Innate versus Adaptive Immunity: A Paradigm Past Its Prime?

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Abstract

Studies in tumor immunology have relied upon the classic paradigm of distinct innate and adaptive parts of the immune system. However, recent advances in immunology suggest that this division may be overly simplistic, with emerging evidence of a breakdown in conventional hallmarks of each system. Here, we provide an overview of this area and discuss how the concept of a continuum of immune cell populations suggests novel areas of investigation in cancer research. [Cancer Res 2007;67(9):3989–93]

Introduction

Classically, the innate and adaptive arms of the immune response have been represented as two separate systems with distinct properties. The innate immune system is widely recognized to use a small number of germ line–encoded receptors that detect a limited set of conserved antigens. This system responds to antigens with fast kinetics and it lacks memory capabilities. In contrast, the adaptive immune system uses a large number of variable immune receptors to generate a vast repertoire. This system responds with relatively delayed kinetics and it possesses effective recall responses (Box I). Recently, several studies have described hematopoietic cells bearing the hallmark characteristics of both the innate and adaptive immune systems. Thus, it is becoming unclear how to classify the increasing number of hematopoietic populations that do not neatly fit within this binary scheme.

At present, there are seven major populations that do not conform to conventional bimodal criteria: natural killer T (NKT) cells, γδ T cells, CD8αα T cells, B1 B cells, marginal zone (MZ) B cells, and subsets of both NK cells and neutrophils. As detailed below, these lymphocyte subsets are recognized to possess seminal properties of both the innate and adaptive responses. One consequence is that B1 B lymphocytes, for example, are alternately referred to as either innate cells (1–3) or innate-like cells (4–6). Yet, B1 B cells fail to develop in *rag*-deficient or severe combined immunodeficient (SCID) mice, a hallmark criterion of adaptive immunity. So which classification of these cells is more accurate, innate, innate-like, or adaptive? Similarly, invariant NKT cells and γδ T-cell subsets are alternately grouped with innate or adaptive responses depending on the criteria emphasized (1, 3, 7, 8). As with B1 B cells, neither invariant NKT cells nor γδ T cells develop in the absence of *rag* gene expression. Importantly, all these interpretations are scientifically justified because the developmental and functional properties blend key innate and adaptive characteristics. Thus, the lack of consensus stems not from promiscuous use of terminology but from an inability of the current framework to accommodate these populations in a biologically meaningful way. Recently, NK cells and neutrophils have been found to possess both memory and variable immune receptors, which have been thought to be specific features of adaptive immune cells. The findings and implications of these provocative studies (9, 10) have yet to be fully appreciated by the scientific community. Below, we review the data underlying all of these newly described cells and provide a perspective.

Box I: Conventional distinguishing characteristics of innate versus adaptive immunity

	Innate immunity	Adaptive immunity
Receptors	Invariant	Variable
Distribution	Non-clonal	Clonal
Memory	No	Yes
Specificity	Degenerate	Specific
Response kinetics	Rapid	Delayed

Characteristics of the Conventional versus Nonconventional Hematopoietic Populations

Germ line–encoded or semi-invariant receptors. The two major molecular mechanisms underlying receptor diversification are V(D)J recombination and N region addition (Box II). Through V(D)J recombination, DNA segments encoding immune receptors are rearranged to produce novel combinations. The theoretical diversity of such a rearranging repertoire is tremendous [i.e., $\sim 10^{18}$ for immunoglobulins and $\sim 10^{20}$ for αβ T-cell receptors (TCR)], although this theoretical diversity is not achieved due to constraints that include biased gene segment usage and recombination failures. The diversity of the αβ TCR complex expressed by invariant NKT cells, for example, is constrained by the expression of a single rearranged TCRα chain (Vα14-Jα18 in mice and Vα24-Jα18 in man) paired with restricted TCRβ chain utilization (Vβ8.2, Vβ2, or Vβ7 in mice and Vβ11 in man; ref. 11). Likewise, CD8αα T cells have skewed Vβ usage that seems to contribute to oligoclonality (12).

Box II: Key concepts in receptor diversity

V(D)J recombination: The mechanism by which V, D, and J gene segments encoding immunoglobulin and TCR loci are rearranged. Recombination is mediated by the V(D)J recombinase complex within which the *rag1/2* genes initiate DNA cleavage.

Terminal deoxynucleotidyl transferase (TdT): Enzyme that adds template-independent nucleotides at the junction between gene segments during V(D)J recombination. Splice variants of TdT delete nucleotides. TdT activity contributes tremendous diversity to the immunoglobulin and TCR repertoires.

N region addition/nontemplated addition: The addition or deletion of nucleotides to V-D-J segment joints during V(D)J recombination by the enzyme TdT.

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Box II continued.

Germ line encoded:

Classic genetic definition: Derived from the original sequence of DNA inherited from a predecessor; heritable genetic material.

Immunologic definition: Derived from the original sequence of DNA inherited from a predecessor in the absence of the somatic addition of non–template-encoded nucleotides. Importantly, and confusingly, immune receptors transcribed from V(D)J rearranged loci are still referred to as germ line encoded, although the DNA configuration has changed. The implication is that these receptors arise from sequences strictly encoded by the original DNA template, in the absence of non-templated modifications by TdT.

N region addition refers to the random insertion or excision of nucleotides at junctions between rearranged segments. Both B1 B cells and γδ T cells predominate during fetal development when TdT, the enzyme that inserts/deletes non–template-encoded nucleotides at D-J and V-DJ junctions, is absent or is expressed at low levels in bone marrow and thymus. The paucity of TdT during this stage of V(D)J rearrangement produces antigen receptors that, while rearranged, are essentially germ line encoded (see Box II). For example, >90% of pre-B cells from newborn infants lack N region additions versus <2% of adult pre-B cells. Within the individual B-cell subsets, 38% of B1a cells lack N region additions at V-D-J junctions compared with 20% of B1b cells and only 7% of B2 cells (13). The different degree of diversity in B1a versus B1b cells is interesting because B1a cells produce natural antibody that provides protection during initial infection, whereas B1b cells provide neutralizing antibodies with slower response kinetics (2). For this reason, B1a cells are considered to mediate innate immune responses, whereas B1b cells mediate adaptive or acquired immunity (2, 14). MZ B cell are also enriched for canonical joints that lack non-templated additions (15). The paucity of N region modifications further exacerbates biased usage of V region segments by favoring homology-directed recombination rather than random rearrangement. For example, diversity of the γδ T cell repertoire is limited to ~70 potential pairs due to the combination of restricted V region gene usage and paucity of N region additions at TCRγ loci. Thus, whereas individual clones bearing junctional diversity at immunoglobulin or TCR loci are detectable, the antigen receptor repertoires of NKT cells, B1 B cells, and γδ T cells are only a fraction that of αβ T and B2 B cells.

Antigenic specificity. Receptors of the innate versus adaptive immune system are also distinguished by the nature and composition of the antigens to which they will react. Innate immune receptors commonly recognize a limited number of target molecules, including lipopolysaccharide, phosphoantigens, lipids, and double-stranded RNA, that are widely expressed by many infectious agents. Adaptive immune receptors recognize complex proteins that can be widely shared or uniquely expressed by individual pathogens. In contrast to innate immune receptors for which ligands seem to be highly conserved, receptors of the adaptive immune system detect both conserved and non-conserved ligands. Although the ligands for innate versus adaptive immune receptors differ, it is important to realize that recognition of a restricted array of antigens does not necessarily imply a lack of specificity in the innate immune system (16), rather the fundamental difference in the innate immune system is in the nature of the antigens it recognizes.

What types of antigens are recognized by non-conventional cells, also termed bridge cells? In the case of B1 B cells, sugar and lipid antigens are recognized. Indeed, ~5% to 8% of the B1 repertoire in the murine peritoneal cavity reacts to phosphorylcholine (14). These patterns contrast with the recognition specificities of αβ T cells and B2 B cells, which are largely, but not exclusively, characterized by peptide epitopes. Alternately, classic NKT cells are defined by CD1-restricted recognition of αGalCer, a mimic of microbial cell wall glycuronosylceramides, as well as other bacterial products. αGalCer-responsive NKT cells mediate effective anti-tumor responses in murine models of fibrosarcoma as well as carcinomas of the colon, breast, or lung (17). The immunotherapeutic potential of these cells was recently highlighted by a phase I trial in which autologous NKT cells expanded with αGalCer and interleukin 2 were shown to be well tolerated by patients with advanced non–small-cell lung cancer (18). In contrast to αβ T cells, γδ T cells do not require binding and presentation by classic MHC. Rather, a high proportion of human circulating γδ T cells recognize small phosphorylated molecules of mycobacterial origin, including organic phosphates and alkylamines. Treatment of human tumor cells with therapeutic drugs containing aminobiphosphonates generates a novel antigen structure that stimulates human γδ T cells, suggesting a new strategy for cancer immunotherapy (19). Human γδ T cells have been shown to prevent or inhibit the growth of breast cancer cell lines *in vitro* (20) and autologous melanoma in a human tumor/SCID model *in vivo*. The distinct *in vivo* trafficking patterns of Vδ1 versus Vδ2 γδ T cells may be useful for targeting specific tumor types (21, 22). The recognition of the distinct reactivities of bridge populations combined with their role in cancer immunosurveillance offers the tremendous potential for novel disease therapies.

Response kinetics. Cells of the innate immune system respond quickly, in minutes to hours, after microbial infection. By contrast, adaptive immunity offers a highly tailored response delivered at the expense of delayed kinetics, which can be on the order of weeks to peak responsiveness. Like innate immune cells, both B1 B and MZ B cells respond rapidly to limit bacterial spread during invasion, with a peak of IgM production occurring 3 to 4 days after antigen encounter. Like conventional B2 cells, the activity of the Blimp-1 transcriptional repressor is also required in B1 B cells despite the different kinetics of responsiveness of these two lineages (6). In a model of *Listeria* infection, γδ T cells can also respond rapidly to infection, with peak expansion at ~10 days following infection (23). Both CD8αα T cells and NKT cells are activated and produce IFNγ within hours after activation. Thus, the combination of rapid response kinetics and patterns of specific reactivity to microbial antigens enables these lymphocyte populations to bridge the temporal gap between innate and adaptive responses.

Clonal selection. Another hallmark of the adaptive response is the clonal distribution of unique immune receptors. The expression of a single type of immune receptor by an individual lymphocyte enables clonal selection of each cell based on the affinity of that receptor for its ligand. Hence, a small number of specific naive cells expand in response to particular antigenic epitopes. One consequence of clonal selection is that the αβ T-cell and B2 B repertoires of the adaptive immune system are unique to each individual. By contrast, germ line–encoded receptors within the innate immune system can be restricted to specific subsets, but

they are not clonally distributed. Thus, groups of individuals within a particular species may share an identical receptor repertoire (16). Consistent with the adaptive immune system, NKT cells, γδ T cells, CD8αα T cells, B1 B cells, and MZ B cells each express a single type of immune receptor. The specific negative and positive selection mechanisms that control entry of these cells into the mature pool remains an active area of investigation.

Candidate Bridge Populations

Memory NK cells? A conventional hallmark of the innate immune system is the absence of memory. Thus, repeated exposure to the same antigen does not lead to a qualitative or quantitative enhancement in the ensuing response. Unexpectedly, murine NK cells have recently been shown to have memory-like activity (9). Using a murine model of contact dermatitis, NK cells were shown to mediate hapten-specific memory responses up to 4 weeks after initial challenge. Contact sensitivity responses were detectable at comparable magnitude in *rag*-deficient animals, showing the B and T independence of this response. By contrast, depletion of NK cells in any of three experimental models, *rag2*$^{-/-}\gamma c^{-/-}$, SCID × beige, or *rag2*$^{-/-}$ + anti-asialo-GM1 treatment, abrogated this memory response. The ability of NK cells to infiltrate sensitized tissue was specific to re-challenge with the original hapten. It remains unclear how long the initiating hapten persists *in vivo* and whether the primary response is fully subsided before re-challenge (3). Moreover, memory responses of NK cells seem to be strongly influenced both by mouse strain and the specific sensitizing hapten. Although the generality of these observations remains to be established, the description of these NK cells as "adaptable innate killers" (3) or "adaptive killers" (24) highlights the importance and the challenge of accurately characterizing these cells within the existing innate versus adaptive framework.

The memory capabilities of bridge lymphocytes are just beginning to be appreciated. B1 B lymphocytes are a lymphoid population also originally thought to lack memory. In a murine model of spirochete infection, IgM-producing B1b cells were shown to provide protective immunity as long as 80 days after the initial challenge (25). This result was unexpected because T-cell–independent responses do not generally elicit B-cell memory. By comparison, γδ T cells do not seem to make a major contribution to the memory pool. Although exceptions exist (26), the majority of effective recall responses seem to be due to αβ T-cell activity. Little is known about the memory capabilities of NKT cells as secondary responses to αGalCer seem to be of lesser magnitude than primary responses. However, this effect may be due to the anergizing effects of αGalCer.

Neutrophils and variable immune receptors? One recent study has suggested the novel hypothesis that a small subset of neutrophils express variable immune receptors that are the product of V(D)J recombination (10). Neutrophils are major proinflammatory mediators that are among the earliest innate effectors recruited to sites of injury and infection. The idea that cells of the innate immune system bear V(D)J rearrangements is not new. Both NK cells and pDCs harbor incomplete rearrangements at immunoglobulin and TCR loci (27). These observations are not surprising given the common lymphoid origins of B, T, NK, and dendritic cells, and that V(D)J rearrangement initiated at the uncommitted progenitor stage of development would be detectable in downstream progeny (27, 28). What is surprising is the reported detection of complete TCR αβ rearrangements in a small population (5–8%) of neutrophils, which are cells of the myeloid lineage (10). These rearranged TCRs are thought to signal through a CD3/CD28 mechanism. TCR$^+$ neutrophils are detectable in *nude* mice, animals that lack conventional T and NKT cells, suggesting that these results could not be attributed to the presence of conventional TCR$^+$ lymphocytes. However, *nude* mice still possess T cells of extrathymic origin, and it will be important to exclude this potential contaminating population in future experiments. It will also be informative to explicitly determine the effects of *rag* deletion on the development and function of neutrophils.

The Immune Response as a Continuum

The overview of the major lineages of hematopoietic cells provided above illustrates clearly that not all immune cells can be assigned strictly to either the innate or the adaptive arm of the immune system. Little doubt exists about the important biological roles of NKT cells, γδ T cells, CD8αα T cells, B1 B cells, and MZ B cells, or that these subsets possess key features of both innate and adaptive immunity. The existence of bridge populations between the two classic subgroups of immune cells prompts a need to expand the paradigm of innate versus adaptive immunity. Revising our perspective on the immune system as an organizational continuum, rather than a dichotomy, acknowledges the bridge population subsets that have functional properties drawn from the innate and adaptive end points. Additionally, it allows one to integrate the concept of the bridge populations of immune cells with a unified terminology (Table 1).

Formal recognition of the bridge populations and their unique functional properties highlights new areas for investigation. A significant therapeutic value may be realized by combining the essential properties of bridge and adaptive subsets to produce a single effector population that responds with rapid kinetics and confers long-term protection to infectious disease or cancer. Effective clearance of *Streptococcus pneumoniae*, a major cause of community-acquired pneumonia, requires a two-pronged immune response (2). B1a cells produce natural antibody that can protect against initial infection, whereas B1b cells are required to clear an established infection and provide long-term immunity. Could the rapidly responding B1a cells be armed through genetic engineering to elicit longer-term protective responses? The molecular differences underlying this division of labor are unclear. Both subsets produce IgM reactive to pneumococcal polysaccharide type 3, indicating that repertoire specificity alone may not be the fundamental difference in this case (2). Rather, other differences, such as the ability to class switch to IgG3 or the differential requirement for CD19 activity, may be important. As a broader question, are specific suites of genes associated with innate, bridge, and adaptive immunity? It has been argued that some of the populations described here, such as NKT cells, should be an innate population rather than a bridge population (29). Comparative analysis of gene expression profiles may help resolve this issue. Transcriptional profiling of three candidate bridge populations, including NKT cells and CD8αα T cells, suggests a shared expression pattern for such genes as GTPases important for resistance to intracellular pathogen (30). Finally, the distinct mechanism of antigen recognition (19), patterns of localization (21, 22), and kinetics of responsiveness of bridge populations (2) highlight their potential application to cancer vaccines and

Table 1. The general organization and functional properties of hematopoietic populations

Subset	Immune receptor	DNA configuration	Non-templated additions	Ligand	Response kinetics	Memory
Innate						
NK cells	Ly49/KIR	Germ line	No	MHC	Rapid	Possible
Macrophages	TLRs, scavenger receptor	Germ line	No	Bacterial products	Rapid	No
Bridge						
NKT cells	αβ TCR	Rearranged	No/limited	Glycolipid	Rapid	No
γδ T cells	γδ TCR	Rearranged	No/limited	Phosphoantigens	Rapid	No
CD8αα T cells	αβ TCR	Rearranged	Diverse	Self-peptide and superantigen	Rapid	Yes
MZ B cells	Immunoglobulin	Rearranged	No/limited	PC, lipoprotein	Rapid	?
B1a B cells	Immunoglobulin	Rearranged	No/limited	PC, glycosylation epitopes	Rapid	?
B1b B cells	Immunoglobulin	Rearranged	Moderate	PC, lipoprotein	Delayed	Likely
Adaptive						
αβ T cells	αβ TCR	Rearranged	Extensive	Complex antigens	Delayed	Yes
B2 B cells	Immunoglobulin	Rearranged	Extensive	Complex antigens	Delayed	Yes

NOTE: The table emphasizes the general characteristics of innate, bridge, and adaptive immune responses that can be thought of as a continuum. See text for details.

immunotherapy. The scheme presented in Table 1 may be refined as further investigations reveal general characteristics underlying each population.

Future Directions

Reorganizing the immune system as a continuum rather than a dichotomy makes at least three interesting predictions. One prediction is that bridge populations may offer excellent targets for vaccine therapy. Rather than providing an impoverished immune response whose activity is elicited in lieu of adaptive immunity, bridge populations may orchestrate entirely distinct patterns of immune responsiveness. γδ T cells neutralize a number of pathogens, including *Klebsiella pneumoniae*, for which αβ T cells are dispensable (31). Likewise, B1a and MZ B cells mount antibody responses in the absence of T cells. Vaccine strategies that target bridge populations may be useful for some situations in which current vaccines fail, such as those that are exclusively targeted to Th-dependent B2 B cells. Such strategies may have particular value for situations in which T-cell activity can be associated with fatal encephalitis, such as in the treatment of cancers of the brain or the therapeutic destruction of amyloid plaques in Alzheimer's patients (32). The identification of a specific subset of dendritic cells that uniquely captures and transports blood-borne antigens to MZ and B1 B cells suggests one mechanism of targeted delivery (33). A second prediction based on the gaps in the continuum is that additional bridge populations will be identified. Notably absent is a bridge population derived from the macrophage lineage. Not only do macrophages and B lymphocytes share key functional properties, such as phagocytic capacity, but they can arise via a bi-potent macrophage/B-cell precursor (34). Whether these unusual bi-potent precursors give rise to functional, mature progeny that retain the characteristics of both lineages remains unknown. The occurrence of leukemias that express traits of both lineages may be one hint that such cells exist (35). A third prediction is that some instances of autoimmunity may be attributable to the activity of bridge populations. The tendency of B1 B cells to produce autoreactive antibodies has not gone unnoticed but the feedback mechanisms that restrain these cells as well as other bridge populations remain largely unexplored. Each of these predictions is a testable hypothesis that affects our basic understanding of the functional organization of the immune system.

Observations that V(D)J rearrangements are detectable not only in B and T cells but also in a minor population of NK, pDC, and possibly neutrophils suggest that *rag*-mediated DNA translocation may be an unappreciated source of oncogenesis in multiple hematopoietic lineages. As 50% of CLPs express *rag1/2* transcripts (36), it is also possible that recombination errors at this stage cause transformation. *rag* complex misrecognition caused by a pseudo-recombination signal sequence or a fragile breakpoint can lead to rearrangements between antigen receptor loci and *bcl2, LMO2, Tgt-1*, or *SIL* (37). Other common chromosomal partners include *cyclin D1, cyclin D3, FGFR3*, and *MMSET* gene loci, all of which lead to unrestricted cell growth (38). NK and NK-like tumors have been identified (39–41), but they remain a perplexing problem because their lineage origins are controversial. Moreover, the molecular changes that lead to transformation of NK cells are unclear, and translocations can be heterogeneous. Similarly, cancers of neutrophilic origin, such as chronic neutrophil lymphoma, require better criteria for diagnosis and identification of the underlying molecular defects including chromosomal abnormality (42). The current appreciation of recombination events in a subpopulation of NK cells and other hematopoietic lineages may aid in clarifying disease definitions and malignancy types.

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References

1. Bendelac AM, Bonneville JF. Kearney. Autoreactivity by design: innate B and T lymphocytes. Nat Rev Immunol 2001;1:177–86.
2. Haas KM, Poe JC, Steeber DA, Tedder TF. B-1a and B-1b cells exhibit distinct developmental requirements and have unique functional roles in innate and adaptive immunity to *S. pneumoniae*. Immunity 2005; 23:7–18.
3. Parham P. Immunology: adaptable innate killers. Nature 2006;441:415–6.
4. Goodyear CS, Silverman GJ. Staphylococcal toxin induced preferential and prolonged *in vivo* deletion of innate-like B lymphocytes. Proc Natl Acad Sci U S A 2004;101:11392–7.
5. Kearney JF. Innate-like B cells. Springer Semin Immunopathol 2005;26:377–83.
6. Savitsky D, Calame K. B-1 B lymphocytes require Blimp-1 for immunoglobulin secretion. J Exp Med 2006; 203:2305–14.
7. Konigshofer Y, Chien YH. Gammadelta T cells: innate immune lymphocytes? Curr Opin Immunol 2006;18: 527–33.
8. Shen Y, Zhou D, Qiu L, et al. Adaptive immune response of Vgamma2Vdelta2$^+$ T cells during mycobacterial infections. Science 2002;295:2255–8.
9. O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH. T cell- and B cell-independent adaptive immunity mediated by natural killer cells. Nat Immunol 2006;7: 507–16.
10. Puellmann K, Kaminski WE, Vogel M, et al. From the Cover: a variable immunoreceptor in a subpopulation of human neutrophils. Proc Natl Acad Sci U S A 2006;103: 14441–6.
11. Godfrey DI, MacDonald HR, Kronenberg M, Smyth MJ, Van Kaer L. NKT cells: what's in a name? Nat Rev Immunol 2004;4:231–7.
12. Gangadharan D, Lambolez F, Attinger A, Wang-Zhu Y, Sullivan BA, Cheroutre H. Identification of pre- and postselection TCRalphabeta$^+$ intraepithelial lymphocyte precursors in the thymus. Immunity 2006;25:631–41.
13. Kantor AB, Merrill CE, Herzenberg LA, Hillson JL. An unbiased analysis of V(H)-D-J(H) sequences from B-1a, B-1b, and conventional B cells. J Immunol 1997;158: 1175–86.
14. Hardy RR. B-1 B cell development. J Immunol 2006; 177:2749–54.
15. Martin F, Kearney JF. Positive selection from newly formed to marginal zone B cells depends on the rate of clonal production, CD19, and btk. Immunity 2000;12: 39–49.
16. Vivier E, Malissen B. Innate and adaptive immunity: specificities and signaling hierarchies revisited. Nat Immunol 2005;6:17–21.
17. Terabe M, Swann J, Ambrosino E, et al. A nonclassical non-Valpha14Jalpha18 CD1d-restricted (type II) NKT cell is sufficient for down-regulation of tumor immunosurveillance. J Exp Med 2005;202:1627–33.
18. Motohashi S, Ishikawa A, Ishikawa E, et al. A phase I study of *in vitro* expanded natural killer T cells in patients with advanced and recurrent non-small cell lung cancer. Clin Cancer Res 2006;12:6079–86.
19. Tanaka Y. Human gamma delta T cells and tumor immunotherapy. J Clin Exp Hematop 2006;46:11–23.
20. Guo BL, Liu Z, Aldrich WA, Lopez RD. Innate anti-breast cancer immunity of apoptosis-resistant human gammadelta-T cells. Breast Cancer Res Treat 2005;93: 169–75.
21. Lozupone F, Pende D, Burgio VL, et al. Effect of human natural killer and gammadelta T cells on the growth of human autologous melanoma xenografts in SCID mice. Cancer Res 2004;64:378–85.
22. Ebert LM, Meuter S, Moser B. Homing and function of human skin gammadelta T cells and NK cells: relevance for tumor surveillance. J Immunol 2006;176: 4331–6.
23. Skeen MJ, Ziegler HK. Induction of murine peritoneal gamma/delta T cells and their role in resistance to bacterial infection. J Exp Med 1993;178:971–84.
24. Leavy O. Adaptive Killers. Nature 2006;6:430.
25. Alugupalli KR, Leong JM, Woodland RT, Muramatsu M, Honjo T, Gerstein RM. B1b lymphocytes confer T cell-independent long-lasting immunity. Immunity 2004;21: 379–90.
26. Hayday AC. [gamma][delta] cells: a right time and a right place for a conserved third way of protection. Annu Rev Immunol 2000;18:975–1026.
27. Borghesi L, Gerstein RM. Developmental separation of V(D)J recombinase expression and initiation of IgH recombination in B lineage progenitors *in vivo*. J Exp Med 2004;199:483–9.
28. Borghesi L, Hsu LY, Miller JP, et al. B lineage-specific regulation of V(D)J recombinase activity is established in common lymphoid progenitors. J Exp Med 2004;199: 491–502.
29. Bach JF, Bendelac A, Brenner MB, et al. The role of innate immunity in autoimmunity. J Exp Med 2004;200: 1527–31.
30. Yamagata T, Benoist C, Mathis D. A shared gene-expression signature in innate-like lymphocytes. Immunol Rev 2006;210:52–66.
31. Moore TA, Moore BB, Newstead MW, Standiford TJ. Gamma delta-T cells are critical for survival and early proinflammatory cytokine gene expression during murine Klebsiella pneumonia. J Immunol 2000;165: 2643–50.
32. Weiner HL, Frenkel D. Immunology and immunotherapy of Alzheimer's disease. Nat Rev Immunol 2006;6: 404–16.
33. Balazs M, Martin F, Zhou T, Kearney J. Blood dendritic cells interact with splenic marginal zone B cells to initiate T-independent immune responses. Immunity 2002;17:341–52.
34. Montecino-Rodriguez E, Leathers H, Dorshkind K. Bipotential B-macrophage progenitors are present in adult bone marrow. Nat Immunol 2001;2:83–8.
35. Greaves MF, Chan LC, Furley AJ, Watt SM, Molgaard HV. Lineage promiscuity in hemopoietic differentiation and leukemia. Blood 1986;67:1–11.
36. Rumfelt LL, Zhou Y, Rowley BM, Shinton SA, Hardy RR. Lineage specification and plasticity in CD19- early B cell precursors. J Exp Med 2006;203:675–87.
37. Lieber MR, Yu K, Raghavan SC. Roles of nonhomologous DNA end joining, V(D)J recombination, and class switch recombination in chromosomal translocations. DNA Repair (Amst) 2006;5:1234–45.
38. Bergsagel PL, Kuehl WM. Chromosome translocations in multiple myeloma. Oncogene 2001;20:5611–22.
39. Loughran TP, Hadlock KG, Jr., Yang Q, et al. Seroreactivity to an envelope protein of human T-cell leukemia/lymphoma virus in patients with CD3- (natural killer) lymphoproliferative disease of granular lymphocytes. Blood 1997;90:1977–81.
40. MacLeod RA, Nagel S, Kaufmann M, Greulich-Bode K, Drexler HG. Multicolor-FISH analysis of a natural killer cell line (NK-92). Leuk Res 2002;26:1027–33.
41. Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. Cancer 2003;97:610–27.
42. Elliott MA. Chronic neutrophilic leukemia and chronic myelomonocytic leukemia: WHO defined. Best Pract Res Clin Haematol 2006;19:571–93.