

# Innate and adaptive immunity: specificities and signaling hierarchies revisited

Eric Vivier & Bernard Malissen

The conventional classification of known immune responses by specificity may need re-evaluation. The immune system can be classified into two subsystems: the innate and adaptive immune systems. In general, innate immunity is considered a nonspecific response, whereas the adaptive immune system is thought of as being very specific. In addition, the antigen receptors of the adaptive immune response are commonly viewed as 'master sensors' whose engagement dictates lymphocyte function. Here we propose that these ideas do not genuinely reflect the organization of immune responses and that they bias our view of immunity as well as our teaching of immunology. Indeed, the level of specificity and mode of signaling integration used by the main cellular participants in the adaptive and innate immune systems are more similar than previously appreciated.

In vertebrates, innate and adaptive immunity are commonly distinguished on the basis of their levels of specificity, with the antigen receptors of the adaptive immune system mediating highly specific responses, in contrast to the more promiscuous, and therefore less specific, recognition of pathogens by the innate immune receptors. Although this 'specific versus nonspecific' opposition between innate and adaptive immune responses might seem at first sight a purely theoretical consideration, it is so commonly used in immunology that this idea should be revisited.

Innate immune receptors recognize a limited number of molecules, some of which are evolutionarily conserved and are shared by many infectious agents (such as lipopolysaccharides, peptidoglycans, non-methylated CpG and double-stranded RNA; **Fig. 1**)<sup>1–4</sup>. These receptors are germline encoded and although their expression may be restricted to particular cell types, they are not clonally distributed (**Table 1**). Many of these innate recognition sensors are called pattern-recognition receptors and include the Toll-like receptor (TLR) family<sup>1,5</sup>. Within a given species, the genes encoding the innate receptors show various degrees of polymorphism. Innate receptor ligands of self origin can also be polymorphic, as exemplified by various natural killer (NK) receptor-ligand pairs (such as killer cell immunoglobulin-like receptor (KIR)–major histocompatibility complex (MHC) class I or NKG2D–NKG2D ligands;

**Fig. 1**). Nevertheless, groups of individuals within a given species share an identical innate recognition repertoire (**Table 1**).

Species with an adaptive immune response have large repertoires of T cell antigen receptors (TCRs) and antibodies, and possibly variable lymphocyte receptors<sup>6</sup>. Together these receptors make up a recognition repertoire that increases the possibility that the adaptive immune response can detect any possible antigen encountered throughout life. TCR and BCR diversity is generated somatically through site-specific DNA recombination, and each receptor of a particular specificity is expressed in a clone of lymphocytes. TCR-mediated T cell responses are governed by molecules encoded by MHC alleles that present antigenic peptides to TCRs<sup>7</sup>, but in contrast to innate recognition sensors, there exists *a priori* no 'specific' or 'physiological' ligand for a given TCR. A given peptide-MHC (pMHC) ligand is operationally qualified as 'cognate' after it successfully activates a specific T cell clone. The definition of 'self' is specified in each individual during the development of the adaptive immune system and varies among individuals based on inherited MHC alleles and the self peptides presented by these alleles. In the case of B cells, the shaping of the antigen-recognition repertoire is also the result of developmental processes that vary between individuals, as it has been established that negative and positive selection events are essential features of B cell development<sup>8</sup>. Therefore, the nature of innate and adaptive repertoire constitutes a key difference between these two types of immunity.

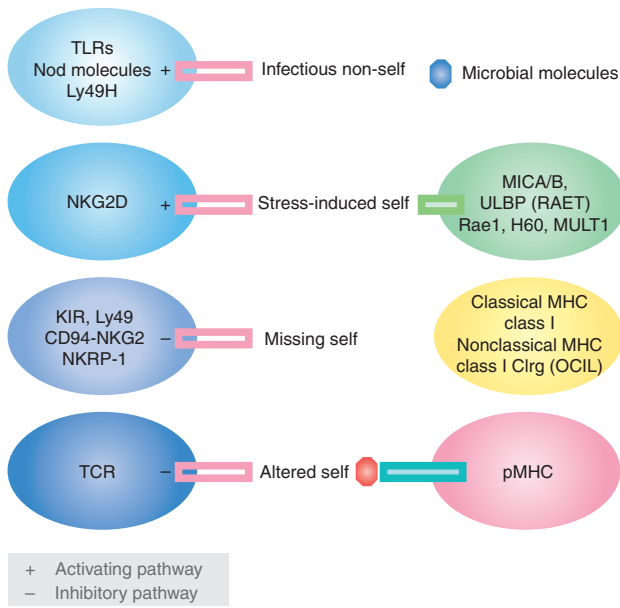
## Binding specificity and degeneracy

Binding specificity and degeneracy are imprecise but widely used concepts in immunology. Degeneracy (also called cross-reactivity, poly-specificity or molecular promiscuity) can be defined as the ability of one receptor to elicit a cellular response following its interaction with a multitude of ligands that are structurally distinct. Conversely, specificity (also called monospecificity or molecular monogamy) can be defined as the ability of a given receptor to interact productively with a single or a few ligands related in structure. However, it should be stressed that degeneracy and specificity constitute the two extremes of a continuum of molecular interactions, and several examples demonstrate that degeneracy in antigen recognition constitutes a fundamental property of adaptive immunity, whereas other examples support the idea that innate recognition can reach a high level of specificity<sup>9</sup>.

TCRs scan the composite surfaces produced by an MHC molecule and the peptide residing in its groove and relay this information to the interior of T cells. Loops homologous to antibody complementarity-determining regions protrude at the membrane-distal ends of both

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**Figure 1** Strategies of immune recognition. In addition to the classical ‘altered self’ recognition of pMHC complexes used by T cells through their TCR<sup>52</sup>, several strategies of immune recognition coexist, sometimes on the same cells. Cells of the innate immune system (as well as some B and T cell subsets) express germline-encoded receptors such as TLR or Nod molecules that can sense infectious non-self molecules<sup>1,3</sup>. In addition, NK cells express the cell surface Ly49H molecule that is an activating innate receptor specific for a virus product (m157 encoded by the mouse cytomegalovirus). Immune effectors can also sense cells in distress without direct recognition of the stress inducer. NKG2D is an example of such a receptor for stress-inducible molecules, such as MICA/B and ULBP (also known as RAET) molecules in humans, as well as H60, MULT1 and Rae1 molecules in the mouse. The function of immune effectors (such as NK cell and T cell subsets) is also negatively regulated by recognition of self through engagement of inhibitory receptors<sup>38</sup>. Examples of inhibitory receptors for self include KIR (in humans) and Ly49 (in the mouse), which recognize classical MHC class Ia molecules; CD94-NKG2A, which recognizes nonclassical MHC class Ib molecules (HLA-E in humans and Qa-1 in the mouse)<sup>53</sup>; as well as NKR1P molecules, which interact with members of the C1r family<sup>54,55</sup>.

TCR V<sub>α</sub> and V<sub>β</sub> domains, where they collectively form the pMHC-binding site. A single TCR antigen-binding site can show both high specificity and degeneracy (Fig. 2). These conflicting properties constitute an essential characteristic that allows the repertoire of T cells in an organism to recognize essentially any peptide and to achieve specific recognition of a cognate peptide in physiological conditions despite a typical excess of 10<sup>3</sup>–10<sup>4</sup> self peptides that may differ from the cognate peptide by only one amino acid at a primary contact residue.

Complementarity-determining region conformational changes similar to those accounting for TCR binding degeneracy are also noted in the antigen-binding sites of primary antibodies. During a secondary immune response, somatic hypermutations coupled to selection in the germinal center can convert a conformationally flexible and low-affinity site into one that binds antigen with an affinity up to 30,000-fold higher through an entropically favorable ‘lock-and-key’ mechanism<sup>10</sup>. Given that TCR genes are not subjected to somatic hypermutation, it is likely that TCR antigen-binding site conformational flexibility is a recurrent feature of TCR-pMHC interactions that is critical for the adaptive immune response, which therefore explains why such conformational plasticity is selected.

What are the consequences of cross-reactivity in antigen recognition? For T cells, it has been calculated that as many as 10<sup>15</sup> distinct αβ TCRs can be generated. Because each person has only about 10<sup>12</sup> T cells, and a mouse even less, it is obvious that the full repertoire of TCR specificities cannot be deployed at any given time. Because the diversity of pMHC

ligands that can be encountered greatly exceeds the number of T cell clones present in a person at any one time, the ability to recognize almost any pMHC with a limited number of T cells and within a time frame compatible with the speed at which infectious agents spread may be achieved only by binding degeneracy at the level of TCR-pMHC recognition<sup>11</sup>. TCR cross-reactivity is also involved during intrathymic T cell positive selection and homeostatic survival in the periphery<sup>12,13</sup>. Furthermore, TCR cross-reactivity between antigenic epitopes expressed by various pathogens allows an infection to reactivate memory T cells with distinct specificities to earlier microbes<sup>14,15</sup>. Therefore, degeneracy in TCR recognition allows the immune system to generate a T cell repertoire capable of recognizing multiple pathogens over the course of a lifetime.

Crystallographic studies of mannose-binding proteins (MBPs) emphasize the degree of specificity that can be reached by innate immune recognition. MBPs trigger the activation of the lectin-complement pathway and can recognize monosaccharides found on microorganisms as well as on vertebrate cell surfaces. The principal factor for distinguishing self from non-self lies in the oligomeric structure of MBPs. As with other lectins, the interactions between MBPs and monovalent ligands are extremely weak, and they only achieve tight, specific binding at the cell surface through multivalent interactions<sup>16</sup>. The trimeric structures of rat and human MBPs show that the sugar-binding sites on the trimer are spaced too far apart to bind to different branches of typical vertebrate high-mannose oligosaccharides. However, they are presumably able to bind multivalently to the dense, repetitive arrays of ligands present on bacterial and fungal cell surfaces<sup>17,18</sup>. Therefore, MBPs represent an example of a pattern-recognition receptor: its molecular specificity is embodied at the level of its monomeric ligand-binding site, and its self–non-self specificity, in the cooperative binding-site that exists within the trimer. However, most innate immune sensors probably do not detect pattern at all, but detect microbial or self molecules<sup>2</sup>.

Specificity in innate immune recognition is also illustrated by analysis of other innate sensors. Despite the limited spectrum of ligands recognized by each of the 13 known mammalian TLR paralogs, the TLR repertoire might detect most, if not all, microbes<sup>3,19</sup>. The fact that the TLR targets are highly represented in the microbial world does not necessarily mean that TLRs have high binding degeneracy. The breadth of TLR recognition may well be due to the recognition of conserved motifs shared by most microorganisms. However, the direct interaction between microbial molecules and most of their innate sensors has not yet been demonstrated, so structural characterization of TLR-ligand complexes will be required to settle this important issue. Members of the nucleotide-binding oligomerization domain (Nod) family also serve as intracellular sensors for bacterial products. Nod1 and Nod2 recognize with an

**Table 1** Distinctive features of innate versus adaptive immunity

|              | Innate immunity   | Adaptive immunity   |
|--------------|---|---|
| Receptors    | Germline-encoded  | Antigen receptors are products of site-specific somatic recombination |
| Distribution | Subset-specific but nonclonal                                       | Antigen receptors are clonally-distributed                            |
| Repertoire   | Limited<br>Selected in groups of individuals within a given species | Immense<br>Selected in each individual within a given species         |
| Memory       | No  | Yes   |

**Figure 2** Degeneracy of the TCR antigen-binding site. The structure of the BM3.3 TCR in complex with two distinct peptides, pBM1 (a) and VSV8 (b), bound to the H-2K<sup>b</sup> MHC class I demonstrates some general features of TCR antigen-binding sites<sup>56,57</sup>. Amino acid residues are indicated with single-letter code.  $\alpha$ , TCR $\alpha$ ;  $\beta$ , TCR $\beta$ ; p, peptide. When the BM3.3 TCR is in complex with both pBM1–H-2K<sup>b</sup> and VSV8–H-2K<sup>b</sup> ligands, it centers on the peptide residue found at position 6, the only one that is homologous between pBM1 and VSV8. In contrast to the pBM1 peptide, for the VSV8 peptide all the other TCR contact positions found are subject to nonconservative replacements. Replacement at position 7 affects TCR binding in a negative way, whereas the replacement at position 4 was beneficial because of the flexibility of complementarity-determining region 3 (CDR3 $\alpha$ ). Although CDR3 conformational changes help to explain BM 3.3 TCR binding degeneracy, the BM3.3 TCR can also show exquisite specificity, in that it fails to recognize most analogs of the pBM1 or VSV8 peptides differing at position 6. The MHC class I  $\alpha_1$  helix is the green cylinder in the background. BM3.3 CDR3 $\alpha$  and CDR3 $\beta$  are thin bars and the interactions they form with the pBM1 and VSV8 peptides are red and blue dotted lines (hydrogen bonds) and gray dotted lines (van der Waals contacts). Reprinted from ref. 56.

exquisite specificity ligands derived from bacterial peptidoglycans, with only small differences distinguishing Nod1 ligands (muramyl tripeptide structures in which the terminal amino acid is diaminopimelic acid) from Nod2 ligands (muramyl dipeptide structures)<sup>20</sup>. Finally, an additional example of fine specificity in innate immunity sensors comes from characterization of the Ly49H receptor expressed by NK cells that is specific for the m157 product of the mouse cytomegalovirus<sup>21–23</sup>.

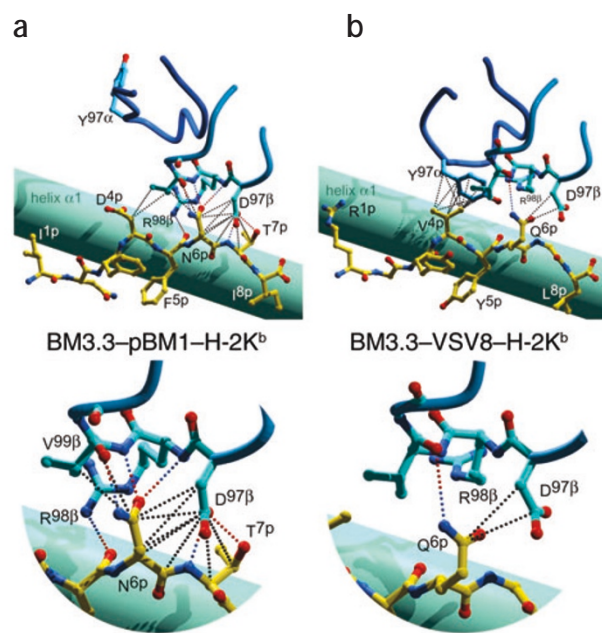
Therefore, by analysis at the molecular level there seems to be no intrinsic difference between innate and adaptive immunity in the fundamental principles of molecular recognition. Both show alternatively, or coincidentally, fine specificity as well as degeneracy. Accordingly, the distinction between innate and adaptive immunity based on the degree of specificity of receptors or on the range of affinity they operate does not necessarily apply to all recognition systems in these two arms of the immune system<sup>24</sup>.

### Receptor versus cellular specificity

At this stage, it is critical to emphasize that receptor specificity and cross-reactivity constitute empirical and assay-dependent properties. The sensitivity of some *in vitro* assays is sometimes much too high and demonstrates cross-reactions that are not biologically relevant<sup>25</sup>. For example, the observation that cytotoxic T cells stain with MHC class I–peptide multimeric probes does not always mean that the CTLs are capable of inhibiting viral replication successfully. The range of cross-reactivity shown by a given TCR is not a property intrinsic to the TCR but also depends on the developmental stage and/or the activation status or the signaling network that acts ‘downstream’ of the T cell clone that expresses it. In support of this view, it has been shown that the protein tyrosine phosphatase SHP-1 can increase the specificity of TCR signaling by inhibiting signals emanating from TCR–pMHC interactions with short half-lives<sup>12</sup>. Therefore, TCR (or more appropriately T cell) specificity-degeneracy is a property of the whole T cell, a situation that can be ‘transposed’ to B cells and NK cells.

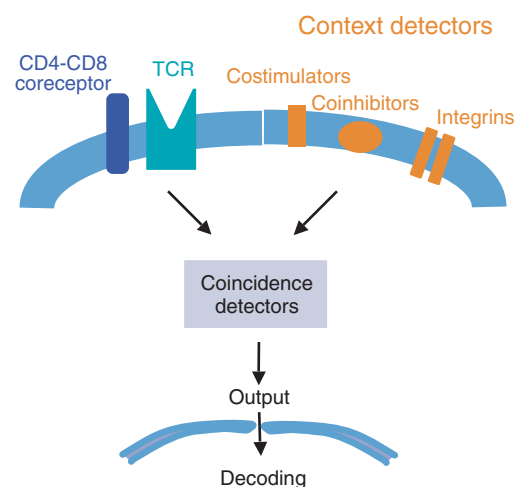
### Figure 3 Is a ‘two-signal’ model of T cell activation still tenable?

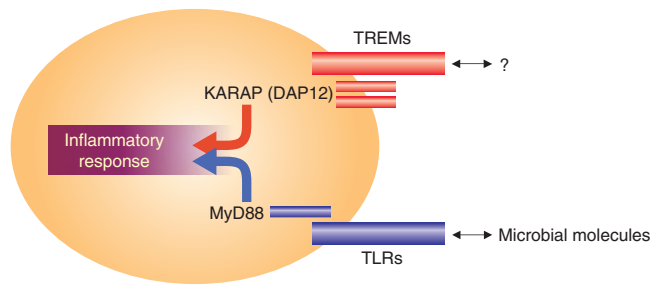
Signals emanating from the TCR (or the BCR) and the optional signals originating from a vast array of cell surface context detectors converge on intracytoplasmic coincident detectors. Among the surface context detectors, much attention has focused on the CD28 costimulator. However, signals originating from the antigen receptor core can also be ‘tuned’ by many costimulators (such as CD5, CD19, NKG2D or integrins) and coinhibitors (such as CD5, CD22, Fc $\gamma$ RIIb or KIRs). The CD8–CD4 coreceptors constitute intrinsic components of the TCR sensor<sup>57</sup>. It remains a daunting task to understand how the antigen-receptor signaling pathways are regulated through the summation of this multitude of positive and negative inputs.



### Master and servant receptors?

In T cells, antigen receptor inputs are often referred to as ‘primary’ signals (known as signal 1), fine tuned by ‘secondary’ signals emanating from the engagement of ‘context’ detectors (such as CD28, NKG2D, KIRs and CD21) that contribute additional information regarding the nature and state of activation of the antigen-presenting cells. However, the engagement of a given TCR expressed at the same density on two T cells that differ in the expression or density of costimulatory and coinhibitory molecules results in different functional outcomes<sup>26</sup>. Moreover, TCR signaling hypersensitivity can be induced after adhesion-induced T cell priming<sup>27</sup>, which minimizes the pMHC density required for activation and substantially broadens ligand cross-reactivity. Although TCRs and BCRs are central to lymphocyte development, these examples thus blur the existence of a fixed hierarchy distinguishing the signals that emanate from antigen receptors (the TCR–BCR ‘masters’) and from context detectors (the costimulator and coinhibitor ‘servants’) on mature effector lymphocytes (Fig. 3). Antigen-independent T cell responses also challenge the ‘master-versus-servant’ view of the TCR versus context detectors expressed by





**Figure 4** Cross-talk between ITAM- and TLR-dependent pathways. Neutrophils and macrophages coexpress TLRs and TREMs (triggering receptors expressed by myeloid cells)<sup>58</sup>. TREMs are coupled to the ITAM-bearing polypeptide KARAP (DAP12)<sup>59,60</sup>. TREMs and TLRs act in synergy for cytokine and chemokine production by monocytes and neutrophils<sup>46</sup>. Moreover, blocking the TREM1 pathway *in vivo* stops the development of sepsis<sup>47</sup>. Finally, KARAP (DAP12) and TREM expression is upregulated after TLR4 triggering<sup>61</sup>. Thus, cross-talk exists between TLRs and TREMs, exemplifying the complex integrative network of receptor-dependent pathways that determine cellular specificity.

T cells. For example, effector and memory CD8<sup>+</sup> T cells have the potential to secrete interferon- $\gamma$  in response to cytokines such as interleukins 12 and 18 in the absence of cognate antigen<sup>28</sup>. Thus, memory CD8<sup>+</sup> T cells seem capable of providing some kind of antigen-independent immune protection against *Listeria monocytogenes* and, likewise, in memory B cells, BCR-derived signals have been shown to be substituted by those emanating from TLR signaling<sup>29</sup>.

The elucidation of lymphocyte signaling mechanisms provides a rationale for the rather intricate and dynamic relationships that occur at the lymphocyte membrane between ‘master and servant’ receptors. Immunoreceptors such as TCR, BCR, Fc receptors or various NK cell receptors are coupled to immunoreceptor tyrosine-based activation motif (ITAM)-bearing signaling polypeptides that connect them to protein tyrosine kinase (PTK)-dependent pathways<sup>30</sup>. Conversely, protein tyrosine phosphatases (PTPs) seem as a common (if not constant) element of inhibitory pathways that negatively regulate lymphocyte activation<sup>31–33</sup>. The PTK-PTP dynamic equilibrium is subject to receptor engagement and thus controls lymphocyte activation. In T cells, many positive (for example, CD28) or negative (for example, KIR) regulators influence the PTK-PTP balance and thus ‘tune’ the strength of the  $\alpha\beta$  TCR signaling in response to antigen<sup>34,35</sup>. Likewise, the inherent autoreactivity of the invariant TCRs (as found on the NKT cells and some  $\gamma\delta$  T cell subsets) seems to be controlled by a balance between inhibitory and activating receptors<sup>36</sup>. In conditions of stress and tissue damage, this balance is tipped in a way that unleashes autoreactivity, as exemplified by engagement of the activating receptor NKG2D through its stress-induced self ligands<sup>37–39</sup> (Fig. 1).

For the BCR, antigens present at the surface of intact infectious agents or at the surface of follicular dendritic cells are very often arranged in a highly repetitive way and can plausibly engage BCRs<sup>25</sup>. However, a complex consisting of CD21 and CD19 molecules additionally ‘tunes’ the initiation of B cell responses. After tagging of antigens by complement, the CD21-CD19 complex becomes juxtaposed with the BCR and potentiates the BCR’s transducing properties, in part through the recruitment of phosphatidylinositol 3-kinase. Thus, the CD21-CD19 complex ensures that fewer engaged receptors per unit of time lead to the same signal output<sup>40,41</sup>. Conversely, when brought into proximity with ligand-engaged BCRs, the inhibitory Fc $\gamma$  receptor IIb (Fc $\gamma$ RIIb) becomes a substrate for the BCR-associated PTKs. After phosphorylation, Fc $\gamma$ RIIb recruits phosphatases that blunt BCR firing, accounting for immunoglobulin G-mediated

negative regulation of antibody responses<sup>33,42</sup>. Therefore, ligand-induced clustering constitutes a way of promoting functional cross-talk between ITAM-containing receptors and coinhibitors or costimulators.

Activation of innate immunity cells also results from the integration of multiple positive and negative signals. For example, the ‘missing-self’ model of NK cell activation is just one of many examples of integration of positive and negative signals in the innate immune system<sup>43</sup>. Indeed, the ‘strength’ of activating signals in NK cells after engagement of activating receptors can override the inhibitory signals induced by engagement of inhibitory receptors for MHC class I molecules. This enables MHC class I-positive cells to serve as NK cell targets, as long as sufficient activating signals are provided<sup>44,45</sup>. Cross-talk also exist between innate sensors belonging to different families. The synergy between TLR-dependent and ITAM-dependent pathways (through the signaling adaptor KARAP (also known as DAP12)) constitutes an important example linked to the development of inflammation and inflammatory pathologies such as sepsis<sup>46,47</sup> (Fig. 4). Therefore, it may be more appropriate to consider the activation of both adaptive and innate immune cellular effectors as an integration of signals emanating from an array of equally contributing receptors that converge onto intracytoplasmic coincidence detectors, rather than as receptors operating in a system in which ‘some are more equal than others’<sup>48</sup>.

## Conclusions and perspectives

The beauty of the somatic mechanisms used to generate antigen-receptor diversity has led to rather ‘TCR- and BCR-centric’ views of the immune system. As a consequence, the specificity of these receptors is often presented as being unique in the immune system, especially compared with that of innate immune sensors. We have attempted to show here that the receptor-ligand pairs used in adaptive and innate immune responses are often capable of both specific and promiscuous recognition. In addition, in both innate and adaptive immunity, receptor specificity is composed of the whole system that integrates, through coincidence detectors, the cross-talk existing between multiple receptors that make up the immunocyte signaling network. Thus, the generation and the size of the repertoire might be the only distinguishing factors between adaptive and innate immunity.

These conclusions have several practical consequences. First, TCR specificity has been (and still is) a chief focus of T cell-based immunotherapeutic strategies. However, the adaptive nature of the TCR-pMHC interface and the fact that TCR (or more appropriately T cell) cross-reactivity is a property of the whole system emphasize the challenge of predicting the outcome of TCR-centered clinical strategies. On one side, the alloreactive potential of TCRs severely limits the manipulation of nonclonal T cell populations in MHC-mismatched adoptive transfer settings. Yet the function of TCR cross-reactivity also remains to be fully appreciated in graft-versus-host disease in MHC-matched hematopoietic transplantations. Indeed, the high occurrence of graft-versus-host disease in this setting (40%) involves the recognition of recipient minor transplantation antigens against which the donor T cells are reactive<sup>49</sup>. On the other side, the exploitation of TCR and antibody cross-reactivity could be of immense importance for vaccine design against infectious diseases. Indeed, increasing evidence now exists of human and mouse TCRs that are cross-reactive between various viruses, such as influenza and Epstein-Barr virus, influenza and hepatitis C viruses as well as papilloma virus and coronavirus<sup>15</sup>. However, the rationale identification of cross-reactive epitopes seems difficult to predict in most examples<sup>50</sup>.

Second, the elucidation of a variety of innate recognition strategies might lead to new immunotherapeutic approaches. There are already clinical situations in which polymorphisms in innate sensors expressed on NK cells can be used in a controlled way. Indeed, MHC-mismatched

bone marrow transplantation in hosts whose MHC class I alleles do not act as inhibitory ligands for the KIRs expressed by donor NK cells functions as an adjuvant therapy to eliminate leukemia relapse and graft rejection and to protect patients against graft-versus-host disease<sup>51</sup>. Although the development of innate immunity-based innovative therapies awaits further development, the manipulation and adoptive transfer of innate immune effectors may be feasible because it is potentially safe and predictable.

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#### COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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## Erratum: Signaling by the kinase MINK is essential in the negative selection of autoreactive thymocytes

Nami McCarty, Silke Paust, Koichi Ikizawa, Ippeita Dan, Xiaoyan Li & Harvey Cantor  
*Nature Immunology* 6, 65–72 (2005)

On page 70, line 28 should read "...IL-7 receptor-positive CD4<sup>lo</sup>CD8<sup>hi</sup> (refs. 34,35)." *Nature Immunology* regrets this error.

## Errata:

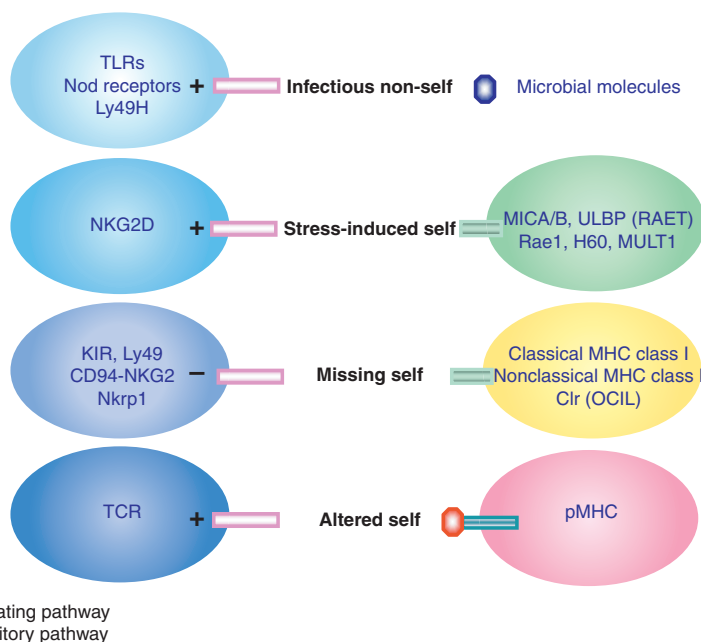
*Nature Immunology* 5, 1190 (2004).

The two corrigenda on page 1190 in the November 2004 issue (volume 5, issue 11) gave incorrect publication dates. Those should be 2004. *Nature Immunology* regrets this error.

## Erratum and corrigendum: Innate and adaptive immunity: specificities and signaling hierarchies revisited

Eric Vivier & Bernard Malissen  
*Nature Immunology* 6, 17–21 (2005)

On page 18, Figure 1 was incorrect. The correct figure is presented here. *Nature Immunology* regrets this error. On page 19, in the legend to Figure 3, line 7 should read "(such as CD19, NKG2D or integrins)...."



## Corrigendum: Building an antibody factory: a job for the unfolded protein response

Joseph W Brewer & Linda M Hendershot  
*Nature Immunology* 6, 23–29 (2005)

On page 26, lines 20 and 21 should read "...CHOP (also known as *DDIT3* or *GADD153*)...."