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Commentary

NKG2C, HLA-E and their association with psoriasis

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Abstract: Natural killer (NK) cell activation is regulated by the integration of signals from inhibitory and activating cell surface receptors. Both NKG2A and NKG2C pair with CD94 to form inhibitory and activating receptors specific for the HLA-E-canonical peptide complex. HLA-E is a non-classical MHC class Ib molecule with limited polymorphism. It preferentially binds to and presents leader sequence peptides derived from classical MHC class I molecules. Wilson et al. have identified an association between NKG2C deficiency and psoriasis. They have also discovered an HLA-C-dependent association between HLA-E and psoriasis. Their research highlights the importance of NK cells in the pathophysiology of psoriasis. Herein, we propose two different models to explain the association between NKG2C, HLA-E and psoriasis. In the first model, we hypothesize that NKG2C deficiency and/or HLA-E O1:01 can inhibit the ability of NK cells to regulate autoreactive T cells, predisposing to psoriasis. The second model proposes that HLA-E 01:03 can disrupt the presentation of the psoriasis-inducing self-determinant by HLA-C, thereby protecting against psoriasis.

Key words: antigen processing – HLA-Cw*0602 – HLA-E – natural killer cells – NK T cells – NKG2A – NKG2C – psoriasis

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Natural Killer (NK) cells, NK T cells and T cells Bearing NK receptors

NK cells are innate lymphocytes that share some properties with cells of the adaptive immune system. They are well known for their cytotoxic and cytokine-producing effector functions. NK cells have the capacity to distinguish diseased cells (virally or bacterially infected, cancerous or otherwise stressed cells) from healthy cells. They also have the ability to proliferate in response to a viral infection and to form a long-lived memory-like population to protect against future pathogen encounters (1). More recently, it has been demonstrated that NK cells can act as immune regulatory cells (2). Specifically, they can promote inflammation by secreting IFN-γ tumor necrosis factor (TNF) and other cytokines. The NK-secreted cytokines can also indirectly affect NK cell function by inducing antigen-presenting cells (APCs) to mature and secrete cytokines (e.g. IL-12), which directly act on NK cells (3–5). In contrast, NK cells can also down-regulate inflammatory responses by killing APCs and activated T cells (6–9). Because of their strong influence over the immune system, it has been suggested that NK cells act as immunologic 'rheostats' (10). Fortunately, the same biologic medications designed to target the psoriasis-inducing Th1 and Th17 cell responses also target the pathologic NK cytokine cascades (11,12).

How an NK cell will respond to an encounter with an autoreactive T cell will depend on a variety of factors. Under normal physiologic conditions, a NK cell's response is tightly regulated by the integration of signals from its activating and inhibitory cell surface receptors. These receptors include killer cell Ig-like receptors (KIRs) and NKG2x receptors (x=2A, 2C, and 2D) (13,14). Of the different KIR molecules, KIR2DL1 and KIR2DS1 are unique in that they bind to the psoriasis-linked HLA-C molecule via its C2 epitope. KIR2DS1 is a NK-activating receptor, which, as HLA-Cw*0602, is associated with psoriasis (15,16). Wilson et al. chose to further explore the relationship between NK cells and psoriasis by searching for additional associations between NK receptors, their ligands and psoriasis. The NKG2 receptors, NKG2A and NKG2C, pair with CD94 to form inhibitory and activating receptors, respectively (Fig. 1). In their article published in Experimental Dermatology, they find an association between NKG2C deficiency and psoriasis (17). CD94/NKG2A and CD94/NKG2C are different from other NK receptors in that they both recognize the non-classical MHC class Ib molecule, HLA-E (18,19). Unlike classical HLA molecules, HLA-E is characterized by a limited polymorphism and a conserved peptide-binding groove. It preferentially binds and presents 9-mer peptides derived from the leader sequence of other MHC class I molecules. Leader sequence peptides for HLA-E-binding are generated by the signal peptide peptidase and further proteasome processing (Fig. 2) (20). Importantly, the two HLA-E alleles, 01:01 and 01:03, differ in their cell surface expression and their peptide-binding affinities.

Some T cells can express a variety of NK molecules, including the characteristic NK-activating and inhibitory receptors. For example, nearly all human $CD8^+$ T cells express the NKG2D activating receptor and a smaller fraction express NKG2A and NKG2C. There is also a specialized population of innate-like lymphocytes referred to as NK T cells. These are specialized glycolipid-specific T cells that are restricted to the non-polymorphic MHC class I-like molecule, CD1d. Human NK T cells that utilize a semi-invariant Vα24-Jα18:Vβ11 T cell receptor (TCR) to recognize CD1d-bound glycolipid antigens are referred to as type I or invariant NK T cells (iNK T cells). Like NK cells, NK T cells and the T cells bearing NK receptors can partake in similar immune regulatory activities. In atopic dermatitis, IL-22 producing NK-like cells are known as 'Th17/Th22 cytokine-producing innate cells' (21) and in allergic contact dermatitis (ACD), iNK T cells function as effector cells by producing cytotoxic granules (22). We do

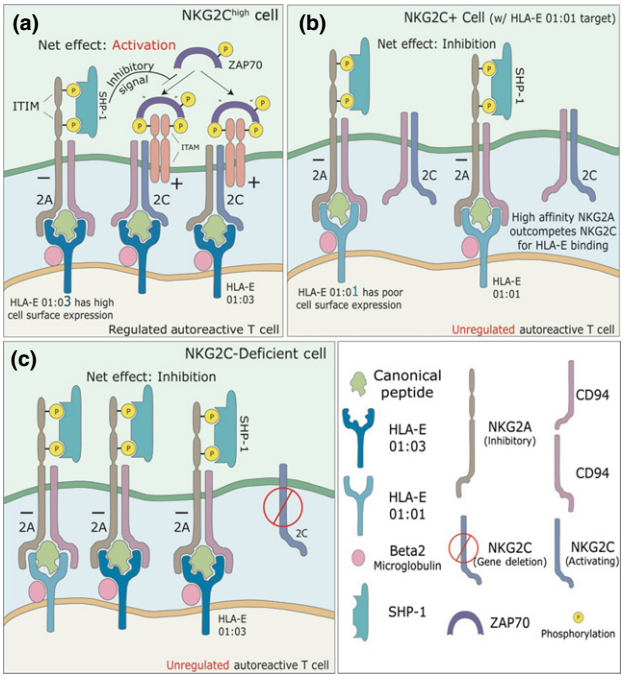

Figure 1. Inhibition of regulatory NK cells (or NK-like T cells) links NKG2C deficiency and HLA-E01:01 to psoriasis. The successful regulation of autoreactive T cells by NK cells (or NK-like T cells) is dependent upon the integration of signals obtained from the NKG2A and NKG2C inhibitory and activating receptors. Peptide-bound HLA-E complexes found on the surface of autoreactive T cells bind to CD94/NK2x (x=A, C) receptors on NK-regulatory cells. When bound to an HLA-E peptide complex, the immunoreceptor tyrosine-based inhibition motifs (ITIM) of the inhibitory receptor, CD94/NKG2A, become phosphorylated, allowing for SHP-1 protein to bind, and dephosphorylated ZAP70. Dephosphorylated ZAP70 is unable to bind to immunoreceptor tyrosine-based activation motifs (ITAMs), thus inhibiting activation of the NK cell. CD94/NKG2C is an activating receptor. When bound to an HLA-E peptide complex, this receptor interacts with ZAP70, via its ITAMs, to transmit an activating signal. Activated NK cells then function to regulate autoreactive T cells. (a) *NKG2C^{high} Regulatory Cell*. High expression of CD94/NKG2C receptors results in a net positive activation signal of the corresponding NK cell, allowing for regulation of autoreactive T cells. HLA-E 01:03 has a higher affinity for antigen peptides and a higher cell surface expression compared with HLA-E 01:01. CD94/NKG2C is protective against psoriasis. (b) *Homozygous for HLA-E 01:01*. Homozygosity for HLA-E 01:01 results in expression of fewer cell surface HLA-E molecules. CD94/NKG2A has a 6-fold higher affinity for HLA-E 01:01 and outcompetes CD94/NKG2C. This results in a net inhibition of NK cells, and thus unregulated autoreactive T cells, predisposing to psoriasis. (c) *Deletion of NKG2C*. Deletion of the activating NKG2C receptors favours inhibition of NK cells, and subsequently, unregulated autoreactive T cells, predisposing to psoriasis.

not limit the mechanisms described herein to any one particular NK molecule-bearing cell type.

HLA-E, NKG2C deficiency and the development of psoriasis

NKG2C high cells are known to expand in response to viral pathogens and remain elevated longitudinally (1). With respect to their ability to prevent psoriasis, cells expressing elevated levels of the activating NKG2C receptor are more likely to become activated in response to an encounter with an autoreactive T cell (Fig. 1a). The activated NKG2C-expressing cell can then kill the autoreactive T cell, thereby preventing psoriasis. Of note, psoriasis plaques apparently have fewer NKG2C-positive cells when compared to NKG2A (23). This may limit the regulatory function of the NK compartment in patients with psoriasis.

When coupled to CD94, both NKG2A and NKG2C can bind to HLA-E molecules presenting canonical peptides derived from the leader sequence of classical MHC class I molecules. However,

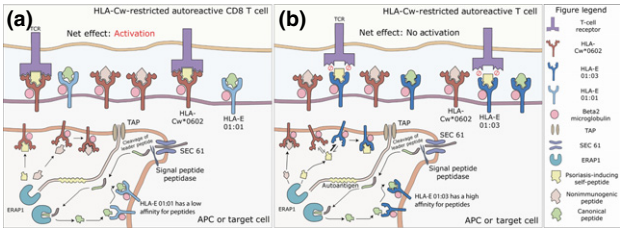

Figure 2. Determinant capture as an alternative model to explain the link between HLA-E and psoriasis. Endoplasmic reticulum aminopeptidase 1 (ERAP1) functions to process peptides within the endoplasmic reticulum, which are then presented by HLA molecules on antigen-presenting cells or target cells to autoreactive CD8$^+$ T cells. (a) *HLA-Cw*0602 Restricted Autoreactive CD8$^+$ T cells*. HLA-E 01:01 has a lower affinity for peptides compared with HLA-Cw*0602. It presents mainly canonical peptides derived from the leader sequence of classical HLA class one molecules. Psoriasis-inducing self-peptides presented by HLA-Cw*0602 on the surface of an APC or target cells are recognized by autoreactive T cells, resulting in activation of pathogenic CD8$^+$ T cells, predisposing to psoriasis. (b) *HLA-E 01:03 captures the psoriasis-inducing self-peptide from HLA-C*. The increased peptide-binding affinity of HLA-E 01:03 allows it to outcompete HLA-Cw*0602 for binding to the ERAP1-processed psoriasis-inducing self-peptide. The HLA-E 01:03-presented self-peptide is not recognized by autoreactive CD8$^+$ T cells due to incompatible binding sites between the TCR and HLA-E MHC molecule. As a result, activation of the autoreactive CD8$^+$ T cell is prevented. HLA-E 01:03 is protective against psoriasis in HLA-Cw*0602-positive patients.

when compared to NKG2C, NKG2A posses higher affinity for HLA-E/peptide complexes (Fig. 1b). Thus, the poor cell surface expression of HLA-E 01:01 creates a competitive state where the higher affinity NKG2A outcompetes NKG2C for HLA-E/peptide binding, resulting in net inhibition of the NK cell. In this scenario, the autoreactive T cell remains unregulated and psoriasis is favoured. Similarly, if someone is deficient in NKG2C due to a gene deletion, the inhibitory signal of NKG2A is not counterbalanced by an activating signal from NKG2C (Fig. 1c). The outcome is again a lack of NK cell activation, resulting in an unregulated autoreactive T cell.

Determinant capture may explain the link between HLA-E and psoriasis

Above we hypothesized a link between HLA-E and psoriasis based upon preferential binding of the inhibitory receptor, NKG2A, to HLA-E. However, this model does not explain the HLA-C-dependent association between HLA-E and psoriasis. We thus propose the following as an alternative model.

HLA-E is known to bind preferentially to the leader sequence of MHC class I molecules (Fig. 2). However, it can also bind to other ERAP 1-processed peptides and elicit HLA-E-restricted αβ T cell responses (24), similar to a classical MHC molecule. The model of antigen processing proposed by Sercarz et al. (25) dictates that the cell surface expression of a particular peptide/MHC complex is the result of a competitive process in which different MHC molecules compete for binding to the same antigenic peptide. As psoriasis is strongly associated with HLA-Cw*0602, it is likely that HLA-C binds to and presents a, yet to be identified, psoriasis-inducing self-peptide. If this psoriasis-inducing self-peptide also binds well to HLA-E, which has five characteristic hydrophobic pockets, then it is possible that HLA-E can compete with HLA-C for binding to the auto-antigen. In this model, HLA-E does not compete with HLA-C for binding to all peptides, just the relatively few that have MHC-binding motifs for both HLA-E and HLA-C. The high peptide-binding affinity of HLA-E 01:03 protects against psoriasis because HLA-E 01:03 can 'capture' the psoriasis-inducing self-peptide from HLA-C (Fig. 2). Contrariwise, the low peptide-binding

affinity of HLA-E 01:01 predisposes individuals to the development of psoriasis because presentation of the psoriasis-inducing self-peptide by HLA-C remains unopposed (Fig. 2).

Author contribution

The authors, Forum Patel, Alina I Marusina, Christopher Duong, Iannis E Adamopoulos and Emanual Maverakis, all contributed equally to the designing, drafting and revising of this manuscript.

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Conflict of interests

The authors have declared no conflicting interests.

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