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Shades of grey — the blurring view of innate and adaptive immunity

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FOREWORD

Shades of grey — the blurring view of innate and adaptive immunity

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Abstract | This special issue of *Nature Reviews Immunology* focuses on the types of lymphocyte that blur the traditional boundaries between the innate and adaptive immune systems. The development and functional properties of 'innate-like' B and T cells and natural killer (NK) cells are reviewed and the emerging understanding of newly discovered innate lymphoid cells (ILCs) is considered.

Historically, immunologists have embraced binary classification. We had two types of lymphocyte (B and T cells); then two types of B cell (B-1 and B-2 cells); and two types of T helper (T_H) cell (T_H1 and T_H2 cells); as well as two immune systems (innate and adaptive). However, the number of lymphocyte subsets seems to expand whenever a lymphoid cell secreting a new cytokine is identified. We now often refer to innate immune features of B cells and T cells and appreciate the adaptive immune properties of natural killer (NK) cells. As these new insights emerge, it is timely to step back and re-evaluate the definitions of innate and adaptive immunity and to consider what constitutes a stable lymphocyte subset as opposed to simply an activation or differentiation stage of a given cell type.

Innate-like B cells and T cells

The definition of B and T cells can be based on definitive and unequivocal criteria. T cells productively rearrange T cell receptor (TCR) genes, express TCRs on their cell surface and use these highly diversified receptors to recognize their cognate antigens. Similarly, B cells productively rearrange immunoglobulin genes, display immunoglobulins on their cell surface as B cell receptors (BCRs) and respond to their cognate antigens by differentiating into mature B cells or plasma cells that secrete soluble antibodies. When naive B and T cells encounter antigens of sufficiently high affinity, this triggers their activation, clonal expansion and differentiation. During this process, T cells acquire distinct effector functions (such as the secretion of a distinct array of cytokines or cytolytic activity), and some B cells undergo immunoglobulin isotype switching and somatic hypermutation, which can increase the affinity of their antibodies. After clonal expansion, some of these B and T cells become memory cells. This is the textbook view of the adaptive immune response. However, not all B and T cells behave according to this simplified schema.

As reviewed by Brenner and colleagues in this issue[1], a distinct subset of T cells — designated invariant natural killer T (iNKT) cells — express an αβ TCR that preferentially uses a single TCRα gene and a very restricted set of Vβ genes. Unlike 'conventional' T cells, which recognize peptide antigens bound to MHC class I or II molecules, iNKT cells recognize lipids displayed on CD1d molecules. Functionally, these iNKT cells have been considered to be 'innate-like T cells', as they appear to be poised to robustly produce cytokines more rapidly than conventional naive T cells. Moreover, it has been thought that iNKT cells do not possess memory after their encounter with an antigen, although this issue should be revisited to explore whether there are stable, heritable alterations in iNKT cells after their initial activation.

The mucosa-associated invariant T (MAIT) cells are another type of T cell with restricted TCR chain usage (human MAIT cells express a Vα7.2Jα33 chain coupled with a limited repertoire of TCR β-chains). MAIT cells are preferentially localized in mucosal tissues and respond to microbial infection by rapidly producing cytokines and cytotoxic effectors[2]. Their distinguishing characteristic is the recognition of the ubiquitously expressed non-polymorphic MHC-related molecule MR1, which binds to riboflavin metabolites from bacteria and fungi. As with iNKT cells, whether MAIT cells possess immunological memory has not been definitively addressed.

γδ T cells constitute another population with innate properties, including the rapid secretion of cytokines and cytolytic activity[3]. Functionally distinct subsets of γδ T cells have been defined on the basis of preferential expression of certain Vγ or Vδ genes. γδ T cells are pre-programmed to acquire their effector functions before egress from the thymus. They do not require MHC or MHC-related molecules for their development and can recognize a wide range of antigens, although the ligands for most γδ TCRs remain elusive. As with other innate T cells, the issue of immunological memory in γδ T cells is unresolved.

B cells with 'innate-like' functions include B-1 cells, which are localized at epithelial barriers, and marginal zone B cells, as reviewed by Cerruti and colleagues[4]. These B cell populations make natural antibodies that recognize

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conserved features of bacterial carbohydrates and phospholipids. Moreover, B-1 cells express Toll-like receptors (TLRs) that allow them to be activated by a broad array of microbial ligands. Although natural antibodies often have a lower affinity than antibodies generated by B-2 cells, they can protect the host against bacterial pathogens early after infection.

Innate B and T cells share several common features. They all possess a relatively restricted repertoire of antigen receptors. In addition, compared with conventional B and T cells, innate B and T cells are enriched in mucosal tissues, where pathogens are first encountered. In some cases, their poised state that allows them to rapidly respond after infection is due to the constitutive transcription of cytokine genes.

Innate lymphoid cells

Whereas recombination activating gene (RAG)-dependent genetic rearrangement of the immunoglobulin and TCR loci serves as a non-reversible marker of B and T lineage cells, respectively, the definition of other lymphoid populations is less precise, and often somewhat arbitrary. Innate lymphoid cells (ILCs) are, in part, defined by what they are not. They are not B or T cells, as they lack expression of a functional BCR or TCR. The term lineage marker-negative has been used to define ILCs, although what constitutes a lineage marker is unclear. ILCs have been designated lymphoid cells based on evidence that they can be derived from a common lymphoid progenitor and on their morphology, although such criteria can be subjective.

The prototypical ILC is the NK cell, which has a lymphoid morphology and arises from the common lymphoid progenitor. NK cells share so many features with T cells that the NK cell lineage must be defined by the lack of TCR expression combined with the presence of an array of other cell-surface markers, all of which can be found on subsets of T cells, particularly γδ T cells and iNKT cells[5,6]. NK cells possess numerous activating and inhibitory receptors that regulate their cytolytic activity and cytokine secretion. Some of these receptor systems — for example, the killer cell immunoglobulin-like receptors (KIRs) in humans and the LY49 family receptors in rodents — are highly polymorphic. As discussed by Parham and Moffett[7], these rapidly evolving NK cell receptors are being diversified to accommodate changes in their polymorphic MHC class I ligands, but possibly also to ensure reproductive success.

Recently, several previously unappreciated types of lymphoid cell have been discovered, as reviewed by McKenzie and colleagues[8]. These newly identified ILCs are difficult to categorize because they lack specific cell-surface markers that are not shared with NK cells, T cells or myeloid cells[9].

A consortium of investigators has proposed a unifying nomenclature that entails the classification of ILCs into three groups[10]. So far, NK cells are the only ILCs known to have cytolytic activity or express perforin, which might be useful criteria to distinguish NK cells from other ILCs. More precise lineage-tracing studies are required to resolve whether the numerous subsets of ILCs truly represent stable, heritable lineages or simply stages of activation or differentiation.

Innate and adaptive immunity

The traditional view that innate immunity is nonspecific and lacks memory whereas adaptive immunity is characterized by specific antigen recognition and memory is no longer an accurate or useful categorization of the immune system. Certainly, the receptors used by innate immune cells are specific. For example, TLR5 is specific for bacterial flagellin and does not bind to lipopolysaccharide (LPS) or CpG DNA, whereas TLR9 recognizes CpG DNA but not flagellin or LPS. Similarly, some natural antibodies have broad cross-reactivity, making them no more specific than the germline-encoded receptors expressed by ILCs and myeloid cells. Categorizing innate immunity as nonspecific becomes rather meaningless and misleading as we gain knowledge about the ligand specificities of the germline-encoded receptors expressed by myeloid cells and NK cells. Many of these innate receptors are also expressed by B and T cells of the adaptive immune system.

Reciprocally, the term adaptive immunity or the concept that an immune cell has memory only implies that its behaviour changes or adapts as a consequence of its initial response to an antigenic or pathogenic challenge. Recent studies of NK cells, as well as evidence emerging from studies in lower organisms, demonstrate that innate immune cells do adapt after their first encounter with pathogens. As we study in more depth the epigenetic changes resulting from the activation of immune cells, it seems likely that most immune cells will indeed be found to adapt following their activation, thereby altering their subsequent responses. Thus, rather than innate and adaptive immunity being viewed as mutually exclusive, it is now apparent that the truth lies in shades of grey with blurring boundaries.

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Competing interests statement

The author declares no competing financial interests.

FURTHER INFORMATION

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