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Review

Missing self recognition and self tolerance of natural killer (NK) cells

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Abstract

Natural killer cells express inhibitory receptors specific for polymorphic MHC molecules, which enables them to mediate "missing self recognition", the capacity to attack self cells that extinguish expression of MHC class I molecules. A key question is: how are NK cells rendered self-tolerant? It was proposed that all NK cells express at least one inhibitory receptor specific for self MHC, but we recently identified an NK cell subset that does not. Instead, these NK cells, like anergic B and T cells, are hyporesponsive to stimulation. These findings indicate that NK cell activity can be modulated independently of inhibitory receptors specific for MHC molecules, and that such modulation may contribute to self tolerance. This review summarizes current understanding of NK cell recognition and self tolerance.

Keywords: NK cell; MHC class I; Tolerance; Anergy; Hyporesponsive

1. Introduction

The missing self hypothesis has been a guiding principle for understanding target cell recognition by NK cells for more than 15 years [1,2]. Missing self recognition was conceived as the capacity of NK cells to attack cells that fail to express sufficient levels of MHC class I molecules of the host, and was discovered in studies of the role of MHC molecules in NK responses to tumor cells. The hypothesis received general attention when it was established that NK cells attack even normal cell types, such as bone marrow cells, when these cells lack MHC class I molecules as a result of targeted mutations [3].

Initially, two models were considered for receptor recognition of cells lacking self MHC molecules [4]. In one scheme, MHC molecules shield or mask a distinct stimulatory ligand on target cells, such that down-regulation of MHC could expose the ligand for recognition by triggering receptors present on NK cells. The competing model, which eventually was proven correct, is that MHC molecules are recognized by inhibitory receptors present on NK cells, and that engagement of these receptors blocks the ability of NK cells to attack the target cells. The latter model was established by the subsequent discovery and characterization of three classes of MHC-specific inhibitory receptors present on NK cells: the Ly49 lectin-like receptors in mice [5], the KIR Ig-like receptors in human [6–9], and the CD94/NKG2A lectin-like inhibitory receptor in both species [10,11].

In its original formulation, missing self recognition was often considered a stand-alone form of recognition, as if absence of self MHC was a sufficient condition to render a cell sensitive to NK cell attack. Studies showing that NK cells could kill normal cell types from MHC class I deficient mice seemed to support this notion [3,12,13]. However, the inhibitory receptor model, once accepted, presented a conundrum as to how the NK cell can engage and kill a target cell simply on the basis that the target cell lacks inhibitory ligands. For several years, it remained unclear whether generalized adhesion molecule-interactions were sufficient for this task or additional stimulatory NK receptors specific for ligands expressed by normal cell types also participated.

More recently, a large variety of stimulatory receptors expressed by NK cells have been characterized. One class of stimulatory receptor, exemplified by Ly49H in mice and possibly NKp46 in humans, recognizes molecules encoded by viral pathogens and displayed on the surface of infected cells [14–16]. Another, exemplified by NKG2D, recognizes self proteins that are poorly expressed by normal cells but at elevated levels in diseased cells such as tumor cells or infected cells [17]. NKp46 (in a second role), NKp44 and NKp30 may also fall into this class [18]. A third class is the high affinity Fc receptor, through which NK cells mediate antibody dependent cellular cytotoxicity [19]. In addition to these receptors, several additional stimulatory receptors have been identified, for which the conceptual basis for their action in facilitating recognition of diseased cells is still not established. Among these receptors are stimulatory members of

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the KIR and Ly49 families [18,20,21], stimulatory forms of the 2B4 receptor [22], DNAM [23], and stimulatory isoforms of the NKR-P1 family of receptors [24,25]. Recent studies demonstrate that while engagement of adhesion molecules such as LFA-1 is usually essential for target cell recognition by NK cells, it is not sufficient to fully trigger a resting NK cell [26]. These studies have led to the notion that NK cell triggering generally requires the engagement of one or more stimulatory receptors. However, the stimulatory signals from these receptors can in most cases be countered by sufficiently strong engagement of inhibitory MHC specific receptors.

As a result of these advances, it no longer appears likely that the absence of self MHC molecules is a sufficient condition to render a cell sensitive to NK cell attack. More likely, NK cell activation generally requires engagement of specific stimulatory receptors by specific ligands, and some of these ligands are expressed by even the normal cell types generally studied, such as T and B lymphoblasts, bone marrow cells, and even mature unactivated lymphocytes [27]. In a few cases, stimulatory receptors involved in recognition of normal cells have been identified. For example, in H-2^d mice the NK subset expressing the Ly49D stimulatory receptor is stimulated because Ly49D binds the D^d MHC molecule present on all cells [28]. In BALB/c strain mice, the NKG2D stimulatory receptor is stimulated by Rae1 ligands which are specifically upregulated on bone marrow cells [29]. In both cases, NK cells can attack these otherwise normal cells if inhibitory Ly49 interactions are blocked or bypassed. On the other hand, neither NKG2D or Ly49D play such a role in B6 strain mice, suggesting the existence of additional stimulatory receptor interactions [29] (Guerra and Raulet, Unpublished data). Thus, it is clearly established that NK cells attack normal cell types when inhibitory recognition is absent or blocked, though only some of the stimulatory receptors involved have been identified.

2. The requirement for self tolerance of NK cells

The capacity of NK cells to recognize normal cell types highlights the importance of mechanisms to establish NK cell self tolerance. That NK cell self tolerance is acquired by a somatic process was suggested by early studies with MHC transgenic mice [4] and knockout mice [3], and established by studies with chimeric mice, in which MHC-different cells co-developed in the same animal [13,30,31]. In such mice, the NK cells are rendered tolerant of cells from either MHC-different parent.

A central question is how this self tolerance is established. A detailed knowledge of receptor and ligand expression patterns, binding affinities, and genetic polymorphisms suggests that the underlying processes are highly regulated. This is because the magnitudes of stimulatory and inhibitory signals that each NK cell receives when interacting with normal cells have the potential to vary dramatically in different individuals, and from one NK cell to another in the same individual. One reason is that some of the stimulatory ligands involved, such as MHC molecules and Rae1, differ in expression on normal cells depending on the mouse strain, as discussed above. Other reasons have been known for years. One of these is the fact that the inhibitory receptors are a family of 10–20 distinct proteins each of which binds to some MHC molecules and not others. As a result of the extreme allelic polymorphism of MHC genes, an inhibitory receptor that binds to one individual's MHC class I molecules may not bind to another's, or may bind with less affinity. Moreover, a second key feature of the inhibitory receptors is that each receptor is not expressed by all NK cells, but rather is expressed by only a subset of 5–50% of NK cells, overlapping with expression of other family members [32]. Studies show that each NK cell expresses an average of 3–5 different inhibitory receptors [33,34]. Furthermore, analysis of the frequencies of NK cells co-expressing different Ly49 molecules or KIR suggest that the set expressed by each NK cell is more or less random, so that all combinations are possible [33–35]. As a result of these variations, the magnitude of the inhibitory signal received by a developing NK cell may vary substantially from one cell to another. Finally, some of the inhibitory and stimulatory receptor genes exhibit polymorphism, including deletions of family members, which also potentially influences the magnitude of both stimulatory and inhibitory signaling that NK cells encounter in different strains [36,37]. Any theory of NK cell self tolerance must address how developing NK cells account for this unpredictable variation in stimulatory and inhibitory receptor and ligand expression.

Until recently, the thinking on this issue emphasized the notion that NK cell tolerance arises by ensuring that each NK cell expresses atleast one inhibitory receptor specific for self MHC molecules (the "at least one" model) [32]. Because initiation of receptor gene expression appears to be largely random, this notion requires that specific somatic processes act on the NK cells or receptor genes to accomplish this outcome. Expression of one or more inhibitory receptor specific for self MHC could be imposed either by selecting against cells that fail to express such receptors, or by a dynamic process in which individual developing NK cells sequentially and cumulatively initiate expression of additional inhibitory receptors until the cell expresses one or more that is self-specific [35]. Support for the latter mechanism came from analyses of NK cell development [38–40] and of natural variations in receptor expression patterns in MHC different mice and transgenic mice [41–43]. However, it was never proven that the sequential, cumulative expression of inhibitory receptors by developing NK cells continues until each NK cell necessarily expresses an inhibitory receptor specific for self MHC, and as described below, recent studies indicate that it does not do so for all NK cells. While this mechanism is expected to reduce the frequency of potentially autoreactive NK cells by equipping many NK cells with inhibitory self MHC-specific inhibitory receptors, it cannot account for the self tolerance of all NK cells.

3. Hyporesponsiveness as an explanation of self tolerance

Initial support for the "at least one" model came from a study showing that in panels of human NK cell clones, each clone expressed a receptor specific for the donor's MHC molecules [33]. However, panels of cloned cell lines do not necessarily reflect the repertoire present in vivo.

Once the tools became available to address whether each NK cell in normal mice expresses a self MHC-specific inhibitory receptor, we addressed the nature of the repertoire in vivo in C57BL/6 (B6, H-2^b) mice [44]. Only three of the known inhibitory receptors bind appreciably to the H-2^b class Ia molecules K^b and D^b: Ly49C and Ly49I which bind to K^b [45,46], and NKG2A/CD94 which binds to a D^b-derived peptide presented by the non-classical MHC molecule Qa-1 [11]. Using monoclonal antibodies that bind to these three receptors, we were able to show that approximately 10–15% of mature splenic NK cells in B6 mice lack the expression of all of them. Significantly, these NK cells were self-tolerant, as shown by an inability to attack B6 (self) lymphoblast target cells, as assessed by target cell cytolysis or production of interferon-γ (IFN-γ) by the NK cells [44]. These findings refuted the "at least one" hypothesis.

Functional analysis provided clues to the basis of the self tolerance of B6 NK cells lacking Ly49C, Ly49I and NKG2A [44]. Unlike NK cells that expressed one or more of Ly49C, Ly49I and NKG2A, NK cells lacking all these receptors failed to attack MHC class I-deficient lymphoblast target cells. This result argues strongly against the possibility that these NK cells fail to attack self lymphoblasts because they express an unidentified H-2^b-specific inhibitory receptor. If that were the case, these NK cells should attack MHC class I-deficient lymphoblasts. Another possibility was that self tolerance of these NK cells might be due to the increased activity of inhibitory receptors specific for non-MHC ligands on target cells. While this explanation has not been ruled out as a contributing factor, a different explanation is suggested by our finding that these NK cells were functionally impaired even when stimulated in the absence of target cells. Indeed, they exhibited impaired capacity to respond in vitro to plate-bound antibody-mediated cross-linking of stimulatory receptors such as NKG2D, NKR-P1C, and Ly49D. The cell surface levels of these stimulatory receptors were normal, and the NK cells responded nearly normally to pharmacological stimulation (protein kinase C activator plus ionomycin), suggesting that the dampened stimulatory responses of these cells may reflect a deficit in intermediate stages of the stimulatory signaling pathway. The defect is also evident in biologically important responses, as shown by the poor response of these NK cells to tumor cell lines, including YAC-1 and cell lines transduced to express Rae1, a ligand for the stimulatory NKG2D receptor. Furthermore, these NK cells were impaired in their capacity to reject bone marrow transplants from MHC class I-deficient mice [44].

Interestingly, earlier studies had established that NK cells in MHC class I-deficient mutant mice are self-tolerant, thus demonstrating that expression of "at least one" self MHC class I specific receptor is not necessary for self tolerance [3,12,13]. Furthermore, similar to B6 NK cells lacking Ly49C, Ly49I and NKG2A, the NK cells in MHC class I-deficient mice exhibited a hyporesponsive functional phenotype [12,47], including impaired responses to cross-linking of stimulatory receptors with plate-bound antibodies [44]. Thus, failure of developing NK cells to engage self MHC results in a similar outcome regardless of whether the failure reflects the absence of MHC class I molecules altogether (as in MHC class I-deficient mice), or the fact that stochastic mechanisms yield some NK cells lacking receptors specific for self MHC (as in normal animals). One hypothesis to explain the impaired functional activity of this special subset of NK cells, or of all NK cells in class I-deficient mice, is that the cells have not been allowed to reach full functional maturity. However, the cells exhibit a cell surface phenotype that is almost indistinguishable from responsive NK cells, including expression of CD11b, DX5 and Ly49 receptors (other than Ly49C and Ly49I) [44], which are thought to mark fully mature NK cells. Hence, these NK cells are mature according to the recognized maturation markers.

4. Mechanisms leading to hyporesponsive NK cells

What mechanisms underlie the formation of hyporesponsive NK cells? Our proposal is based on the following reasoning. The capacity of NK cells to attack normal self cells when inhibitory receptors are blocked is strong evidence that self cells express ligands that stimulate NK cells. We predict, therefore, that NK cells that lack inhibitory receptors for self MHC receive stimulatory signals that are not counterbalanced by inhibitory signals from MHC-specific inhibitory receptors. This could be expected to result in persistent net stimulation of these NK cells during their differentiation process. Persistent stimulation of T cells or B cells can lead to induction of anergy, a quasi-stable hyporesponsive state [48,49]. Our hypothesis is that as a response to persistent stimulation, developing NK cells that lack inhibitory receptors for self MHC adopt a hyporesponsive state comparable to anergy of T cells or B cells (Fig. 1).

Results reported by the Yokoyama laboratory are similar to ours in some respects but quite different in others [50]. They observed that NK cells that express Ly49C in B6 mice respond well to stimulation via the NKR-P1 stimulatory receptor, whereas those lacking Ly49C are much less functional. Because many NK cells that lack Ly49C express one or both of two other receptors that bind to MHC molecules in B6 mice, Ly49I and CD94/NKG2A (Treiner and Raulet, Unpublished data), it is not immediately obvious why the Ly49C-negative NK cells were functionally incompetent. But the most significant difference from our work was in the interpretation of the underlying mechanism. It was proposed that the engagement of the inhibitory receptors specific for self MHC molecules induces the cells to undergo a terminal maturation step. This was viewed as a "licensing" step that confers functionality specifically to NK cells with inhibitory receptors for self MHC [50]. Our model, in contrast, can be viewed as an active mechanism that "disarms" potentially autoreactive NK cells (Fig. 1).

Further studies will be necessary to elucidate the processes underlying hyporesponsiveness. However, some published experiments support our interpretation of the process. If persistent stimulation disarms NK cells, then it would be predicted that all the NK cells developing in a chimera consisting of a mixture of normal cells and MHC class I deficient cells would receive such stimulation from the class I-deficient cells and would adopt the hyporesponsive state. On the other hand, the licensing model would predict that in such chimeras, the MHC-

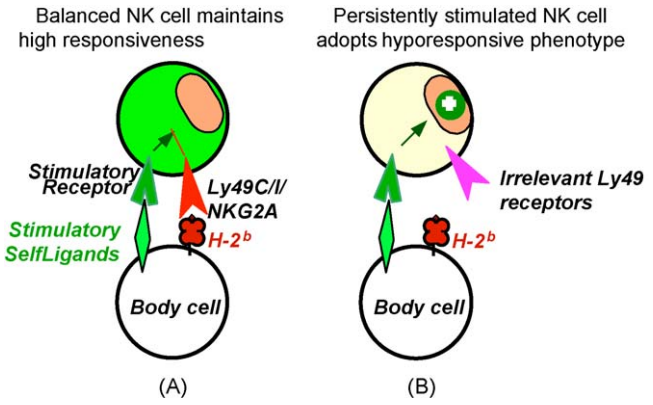

Fig. 1. Model to account for self tolerance of NK cells. Two NK cells are considered. (A) The NK cell on the left expresses a self MHC-specific inhibitory receptor (Ly49C, Ly49I or NKG2A in B6 mice), engagement of which counters constitutive signaling by stimulatory receptors specific for self ligands on normal cells. Under steady state conditions, the combined effect of both interactions (the "net" signal) is little or no stimulation by normal cells, which allows the NK cell to maintain a high degree of responsiveness. Infected or transformed cells that express higher levels of stimulatory ligands or lower levels of MHC can activate this NK cell. (B) The NK cell on the right does not express a self MHC-specific inhibitory receptor to counter constitutive stimulatory signaling. Consequently, it is subject to persistent stimulatory signaling, which ultimately causes the cell to adopt a hyporesponsive phenotype, defined as a dampened capacity to transmit activating signals by stimulatory receptors. The dampened response may be similar to that of T cells and B cells that are rendered anergic as a result of persistent stimulation in vivo. Under steady state conditions, the hyporesponsive NK cell is less responsive to stimulatory ligands expressed by normal cells, contributing to self tolerance. Infected or transformed cells that express higher levels of stimulatory ligands can activate this NK cell. However, decreased expression of MHC molecules does not increase the sensitivity of infected or transformed cells to the hyporesponsive NK cell, which cannot respond to such changes because it does not express receptors specific for self MHC molecules.

positive cells would dominantly license the NK cells. Results obtained in two different systems indicate that hyporesponsiveness, rather than responsiveness, is dominant in mixed chimeras [30,31]. These studies support the disarming model rather than the licensing model: persistent stimulation of NK cells by self cells that lack inhibitory MHC ligands disarms the NK cells, by inducing the cells to transition to the hyporesponsive state.

5. Quantitative and contextual aspects of tolerance

The concept of anergy as applied to lymphocytes is often discussed in terms of an on/off switch, as if individual lymphocytes are responsive or not to antigens or cells. However, it is more likely that hyporesponsive cells are turned down but not off, and that responsiveness to stimulation varies in different lymphocytes depending on: the quality of the inhibitory and stimulatory receptors they express, the ligands expressed in the host, and other factors. For example, some NK cells express no inhibitory receptors for self MHC, while others express one or more with weak affinity, and yet others express one or more with high affinity. Everything else being equal, we would predict that the outcome would differ for each set of developing NK cells, with the latter cells acquiring the greatest intrinsic responsiveness to stimulation. Variations in expression of stimulatory receptors for self ligands would be expected to have the opposite effect. These predictions are currently being tested.

Possibly relatedly, hyporesponsiveness may be 'contextual', in the sense that it impairs some functional outcomes and not others. Indeed, we found that despite the intrinsic responsiveness defects of NK cells that lack inhibitory receptors for self MHC, the cells were indistinguishable from other NK cells with respect to their capacity to produce intracellular IFN-γ in vivo in mice infected with several pathogens, including mouse cytomegalovirus (MCMV) and *Listeria monocytogenes* [44]. Thus, after infection, the cells are competent to execute at least one functional activity: production of IFN-γ. IFN-γ production by NK cells is important in controlling infections with viruses (including MCMV) and other pathogens [51]. Whereas our data did not address the capacity of these NK cells to control infection, an early study provided evidence suggesting that NK cells in MHC class I-deficient mice were as capable as wild type NK cells of controlling splenic MCMV infections in vivo [52]. These findings suggest that hyporesponsive NK cells can be functionally competent in vivo in some contexts. Clearly, the functional role of such NK cells needs to be characterized more deeply.

It remains possible that the residual competence of hyporesponsive NK cells in vivo reflects the activation of NK effector functions solely through the action of IL-12 and other cytokines, independent of the action of stimulatory receptors on the cells. However, it is also possible that these functions depend on stimulatory receptor engagement. It may be envisaged, for example, that the dampened signals such NK cells receive through stimulatory receptors are compensated by the failure of the cells to receive opposing inhibitory signals dependent on MHC recognition. The net stimulation resulting from the combination of a weakened stimulatory signal and no inhibitory signal may be comparable to that received by a more responsive NK cell that also received inhibitory signals via MHC specific receptors. Hence, the 'hyporesponsive' NK cells may be capable of attacking infected cells or tumor cells in some circumstances. Note that this situation applies to NK cells responding to cells expressing MHC molecules, and differs from the responses resulting from cross-linking stimulatory receptors, where inhibitory signaling plays no role. In the latter situation, the weak responses reflect the dampened stimulatory signaling of these cells in isolation, and not the combined effects of stimulatory and inhibitory signaling.

6. Concluding remarks

The various considerations discussed here suggest that hyporesponsive cells are not necessarily non-functional cells. We predict that many functions of NK cells remain intact in hyporesponsive NK cells. The absence of inhibitory receptors for self MHC should, however, prevent them from accomplishing "missing self recognition", defined as enhanced targeting of cells that express lower levels of self MHC class I molecules. This prediction is fulfilled by our finding that these NK cells are specifically defective in attacking MHC class I-deficient bone marrow cells in vivo, or lymphoblasts in vitro.

This line of thinking raises an interesting basic question which has not yet been adequately addressed: what are the relative contributions of missing self recognition versus other forms of recognition to the effectiveness of NK cells in biologically important responses such as those to specific viruses, tumors, etc? Recent progress in the field indicates that effective responses to infected cells and tumor cells usually involves engagement of stimulatory receptors by ligands that are expressed specifically on the diseased cells. Indeed, the necessity for missing self recognition in controlling naturally occurring diseases remains untested in most instances. An important future goal will be to distinguish the contributions of different components of NK cell recognition in immune responses, a task which can be addressed with studies combining mouse genetics, pathogen genetics and cellular immunology.

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