them appear more foreign to the immune system. The mechanism of iNKT cell activation can impact the types of cytokines released with direct CD1d activation resulting in both Th1 (IFNγ) and Th2 (IL-4/IL-13) release while indirect activation causes predominantly Th1 (IFNγ) expression (Brigl et al., 2003). iNKT cells producing Th2 cytokines modulate NK cells to express TGFβ and TGFβ promotes T regulatory cell activation(Chen et al., 2009; Monteiro et al., 2010). Thus, depending upon the mode of iNKT cell activation, these effectors can be either pro- or anti-inflammatory. Type 2 NKT cells also can have a Th1 or Th2 phenotype with corresponding cytokine profiles, and therefore may have either potentiating or protective roles in infections and autoimmune diseases (Arrenberg et al., 2009). A number of reports indicate that Type 1 and Type 2 NKT cells are antagonistic to each other and form a regulatory network to control adaptive immunity. Most reports suggest an anti-inflammatory role for Type 2 NKT cells which can be protective in autoimmune diabetes in NOD mice (Duarte et al., 2004), experimental allergic encephalomyelitis (Jahng et al., 2004) and Con-A induced hepatitis (Halder et al., 2007). Furthermore, while type 1 NKT cells may increase tumor immunosurveillance, Type 2 NKT cells may suppress anti-tumor immunity (Ambrosino et al., 2007; Terabe & Berzofsky, 2008). Activation pathways for γδ T cells can also be diverse with both direct antigen presentation in MHC or MHC-like molecules or indirect with minimal or no antigen presentation (Kaufmann, 1996). Unlike NKT cells, γδ T cells may either react to CD1 itself in the absence of any antigen or to antigen without presentation by MHC/MHC-like molecule involvement. Although both human and mouse γδ T cells have been found to recognize antigens presented by Group 1 CD1 and other non-classical MHC antigens (Chien & Konigshofer, 2007; Cui et al., 2009; Spada et al., 2000; Van Kaer et al., 1991), only this laboratory has reported a subpopulations of γδ cells (Vγ4 TCR) recognizing CD1d (Huber et al., 2003).

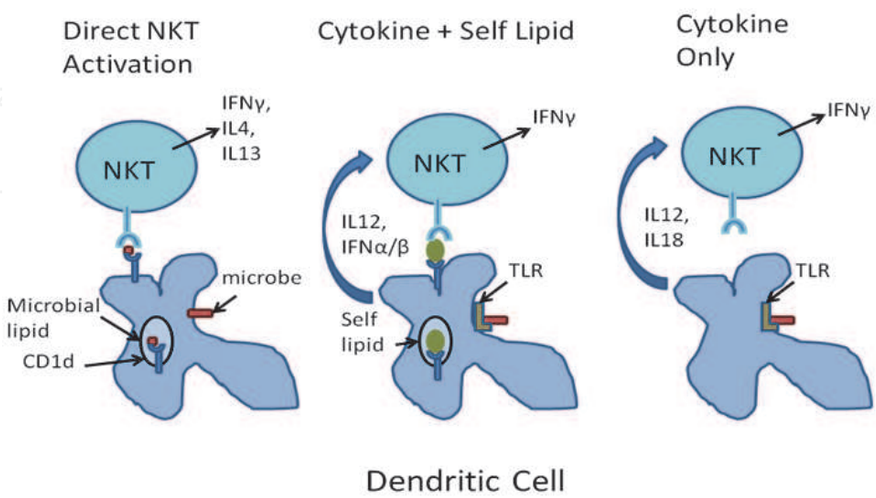

Fig. 2. Mechanisms for NKT cell activation.

There are three major mechanisms for activating NKT cells. Direct activation involves phagocytosis of microbes and binding of microbial lipids into the CD1d groove in the late endosome with transport of the CD1d-lipid complex to the antigen presenting cell surface. NKT cells activated through this pathway produce a broader range of Th1 and Th2 cytokines. A second pathway involves microbial stimulation of TLR on the antigen presenting cell which can both affect self-lipid expression/availability and stimulate cytokine expression from the antigen presenting cells. NKT cells stimulated by the recognition of self-lipid/CD1d and the cytokine milieu secrete primarily Th1 cytokines. The third mechanism is either not or substantial less dependent upon CD1d recognition by the NKT cells but NKT cell activation is primarily induced through cytokines alone.

3.3 NKT and γδ T Cells in myocarditis

Several cases of clinical cardiomyopathy have been reported where substantial numbers of γδ cells are in the inflammatory infiltrate (Eck et al., 1997; Takeda et al., 2008; Takeda et al., 2005). However, there is little direct evidence for a pathogenic role for these innate effectors in humans. As indicated above for NK cells, the lack of direct evidence for innate effectors in clinical myocarditis may simply reflect the fact that innate immunity should function early after infection and may disappear from the heart by the time that clinical symptoms are evident. In contrast to myocarditis in humans, substantial evidence implicates innate lymphocyte effectors in mouse models of coxsackievirus B3 (CVB3) and Borrelia burgdorferi (Lyme disease) myocarditis (Figure 3). As described above, mice lacking CD1d fail to develop myocarditis subsequent to CVB3-H3 (highly myocarditic variant of CVB3 (Knowlton et al., 1996)) infection despite high levels of virus replication in the heart (Huber et al., 2003). Infecting iNKT deficient mice with CVB3-H3 had no effect indicating that iNKT cells do not contribute to pathogenesis with this CVB3 variant. Surprisingly, CD1d deficient mice had significantly reduced numbers of activated γδ T cells belonging to the Vγ4 subset, and further analysis demonstrated that these Vγ4 cells are CD1d restricted as they killed CVB3-H3 infected CD1d+ but not infected CD1d- cardiac myocytes and cytotoxicity of the CD1d+ myocytes was blocked by anti-CD1d antibodies but not by antibodies to the classical MHC I and MHC II antigens (Huber, 2000; Huber et al., 2003). More importantly, activation of Vγ4 cells correlated to induction of CD4+IFNγ+ (Th1) virus-specific cells, which indicates that γδ cells might impact myocarditis through their effects on the antigen-specific, adaptive immune response (Huber & Sartini, 2005a; Huber et al., 2002). Previous studies had shown that heart-specific, autoimmune CD8+ cytolytic T lymphocytes are the primary immunopathogenic effector in CVB3 induced myocarditis (Guthrie et al., 1984; Henke et al., 1995; Huber & Lodge, 1984; Huber et al., 1988; Huber et al., 2002). These autoimmune CD8 cells kill uninfected cardiocytes through recognition of cardiac myosin epitopes (Huber & Gauntt, 2000) and can adoptively transfer myocarditis into uninfected recipients (Huber et al., 1987). However, the autoimmune CD8 T cell response is absolutely dependent on CD4+IFNγ+ cells (Huber et al., 2002). This is not surprising as many studies have shown that CD4+ Th1 cells promote CD8 T cell activation (Krawczyk et al., 2007; Serre et al., 2006). Although Vγ4 cells are required for generation of CD4+IFNγ+ cells, once the CD4+IFNγ+ cells exist, Vγ4+ cells are no longer necessary for autoimmune CD8 cell induction or myocarditis (Huber et al., 2002). The CVB3 model is not the only one showing that γδ T cells are required for immunopathogenic CD4 and CD8 T cell responses. Trypanosoma cruzi, the etiological agent in Chagas' disease, causes myocarditis with cardiac injury at least partially mediated by T cells and IFNγ (dos Santos et al., 2001; Marin-Neto et al., 2007; Ribeiro-Dos-

Santos et al., 2001; Soares et al., 2001). As with the CVB3 model, γδ cells are required for the pathogenic CD4 and CD8 responses in T. cruzi infections (Nomizo et al., 2006). However, unlike the CVB3 myocarditis model, the relevant γδ cell in T. cruzi infection expresses the Vγ1 T cell receptor. Why Vγ4 cells are operational in CVB3 disease while Vγ1 cells function in T. cruzi infection, is not currently known, but might reflect the difference between a virus and protozoa as the etiological agent. Nonetheless, the principle is the same: innate effectors control the activation of pathogenic antigen-specific adaptive immunity which subsequently causes cardiac damage.

The next question is how γδ cells control induction of adaptive immunity. Regulatory T cells (Tregs) are important negative immune modulators, constitute up to 10% of peripheral CD4+ T cells in naive mice and humans, and express CD25 (IL-2 receptor α chain) (Sakaguchi, 2005; Sakaguchi et al., 2008; Torgerson, 2006). There are several types of T regulatory cells which can basically be divided into natural (nTreg) and inducible (iTreg) populations. nTreg cells are generated in the thymus, and presumably arise from T cells with high affinity TCR for self antigens. nTreg cells are functionally mature when leaving the thymus and do not require antigen exposure peripherally to generate immunosuppressive activity. In contrast to nTreg cells, iTreg can be converted from effector T cell populations in the periphery subsequent to antigen challenge. The transcription factor, FoxP3, is usually associated with Treg cell development and transduction of exogenous FoxP3 into CD4+CD25- cells converts these cells into CD4+CD25+ Treg cells (Sakaguchi et al., 2008). Induction of FoxP3 expression and therefore, Treg cell activation depends upon the presence of TGFβ (Mantel & Schmidt-Weber, 2010). While FoxP3 is necessary for conversion of CD4+ cells to Treg cells, IL-2 is required for Treg cell maintenance/survival. Animals lacking either CD25 (IL-2R) or IL-2 develop lymphoproliferative and autoimmune diseases (Malek & Bayer, 2004) associated with a decrease in Treg cells. Three mechanisms have been proposed for Treg cell function (Sakaguchi et al., 2008). The first mechanism hypothesizes that Treg cells out-compete effector T cells for MHC-antigen complexes on antigen presenting cells which effectively blocks effector T cell activation. In the second mechanism, Treg cells directly interact with dendritic cells through CTLA4 which down-regulates required accessory molecule expression needed for successful antigen stimulation of effector T cells. Finally, Treg cell secretion of TGFβ or IL-10 may inhibit T cell differentiation (Ozdemir et al. , 2009; Ray et al., 2010).

CVB3 infection up-regulates CD1d on infected cardiac myocytes and myeloid cells. CD1d activates NKT and Vγ4 T cells which can either recognize CD1d on myocytes leading to myocyte death or interact with dendritic cells (DC) through CD1d to alter antigen presentation function of the dendritic cells or to produce cytokines. NKT cells may also activate NK cells. NK and NKT cells promote activation of Treg cells by promoting myeloid derived suppressor cell differentiation, while Vγ4 T cells have the opposite effect and either directly kill Treg cells through CD1d expressed on the Treg cell population or induce dendritic cell maturation and enhanced antigen presentation to adaptive immune (CD4, CD8) effectors. Treg cells inhibit activation of CD4+IFNγ+ (Th1) cells which are required for generation of cytolytic, autoimmune CD8 effector cells. The CD8 effector cells are the primary immunopathogenic mediator to cardiac injury in CVB3 induced myocarditis.

Treg cells prevent autoimmunity in myocarditis (Frisancho-Kiss et al., 2006; Huber et al., 2006; Wang, 2010). Distinct populations of innate effector T cells can have dramatically different effects on Treg cell responses. iNKT cells can promote Treg cell activation (Nowak et al., 2006; Roelofs-Haarhuis et al., 2004; Roelofs-Haarhuis et al., 2003). Under appropriate

stimulation (see Figure 2), iNKT cells produce IL-13, a Th2 cytokine, which can induce TGFβ production from CD11b+Gr-1+ myeloid derived suppressor cells. TGFβ promotes FoxP3 expression and Treg cell differentiation (Mantel & Schmidt-Weber, 2010). Indirectly, NKT cells activate NK cells (Carnaud et al., 1999) and subpopulations of NK cells suppress adaptive immunity either through their effects on dendritic cells or T cells (Flodstrom-Tullberg et al., 2009; Lunemann et al., 2009). CD1d and NKT cells are crucial to Treg cell development (Sonoda et al., 1999), and treating mice with αGalCer increases Treg cell activation (La Cava et al. , 2006) and suppresses autoimmune diabetes in NOD mice (Cardell, 2006; Ly et al., 2006). NKT cells secret high levels of TGFβ and IL-10 (Sonoda et al., 2001; Stein-Streilein et al., 2000) which alter dendritic cell (DC) cytokine (IL-10) and accessory molecule (CD40, CD80 and/or CD86) expression (Kumanogoh et al., 2001; McGuirk & Mills, 2002; Salomon et al., 2000) that favors T regulatory cell responses. (Bach et al., 2004; Chen et al., 2009). NKT cells are protective in Chagas' disease (Duthie & Kahn, 2006; Olson et al., 2009) and IFNγ expression by the NKT cells appears to be crucial to their protective effect. Similarly, treating CVB3 infected mice with αGalCer is protective, again indicating a role for NKT cells in preventing myocarditis (Wu et al., 2010). However, whether these NKT cells also suppress immunopathogenicity by enhancing Treg cell responses is not clear. γδ T cells appear to have the opposite effect on Treg cell responses. IL-23 activated γδ cells prevent conversion of effector T cells to iTreg cells (Petermann et al., 2010). Similarly γδ cells reduce IL-10 producing Treg cells in the lung in an asthma model γδ cells (Hahn et al., 2008). Vγ2Vδ2 cells prevent IL-2 induced expansion of CD4+CD25+FoxP3+ T (Gong et al., 2009). γδ T cells promote dendritic cell maturation and enhance antigen presentation. Also, these innate effectors suppress IL-2 expression which is needed for Treg cell maintenance. Recently, it has been shown that CVB3-H3 infection of mice deficient in γδ cells results in significant increases in Treg cells and accumulation of a population of CD1d+ Treg cells (Huber, 2009, 2010). These CD1d+ Treg cells are substantially more immunosuppressive to myocarditis than the CD1d- Treg cells on a per cell basis. These CD1d+ Treg cells are absent in mice containing γδ cells, and adoptive transfer of activated γδ cells into CVB3-H3 infected γδKO mice both restores myocarditis susceptibility and eliminates the CD1d+ Treg cell population. Direct co-culture of the activated γδ cells on CD1d+ and CD1d- Treg cell populations shows that the γδ effector cells are lytic to the CD1d+ Treg in a CD1d- and caspase-dependent manner. (Huber, 2010).

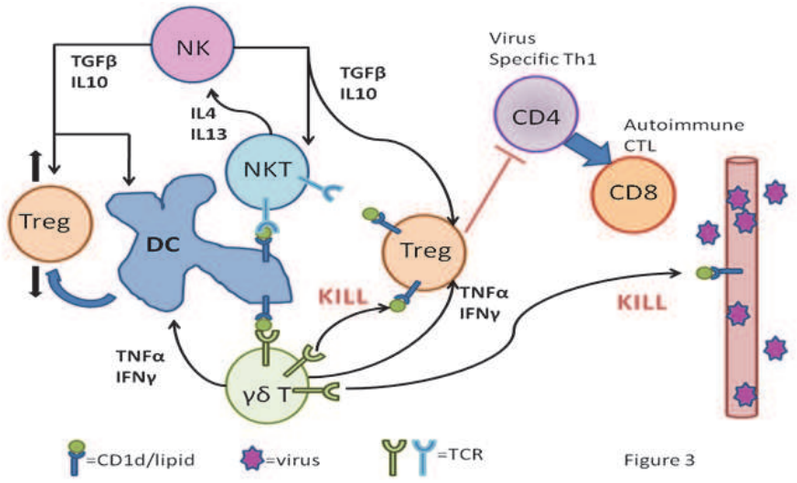

Fig. 3. Cross-talk between innate effectors in control of adaptive immunity.

4. Conclusions

Innate immunity is the rapid host response and occurs within hours of microbial infections. Although a major role for innate immunity is to help dampen microbe replication until the adaptive immune response is adequately developed for final microbial elimination, another major role for innate immunity is to control and direct the developing adaptive immune response. There is substantial cross-talk between innate lymphocyte effectors during myocarditis. Both NKT and a population of γδ cells recognize CD1d, a non-classical MHC class I-like molecule. However, evidence implies that while NKT cells are protective in myocarditis, γδ cells are pro-inflammatory and pathogenic. Interesting similarities have been found in the role of NKT and γδ cells in two different myocarditis mouse models: CVB3 and Trypanosoma cruzi induced myocarditis. The fact that similar immune processes of pathogenicity and protection appear to function in these two models provides circumstantial evidence that these innate effectors may have identical roles in other forms of myocarditis and also in clinical disease. To date, little evidence actually exists for innate effectors in clinical disease. However, the strong association between microbial infections and myocarditis in humans means that innate immunity should be important.

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6. References

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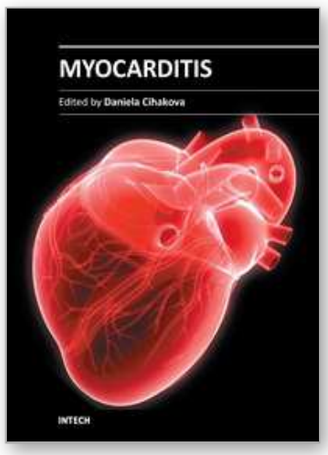

Myocarditis

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Myocarditis, the inflammation of the heart muscle, could be in some cases serious and potentially fatal disease. This book is a comprehensive compilation of studies from leading international experts on various aspects of myocarditis. The first section of the book provides a clinical perspective on the disease. It contains comprehensive reviews of the causes of myocarditis, its classification, diagnosis, and treatment. It also includes reviews of Perimyocarditis; Chagasâ€™ chronic myocarditis, and myocarditis in HIV-positive patients. The second section of the book focuses on the pathogenesis of myocarditis, discussing pathways and mechanisms activated during viral infection and host immune response during myocarditis. The third, and final, section discusses new findings in the pathogenesis that may lead to new directions for clinical diagnosis, including use of new biomarkers, and new treatments of myocarditis.

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