4.3 Adaptive immunity 325

4.3 Adaptive immunity 325

ESSENTIALS Following the innate immune response, which acts very rapidly, the adaptive immune response plays a critical role in host defence against infectious disease. Both types of immune response work together in order to achieve immunity (protection from disease). Unlike the in- nate response, which is triggered by pattern recognition of patho- gens (i.e. features that are common to many bacteria or viruses, the adaptive response is triggered by structural features—known as antigens or epitopes—that are typically unique to a single organism). Cells involved in the adaptive immune response—these are B lympho- cytes and T lymphocytes, the latter divided into CD4+ (helper) and CD8+ (cytotoxic) populations. All of these lymphocyte subsets can potentially respond to a huge variety of antigens through the gener- ation of great diversity in their antigen receptors (T-cell receptors and B-cell receptors), some of which is genetically encoded, but much is created by recombination between gene segments as the receptors are expressed. Recognition of antigens—(1) B cells—a membrane-bound form of the soluble antibody molecules that the cell is destined to secrete acts as the B-cell receptor, which can bind to a range of antigens, including nonprotein antigens such as carbohydrates. (2) T cells— these can only survey antigens that have been cleaved to short pep- tides and presented on surface of cells bound in the groove of the hugely diverse major histocompatibility complex class I and class II molecules. Dendritic cells have a central role since they can not only present the peptides efficiently, but also provide critical extra signalling in the form of specialized ‘costimulatory’ surface molecules and soluble cytokines. Response to antigens—once T cell and B cells have been triggered by antigen, they proliferate rapidly and display a range of effector functions. (1) B cells—secrete antibodies, initially in the form of im- munoglobulin M (IgM), but subsequently ‘class switching’ to IgG, IgA, or IgE. (2) T cells—(a) CD8+ T cells—response includes migration to sites of infection, killing of infected cells, and secretion of soluble me- diators; (b) CD4+ T cells—play a key role in providing ‘help’ for B cells (e.g. in class switching), ‘help’ for proliferation of CD8+ T cells, and also conditioning of dendritic cells. CD4+ T cells which secrete a panel of cytokines promoting cell mediated immunity (such as interferon-γ (IFNγ)) are described as Th1 (T helper 1), while others which secrete cytokines involved in responses to extracellular parasites such as hel- minths (such as interleukin 4 (IL-4)) are Th2, and a third group which secrete IL-17 are termed Th17. A further recently delineated set of follicular helper T cells (Tfh) are able to provide help for B cells in lymphoid organs. T cells which counterregulate these responses can also be induced and are described as regulatory T cells (Treg). Immunological memory—once an infection is contained, the B- and T-cell populations contract and enter a phase of immunological ‘memory’ keeping the antigen selected receptors and some of the cell changes acquired during the response. These memory popu- lations are found largely in lymph nodes, although some ‘effector memory’ T cells may be found in nonlymphoid

organs (e.g. liver). They are retained long term at much higher cell frequencies than are found in an unexposed person, and can respond to re-encounter with antigen with very rapid proliferation and effector function. A set of ‘tissue-resident’ memory cells (Trm) have been described which do not recirculate and provide very early memory responses in tissues. Regulation of immune responses—the functions of the adaptive immune system are tightly regulated to limit immune-mediated pathology. T cells develop initially within the thymus, where those which recognize host (‘self’) antigens are eliminated (‘central toler- ance’). Self-reactive T cells may be further controlled in the periphery through a variety of mechanisms, including Tregs and expression of inhibitory molecules. B cells develop mainly in the bone marrow where self-reactive cells can be eliminated or undergo receptor editing that change cell specificity rescuing them from elimination. However, this multilayered control sometimes breaks down, thereby allowing pathological responses to harmless antigens (hypersensi- tivity) or self-antigens (autoreactivity). Pathogens such as HIV, and various cancer types may exploit downregulatory mechanisms to allow their long-term persistence in the body. Clinical impact of understanding the adaptive immune system— this may be harnessed to generate novel diagnostics, therapies
(e.g. monoclonal antibodies) and vaccines, but many challenges
remain in translating our increasing knowledge about molecular control of adaptive immunity into protection against complex per- sistent infections. 4.3 Adaptive immunity Paul Klenerman and Constantino López-Macias

326 SECTION 4 Immunological mechanisms Introduction The adaptive immune response is distinguished from the innate im- mune response by two main features: its capacity to respond flexibly to new, previously unencountered antigens (antigenic specificity), and its enhanced capacity to respond to previously encountered antigens (immunological memory). These two features have pro- vided the focus for much research attention, from the time of Jenner, through Pasteur onwards. In recent years, the molecular basis for these phenomena has become much better understood. Antigen recognition by the adaptive immune system is performed through the T-cell receptor (TCR) and B-cell receptor (BCR) expressed on the surface of T or B cells, whereas molecular recognition by innate immune system is performed by ‘pathogen recognition receptors’ (PRRs). PRRs do not undergo changes during immune responses (innate response), leading to a repertoire of around 102, whereas TCRs and BCRs are formed by a process of gene rearrangement that can also undergo additional changes after antigen recognition (adaptive responses), leading to a repertoire of orders of magnitude larger. T and B cells activated by the specific antigen proliferate and differentiate, and some of these will be retained long term and repre- sent the pool of memory cells. Historically, innate and adaptive immune responses have often been treated as separate, with the latter being considered more ‘ad- vanced’ because of its flexibility. It is now clear this not the case. Innate immune responses provide the essential early controls and conditioning required for an adaptive immune response to function. This arises because of the differential speed of the two responses. Innate responses occur within minutes or hours of infection, whereas initiation of effective adaptive immunity may take days. Not only do mediators such as type I interferons have direct antiviral effects, but they also activate antigen presentation pathways and thus have a critical role in priming the adaptive immune response. Thus, the adaptive immune response to a given antigen may be vig- orous or absent depending on the quality of innate signalling that accompanies it. To integrate this further, T and B cells themselves can express innate receptors that contribute to their development and function. Several lymphocyte types with a ‘bridging’ innate and adaptive role have been discovered, including

‘innate lymphoid cells’ which share many phenotypic features of T cells, but lack TCR and respond to innate signals. The immune response evolved to deal with pathogens, of which viruses are good examples. This is the focus of this chapter, but the same responses against self-, allo- or environmental antigens lead to autoimmunity (Chapter 4.6), transplant rejection (Chapter 4.7) and hypersensitivity/allergy (Chapter 4.5). Antigen specificity of adaptive immune responses Antigen is a word with a long history, originally associated with anti- body binding, but currently used broadly to mean anything to which BCR or TCR can bind. An alternative description is ‘immunogen’ meaning anything can trigger B- or T-cell responses. Largely these are protein structures, and in the case of T cells short peptides and in some cases lipopeptides, but for B cells the targets may be much more diverse such as lipoproteins, lipids, carbohydrates, and nucleic acids. If a large molecule, such as influenza matrix protein, is defined as the antigen, the small regions within it which are recognized by the cells of the adaptive immune response are termed ‘epitopes’. Antigen recognition by T cells T cells are divided simply into two lineages according to the type of TCR: αβ and γδ. αβ T cells are in general divided into CD4+ T cells (or T helper, Th cells) and CD8+ T cells (or cytotoxic T cells). There are also unconventional αβ T cells comprising invariant nat- ural killer T (iNKT) cells and mucosal associated invariant T cells (MAIT), which can be CD8+, CD4+, or double-negative. CD4+ and CD8+ T cells have distinct, if overlapping functions, but crucially they recognize antigen delivered through distinct path- ways. Both sets of T cells can recognize antigenic peptides only if they are presented by specific host major histocompatibility com- plex (MHC) molecules at the cell surface. These molecules vary substantially between individuals, which is the basis of MHC restric- tion of the capacity of T cells to recognize a given antigen when pre-sented by a specific MHC molecule. In contrast, unconventional T cells and γδ T cells recognize nonpeptide antigens and do not bind classical MHC molecules. Antigen presentation to CD8+ T cells CD8+ T cells recognize antigen presented largely from intracellular compartments. In the case of a virus infection, this means newly synthesized viral proteins can be presented on the surface of an in- fected cell (Fig. 4.3.1). The proteasome Proteins destined for the antigen presentation pathway are tagged with ubiquitin and delivered to the cellular proteasome, a multicomponent proteolytic complex present constitutively in all cells (although modified under inflammatory conditions to an immunoproteasome). The outputs from these proteasomes are sets of short peptides derived by specific cleavage of the larger input pro- tein. Typically, these are 9 to 11 amino acids in length. Further pep- tide ‘trimming’ may occur at later stages. Peptide transport The next stage of antigen presentation is transport through an ATP-dependent peptide transporter (TAP, transporters associ- ated with antigen processing) into the endoplasmic reticulum. Patients with genetically deficient TAP transporters have been de- scribed, which fail to present peptides at their cell surfaces bound to MHC class I molecules (see paragraphs to follow). Their clinical presentation is with bacterial and vasculitic disease and they show overactivated natural killer (NK) cells. Binding to MHC class I The next step for antigenic peptides is loading on to an MHC class I molecule. These comprise a heavy chain with three major extracellular domains (α1–3), which dimerizes with an invariant light chain β2-microglobulin (β2m). The α3 domain acts as a membrane- proximal stalk, which provides the binding site for β2m, and stability for the complex. The α1 and α2 domains form a groove with closed ends lying above the stalk. Peptides lie stretched out lengthways in the groove, with

 two to four specific amino acid residues bound into ‘pockets’ in the floor. These act as ‘anchors’ and provide stability for the peptide– MHC interaction. Only specific amino acids can form anchor res- idues in any given MHC class I molecule. As a result, many

peptides cleaved from a given protein will not be presented by host MHC molecules and the cellular immune system is essentially ‘blind’ to these. The other nonanchor amino acids within the peptide are dis- played above the lips of the groove and are available for binding by the T-cell receptor. Recognition by the T-cell receptor The T-cell receptor is the molecule responsible for sensitive and spe- cific recognition of peptide–MHC complexes by T cells. TCRs are made up of pairs of chains—either α and β chains or γ and δ chains. TCRs comprising α and β chains (αβ T cells) are able to recognize MHC class I molecules through an interaction of low avidity but high specificity. Cocrystallization studies of a limited number of molecules have revealed that the tips of the TCR αβ complex interact in a diagonal fashion with the top surface of the MHC class I pep- tide complex. Thus, the strength of the interaction comes not only from binding of the TCR to the available peptide residues, but also from binding to the MHC class I molecule. This encapsulates the fundamental principle of the cellular immune response. The MHC molecule provides the central focus (restriction), but the peptide provides the essential specificity. Even subtle changes in the pep- tide sequence such as conservative amino acid exchanges (e.g. ly- sine to arginine) can substantially change the strength of the TCR interaction and radically affect the recognition by the T cell, a feature that has been fully exploited by variable viruses such as the human immunodeficiency virus (HIV; see Chapter 8.5.23). Antigen presentation to CD4+ T cells Like CD8+ T cells, CD4+ T cells also survey antigens as peptides presented on the cell surface through MHC molecules. Unlike CD8+ T cells, these peptides are not principally derived from cyto- solic antigens (Fig. 4.3.1). Two key points must be noted. First, while MHC class I molecules are present on virtually all cells, class II molecules are normally present on only a limited number of cell types. Secondly, the pathway requires specific machinery for soluble or particulate antigen outside the cell to be taken into the cellular endosome, which is notably greater in phagocytic cells. The pathway of autophagy may also provide a route into the class II pathway for intracellular proteins. MHC class II molecules Proteins within the endosome, after fusion with lysosomes, are de- graded to peptides, which subsequently bind MHC class II mol- ecules. These are polymorphic dimeric molecules, like class I, but differ in that both α and β chains are equal partners in peptide binding and presentation. An important difference from MHC class I is that the ends of the groove are open, allowing longer pep- tides to be bound (12–15 residues). MHC class II molecules initially bind an ‘invariant chain’ (CLIP) in the endoplasmic reticulum which protects the binding groove. In CD4+Tcell CD8+ Tcell B cell Virus protein proteasome TAP peptide E.R MHC Class I β2-microglobulin Anchor residues Phagosome/ lysosome Virus peptide TCR contact residues T-cell receptor (TCR) B-cell receptor (BCR) CLIP MHC Class II exchange α-chain β-chain Virus protein replication Viral antigen Target cell Target cell Antigen-presenting cell Fig. 4.3.1 Antigen presentation to T and B cells. A viral antigen is used as an example. Peptides are generated in infected (target) cells and in the case of class I transported to the endoplasmic reticulum (ER) via the TAP (transporters associated with antigen processing) complex. CD4+ T cells are triggered by professional antigen-presenting cells, while B cells engage antigen directly.

 the lysosome/endosome fusion compartment, the invariant chain is exchanged for peptides that can specifically bind into the groove if they possess the key anchor residues. Class II–peptide complexes are then presented at the surface of the cell, and can be recognized by specific CD4+ T cells. Antigen recognition by ‘bridging’ T-cell subsets Some subsets of human αβ T cells are described as possessing in- variant or ‘semi-invariant’ TCRs and show a distinct biology. MAIT cells make up around 10% of human CD8+ T cells in blood and are highly enriched in the liver and lung. These cells recognize small metabolic intermediates

derived from the bacterial riboflavin syn- thesis pathway, presented in the groove of the conserved surface molecule MR1. The much rarer invariant NK-T cells or iNKTs rec- ognize bacterial glycolipids presented by CD1d. Both of these sets of T cells, and related cells recognizing other members of the CD1 family, play a bridging role between innate and adaptive immunity, and likely a primary role in host defence in epithelia. T cells in which the TCR comprises γδ chain (γδ T cells) make up around 5% of the normal human T-cell pool in blood, although they may be concentrated in tissues. The molecular targets of such cells are not fully established, but they are able to recognize small phosphorylated antigens (e.g. derived from bacteria), with a role for Butyrophilin 3A1 as a presenting molecule. Functionally, γδ
T cells are thought to play a role more aligned with innate immune responses. Antigen recognition by B cells Unlike T cells, which can mainly survey peptides (or other lipid related molecules) antigens displayed on cells bound to MHC molecules, the range of antigens which can be bound by B cells and antibodies is much more diverse and includes nonprotein antigens, such as carbohydrates, lipids, and nucleic acids. Recognition by B cells occurs through the B-cell receptor, a membrane-bound form of the soluble antibody molecules that the cell is destined to secrete (Fig. 4.3.1). The basic structure of an antibody (immunoglobulin G, IgG, in this case) is illustrated in Fig. 4.3.2. Essentially each antibody unit comprises one heavy (H) and one light (L) chain. Despite the functional differences from T cells, the basic structure of the TCR and the BCR/Ig is quite similar. The TCR resembles the key antigen- recognizing subunit of the Ig known as a Fab fragment. Because B cells can react to intact antigen, no specific antigen- presenting pathway is required (Fig. 4.3.1). However, there are simi- larities with T-cell recognition of antigen, such as the size of the epitope recognized. Detailed mapping studies, using antigens such as influenza haemagglutinin, have revealed that the sites of B-cell recognition are discrete, each comprising less than 10 amino acids. Similar studies of carbohydrate antigens reveal a footprint of around seven sugars. Small synthetic molecules, typically described as haptens (haptenes), can also act as B-cell targets but priming occurs only if they are linked to a conventional protein antigen. One important difference from the peptide antigens recognized by T cells is that B-cell epitopes may be conformational. This means that the amino acids which interact with the B-cell receptor need not be in a continuous sequence, but may come together as the pro- tein folds. Other B-cell responses may be directed against so-called ‘linear’ epitopes, in which case they can be mimicked by a shorter peptide. Perhaps more important functionally is the definition of epitopes that, when bound, lead to neutralization of a virus (i.e. loss of the capacity of the virion to enter a cell). Typically these epitopes CD4+ T cell CD8+ T cell B cell C V C V α-chain β-chain C V C V α-chain β-chain C C C C C C V C C Antigen recognition region Disulphide bonds C C V TCR IgG Fab papain Cytoplasmic tail V V V V Fig. 4.3.2 Antigen binding by T and B cells. The T-cell receptor (TCR) is composed of two chains, bound by disulphide bonds, with antigen recognition occurring in a variable region. This is analogous to the variable region of an immunoglobulin molecule (IgG is illustrated here); the TCR-equivalent region (Fab fragment) may be cleaved from the full molecule using papain.

 occur on viral glycoproteins required for binding cellular entry re- ceptors. The development of such neutralizing antibodies is the basis for many vaccines and for sterilizing immunity. Generation of diversity within the immune system The previous discussion gives some indication of the nature of antigens and the common features of their presentation to T and B cells. However, the key feature of the system is its huge adapt- ability to diverse antigens. How is this diversity of antigen receptors generated? Generation of diverse T-cell receptors T-cell

receptor diversity arises initially through genetically encoded variation, and is hugely expanded through combinatorial processes (Fig. 4.3.3). First, consider the β chain destined to become part of a TCR αβ complex. The genetic organization of this chain includes a variable (V), a diversity (D), and a joining (J) segment, which are spliced and recombined with a constant (C) chain to form the final sequence. The organization is similar for the α chain, but with the absence of the small D segment. The diversity arises first from the fact that the V, D, and J regions exist in multiple copies, each distinct. It is expanded by the process of recombination whereby, in the pro- cess of generating a new T cell from a precursor, any combination of V, D, and J can be used to generate the new β chain. During this process, the action of the terminal deoxynucleotide transferase en- zyme creates further diversity at junctions. Since α and β chains re- combine independently, further diversity is generated as these form heterodimers. It has been estimated that this process could generate 1014 distinct T-cell receptors. Diversity of B-cell receptors and antibody The generation of diversity is similar to that of the TCR α and β chains described here (Fig. 4.3.3). V, D, and J regions exist in mul- tiple copies which, as the B cell develops, are recombined randomly (D regions are only present in the H chain), incorporating add- itional diversity as this occurs. Further variability is introduced as two loci for the generation of light chains exist, producing either κ or λ chains. However, in any given cell, only one heavy and one light chain is used, a process known as allelic exclusion. The aforementioned process allows for a huge variability in the key regions which act as binding sites, within the ‘variable’ domain at the N-terminus. However, there is an additional biological variation between antibodies, not dependent on their specificity, which is pro- vided by further recombination with a constant region (Table 4.3.1). In the heavy chain locus, nine potential C chains can be used to create a palette of diverse antibody types. For the heavy chains, the initial constant (C) chain used is μ, leading to the creation of an early IgM antibody in typical immune responses. Subsequent class switching, which is a one-way process through further recombination events, may lead to use of any of the other chains. This switching event is largely but not exclusively determined by T-cell help and cytokines. CD8+ T cell CD4+ T cell B cell α- chain β- chain V J C V D J C N and P nucleotides TCR genes α-chain β-chain T-cell receptor (αβ TCR) κ/λ- L chain H chain BCR/Ig genes Recombination β2-m A B C DRA DRB1 DRB3-5 DQa/b DPa/b B-cell receptor (sIg) MHC complex Class I Class II V D J C Somatic hypermutation Polymorphism Fig. 4.3.3 Generation of diversity in the immune system. Both TCRs and BCRs are generated through recombination. For Ig H chains there are 65, 27, and 8, V, D, and J genes encoded in the germ line, respectively. Somatic hypermutation occurs only in B cells. The MHC complex is highly polymorphic—the class II genes actually lie upstream of the class I genes on chromosome 6. DRA encodes the α chain which is conserved and pairs with polymorphic β chains from the DRB1 locus.

 The constant regions determine critical factors in the distribution of the antibodies. Notably, only IgG can cross the placenta and protect the fetus, but IgA is secreted across epithelial membranes, including into breast milk for protection of the newborn. Finally, an important process which creates further diversity, and one which distinguishes B cells from T cells, is the emergence of somatic hypermutation. Once B cells have developed during an initial immune response, the action of the mutagenic enzyme AID within the hypervariable regions leads to the creation of somatic mutants. The B-cell receptors of some of these mutant clones may have increased avidity for their original antigen, and are further selected. This molecular process is observed functionally by affinity maturation of the antibody response over time. Diversity among MHC molecules MHC molecules are glycoproteins expressed on the cell surface that are highly polymorphic and therefore a molecular ‘self-marker’ of the organism. These

molecules are fundamental for the activation and regulation of the immune system in health and disease, and in the context of transplantation. Class I molecules These molecules provide the key platforms for antigen presentation, but only a small number of peptides can bind any given class I mol- ecule, potentially limiting the T-cell response. This limitation has been solved for human MHC molecules (human leucocyte antigens, HLA) first by reduplication of these genes, such that for class I, there are three loci—A, B, and C (Fig. 4.3.2). However, more important, at each locus there exists a huge range of alleles or HLA types, which are rep- resented at varying frequencies in different populations. In Western populations the commonest A allele is HLA A*0201, which occurs in up to 50% of individuals, but there are over 3000 alleles, all of which are much less common. The B locus is even more diverse, with nearly 4000 alleles described. HLA-C molecules are of slightly more limited diversity, and also play a major role in signalling to NK cells.
Class II molecules The principles are similar for HLA class II, although there are four loci, the most diverse of which is DRB1, encoding the β chain of a range of DR molecules (the α chain is invariant). The next locus en- codes only three alleles, DRB3, 4 and 5 (previously DR51, 52, and 53). DR molecules are highly expressed on antigen-presenting cells and are restricting elements for important CD4+ T-cell epitopes. DQ and DP are also polymorphic loci, although the latter is less so, and is also expressed in lower amounts. In total there are over 3000 HLA Class II alleles described. Thus an antigen-presenting cell will present potentially six dif- ferent class I molecules and eight different HLA class II molecules, each binding distinct peptides from a given antigen. However, these molecules are not typically inherited independently, since they are often in strong linkage disequilibrium. Adaptive immune responses and the basis of immunological memory The previous discussion has outlined the molecular basis for antigen recognition, but how is this process coordinated in order to establish and maintain immune responses? The naive state Lymphocytes are generated from common lymphoid progenitors within the bone marrow and undergo a series of maturation steps to create naive B and T cells (Fig. 4.3.4). Naive in this context means ready to respond functionally to an as yet unencountered antigen. Reaching this stage requires education within the thymus (for T cells) and bone marrow (for B cells). T-cell development T-cell education occurs in the thymus, through interaction of thymocytes with specialized thymic cells (cortical epithelial cells and bone marrow derived cells). These present a range of self-antigens, including nonthymic tissue-specific antigens (e.g. from pancreas), the expression of which is liberated by the AIRE gene. The process of thymic development is initially similar for CD4+ and CD8+ thymocytes, which pass through a CD4+ CD8+ phase, before downregulating either receptor. Those that interact strongly with host MHC and self peptides receive signals which Table 4.3.1 Diversity of immunoglobulin types. The different immunoglobulins have different biological properties, some of which are illustrated here. There are further subtypes of the IgG classes Isotype H+L chains Mr (kDa) Serum conc. (mg/ml) t1/2 (days) C1q bound Placental transport Mast-cell binding IgG1 2+2 146 9 21 + + ± IgG2 2+2 146 3 20 + + – IgG3 2+2 165 1 7 + + ± IgG4 2+2 146 0.5 21 – + ± IgM 10+10 970 1.2 5 + – – IgA1 2+2 160 2 6 – – – IgA2 2+2 160 0.5 – – – – sIgA 4+4 405 0.5 – – – – IgD 2+2 170 0.06 3 – – – IgE 2+2 190 0.0002 3 – – ++ sIgA, secretory IgA; this also contains a J chain linking the multimeric structure.

 lead to elimination through a process termed negative selection. Thymocytes which fail to interact with host MHC molecules do not receive sufficient signals to survive and thus many thymocytes are eliminated at this stage. Positively selected CD8+ or CD4+ T cells are therefore those that interact weakly with MHC–self-peptide com- plexes (class I or II, respectively), providing a broad but non-self- reactive naive repertoire. B-cell development Early B-

cell development within the bone marrow occurs through pro- and pre-B-cell stages, during which time immunoglobulin genes are rearranged. Immature B cells possess rearranged surface IgM. Self-reactive B cells may be eliminated at this stage through clonal deletion, induction of an anergic state, or by secondary re- arrangements of the BCR genes (receptor editing). Further B-cell maturation towards functional antibody-secreting cells occurs within lymphoid follicles. As for T cells, a ‘bridging’ subset of B cells with innate-like characteristics also develops, known as marginal zone (MZ) B cells and B1 B cells. These B-cell populations are the main contributors of T-cell-independent antibody responses and are important players in the immunity to pathogens. Marginal zone B cells (MZB) cells are key components of the first line of de- fence against blood-borne pathogens in the spleen. B1 B cells are capable of self-renewal, are enriched in peripheral sites such as the peritoneal and pleural cavity, and are responsible for the secretion of ‘natural’ (pre-existing) antibodies and contribute substantially to mucosal immunity. Lymphocyte localization Naive lymphocytes are found in blood and in lymphoid organs (spleen, lymph nodes, and the gut-associated lymphoid tissue or GALT). Within lymph nodes, the B and T cells segregate into the primary follicles and paracortex, respectively (Fig. 4.3.4). The re- circulation and organization of these cells is important in under- standing the restrictions on priming of immune responses. Naive T cells do not home to tissues, even inflamed tissues. This is because their homing receptors and chemokine receptors (most import- antly CD62L, or L-selectin, and CCR7) allow for entry through high endothelial venules into lymphoid organs. From there they can re- circulate back into the blood via the efferent lymphatics. Since they cannot meet antigen at a peripheral site, it is therefore essential that antigen is delivered appropriately to the lymph node, and this is achieved by the dendritic cell (DC). The scaffolding of the lymph node in the form of stromal cells and follicular dendritic cells also plays an important role in guiding this process. Priming of an immune response DCs are the most important antigen-presenting cells as they pos- sess not only the appropriate class I and class II molecules, but three further important biological features. First, within tissue, they are very efficient at taking up antigen and delivering this to the class II pathway. Some antigen may enter the cytosol and thus the class I pathway through a process known as cross-presentation. Secondly, they are mobile, and once antigen is taken up, they are able to migrate through chemokine signalling through afferent lymph- atics to local lymph nodes. Thirdly, they possess an array of cell surface molecules and soluble mediators which allow for primary activation (priming) of naive T cells. All three of these functions are strongly influenced by local innate immune signalling including sol- uble factors such as interferon (IFN)-α, or direct signalling through Toll-like receptors (TLRs) that promote ‘maturation’ of the DC, improving its priming ability. Thymus Bone marrow Lymphoid progenitor Early CD4-CD8- thymocyte CD4+CD8+ T cell aβTCR CD4+ T cell CD8+ T cell γδT cell T-cell precursor Pro B cell Pre B cell Immature B cell sIgM H+L chains H chain Lymph node Naive T cells Naive B cell DC Antigen Fig. 4.3.4 Generation of a naive B- and T-cell repertoire. T- and B-cell precursors are generated in the bone marrow, but T-cell development occurs in the thymus. This includes negative selection and more than 90% of thymocytes die through apoptosis. Deletion, anergy, and receptor editing of autoreactive immature B cells occur in the bone marrow.

 T-cell priming requires TCR interaction with cognate MHC– peptide. However, the TCR triggering requires support through signals from other cell surface molecules. A vast array of these is present, but some of the most important are shown in Fig. 4.3.5, including the interaction between CD28 on the T cell, with CD80/86 on the DC. Additionally, soluble cytokines (e.g. interleukin (IL)-12) are secreted by the DC, which signal through cytokine receptors

on the T cell to promote maturation to a full effector cell. Triggering within the T cell requires the integration of all of these signals for full activation. Important signalling pathways within the cell include a cascade of tyrosine kinases starting at the TCR CD3 complex. Critical motifs on the cytoplasmic tails of signalling mol- ecules (immunoreceptor tyrosine-based activatory motifs, ITAMs) initiate these cascades. Downstream, some cellular pathways are in- volved leading to a calcium flux and induction of key transcription factors such as NFAT, NF-κB, and AP-1. Similar intracellular path- ways are involved in B-cell triggering. T-cell effector functions Proliferation The most important consequence of T-cell priming is cellular prolif- eration. This is crucial because while there is huge diversity among the naive repertoire, the precursor frequency is extremely low, less than 1 in 1 000 000. Rapid clonal proliferation of responding CD4+ and CD8+ T cell may be observed, but particularly the latter. CD8+ T-cell responses to specific epitopes may reach 20 to 50% of the CD8+ T-cell pool within a few days of encounter with viruses such as Epstein–Barr virus (EBV). Homing A second key feature of T-cell activation is altered homing poten- tial. Instead of homing to lymphoid tissue, these cells refocus their attention on peripheral organs (Fig. 4.3.6). They lose expression of CD62L and CCR7 and gain expression of chemokine recep- tors such as CCR5, which allow for distribution to inflamed sites (CCR5 is also the coreceptor for HIV entry). A diaspora of such cells therefore occurs to many organs, where innate mediators such as macrophages may secrete appropriate chemokines—a family of small molecules which play a crucial role in regulating cellular mi- gration. Several other cell surface receptors change in primed cells; one useful marker is CD45, which switches isoform from RA to RO. CD8+ T-cell functions These functions are broadly divided into killing and secretory. Killing of target cells occurs by two major means. (1) Lytic function is mediated through secretion of lytic granules, specialized secretory lysosomes which contain perforin, and a set of granzymes. When CD8+ T cells encounter a target cell, the molecules at the contact point reorganize to form an immunological synapse. Lytic granules are released across the synapse and lead to disruption of the target cell membrane and apoptosis. (2) Killing may also occur through interaction of Fas Ligand (FasL) on the CD8+ T cell with Fas on the appropriate target, leading to apoptosis. CD8+ T cells also secrete a range of cytokines, the most important of which is IFN-γ, which has proinflammatory and antiviral effects. They may also secrete tumour necrosis factor (TNFα), interleukins, and chemokines. Some of the latter serve to attract further lympho- cytes; they may also have important inhibitory effects on HIV entry, as they compete for binding to key entry receptors for the virus. Overall these functions are critical in the control of intracellular pathogens such as viruses. Mice where CD8+ T cells are deficient (e.g. CD8 or perforin knockout) are susceptible to infection with lymphocytic choriomeningitis virus. Similar inferences are made for human persistent virus infections. MHC class I genes such as HLA B27 and B57 are associated with protection against both HIV and hepatitis C (HCV), probably through promoting efficient antiviral CD8+ T-cell responses. CD4+ T-cell functions CD4+ T cells provide essential help for other cell types such as CD8+ T cells, B cells, DCs, and macrophages. This is largely through cytokine se- cretion, but one important interaction, through CD40L/CD40, serves as a further important maturation signal for DCs. The type of cytokines secreted by the priming DC, in turn influenced by the original innate CD8+ T cell CD4+ T cell B cell CD40L CD40 IL-2 IL-4 Antigen Innate signals TLR CD28 IL-12 Priming DC MHC class I CD80 CD86 MHC class II Fig. 4.3.5 Priming of naive B and T cells. Priming of T cells occurs through antigen presentation by a mature DC. Signals for maturation include innate signalling and also CD40L signals from primed T cells (not shown for the DC, but also occurring on B cells). A large number of other costimulatory molecules, and regulatory molecules are also expressed. Expression of these strongly modifies the quality of the T-cell response and thus the B-cell response.

4.3 Adaptive immunity 333 signalling, has an important influence on the quality of the CD4+ T cell. Broadly, CD4+ T cells were first described to mature in the dir- ection of Th1 cells (which secrete IFN-γ, driven by the transcription factor Tbet), or Th2 cells, which secrete IL-4, IL-5, IL-10, and IL-13, driven by GATA3. The former are critical in responses against intra- cellular pathogens such as viruses and mycobacteria, while the latter are involved in extracellular defence, including IgE production and eo- sinophilia. A third effector subset includes cells secreting IL-17 (Th17 cells). Their evolution is driven by IL-6 and IL-23 and the transcription factor RORγT, and this pathway has been linked to autoimmunity and antibacterial/antifungal defence. 'Regulatory' CD4+ T cells (Treg) can also emerge, under control of the master regulator FoxP3 (see next). More recently a set of follicular helper cells (Tfh) have been identified, controlled by BCl-6 and function in the germinal centre reaction. Overall, CD4+ T cells play a central role in host defence, and, in their absence, there is failure of CD8+ T-cell-mediated immunity, generation of new antibody responses, and macrophage-mediated immunity, creating susceptibility to viruses, mycobacteria, and tu- mours. This is most evident in the case of HIV, where CD4+ T-cell populations are depleted. Genetically determined variation in CD4+ T-cell responses plays a major role in host defence and also auto- immunity (e.g. the association of specific HLA class II alleles with protection and susceptibility to viral hepatitis). Priming and functions of B cells As with T cells, full activation of B cells requires encounter with antigen binding the B-cell receptor on the lymphocyte surface, but also further signals. These can be provided through innate signalling via TLRs, but additionally signals from CD4+ T cells, both cell:cell (CD40L/CD40) and soluble (IL-4). Mutations in the gene for CD40L result in a failure of class switching and presents clinically as the hyper-IgM syndrome. B cells also undergo clonal proliferation upon appropriate signalling, and move from the state of naive B cell, through lympho- blast and plasmablast to plasma cell (Fig. 4.3.6). Unlike T cells, a diaspora through the body is not seen, but reorganization within the lymph node occurs. Accumulation of B cells during an immune response leads to generation of a secondary follicle, containing add- itionally CD4+ T cells. Ultimately immunoglobulin secreting plasma cells migrate to cords within the medulla (and also bone marrow). As well as secreting antibody, B cells have roles as antigen-presenting cells. They express MHC class II and can take up antigen, most efficiently cognate antigen via their BCR, for presentation to CD4+ T cells. They also secrete cytokines, including IL-10, which has an immunoregulatory role. Generation and maintenance of memory Once an immune response has been initiated, the first acute phase may last days to weeks, depending on the type of challenge, but typ- ically the antigen is controlled through the effector mechanisms just outlined. Thus, the expanded populations seen in the acute phase col- lapse down to smaller levels, although still much greater than seen previously. This elevated precursor frequency of cells with the selected antigen-specific receptor is the hallmark of immunological memory. Lymph node Naive T cells Naive B cell Germinal centre Plasma cells Activated B cells Th1 Th2 Th17 Treg Effector CD4+ T cells TBet GATA3 RORgT FOXp3 Effector CD8+ T cells Nonlymphoid organs Memory CD8+ and CD4+ T cells Effector memory T cells Central memory T cells Medulla CD62L+ CCR7+ CD62L- CCR7- High endothelial venule Afferent lymph DC Antigen Tfh Bcl-6 Tissue-resident memory cells Fig. 4.3.6 Induction and maintenance of memory responses. Effector T-cell populations migrate from the lymph node and may enter nonlymphoid tissue. Subsequently they may revert to a central memory pool, in the absence of further antigenic encounter, or retain some effector functions and continue recirculating through nonlymphoid organs (effector memory). Some may remain long-term in tissues as tissue-resident memory cells.

 T-cell central and resident memory For antigens that are not re-encountered or do not persist, memory T-cell pools over time lose their capacity for immediate effector functions (e.g. secretion of perforin), and their tendency to home to organs. They may regain expression of CD62L and CCR7 and home to lymph nodes (Fig. 4.3.6). These populations are termed central memory. They retain the capacity to respond very rapidly to antigen (within hours), proliferate, and regenerate effector populations. Specialized memory T cell populations are retained at rest in tissues (tissue resident memory), with local protective functions. T-cell effector memory For antigens which persist or are re-encountered, ‘memory’ popula- tions exist which retain some features of effector cells (e.g. expression of perforin), and are found distributed throughout organs. These are termed effector memory cells and are thought to provide more im- mediate protective function. Within these pools, there is still further variation between cells which are considered more or less ‘mature’ as judged by a range of surface and intracellular markers which may be lost or gained over time. The net result of this is that such cells re- ceive less costimulation (e.g. via CD28) and more inhibitory signals (via NK-type receptors). The proportion of such cells varies in dif- ferent infections, with CMV-specific memory CD8+ T cells showing the most mature phenotype, as well as the largest populations (often 1–10% of CD8+ T cells specific for a single epitope; Fig. 4.3.7). B-cell memory Immunological memory due to the B cells is composed of two main populations, memory B cells and long-lived plasma cells (PCs). Memory B cells express the BCR that has been selected during the first infection or exposure to the antigen. These cells are in a resting state, but have unique properties such as longevity, robust respon- siveness, and a capacity for rediversification. In contrast, long-lived PCs are terminally differentiated cells that continuously secrete the antibodies induced during the immune response. These cells are lo- cated mainly in the bone marrow and are responsible for maintaining circulating antibody levels over long periods of time. Downregulation of immune responses The focus so far has been on the initiation of responses against pathogens, but these responses must also be controlled to limit immune-mediated pathology. Responses against self-antigens must also be minimized. The limitation of responses against self is termed tolerance, but many of the same mechanisms also limit responses against pathogens. These issues are briefly outlined next, but are also discussed further in Chapter 4.7 on transplantation and Chapter 4.6 on autoimmunity. Mechanisms of T-cell tolerance As discussed earlier, negative selection within the thymus serves to delete many autoreactive T cells. This process of central tolerance is, however, leaky and further peripheral tolerance mechanisms are required. First, since naive T-cell priming occurs predominantly within lymphoid tissue, failure of antigen to reach this tissue provides an important checkpoint. This has been described as ‘ignorance’ and may be relevant so-called immune privileged sites, or rare antigens. Secondly, anergy may occur through triggering of a T cell via its T-cell receptor, without costimulation (via cell surface signals and cytokines). Such anergic cells subsequently fail to respond to antigen. This may occur if the antigen is encountered on a non-professional antigen-presenting cell that lacks costimulatory cap- acity. Another important contributor to anergy may be encounter of T cells with DCs which have not been fully activated. Antigens encountered without appropriate inflammatory or ‘danger’ signals (e.g. through TLRs) may lead to self-tolerance. The corollary of this is that self-antigens encountered under conditions of ‘danger’ may prime autoreactive responses. Thirdly, CD4+ T-cell subsets with a regulatory role (Tregs) may emerge, driven by expression of the transcription factor FOXP3. Such regulatory subsets may be generated in the thymus against self- antigens (natural Tregs), or after antigen/cytokine stimulation (adap- tive Tregs). Their modes of action include secretion of transforming growth factor β (TGFβ) and IL-10, and upregulation of CD39, an ecto-enzyme which

leads to breakdown of pro-inflammatory ATP (derived from damaged cells) to adenosine, which is inhibitory. Finally, downregulation may also be achieved through upregu lation of inhibitory molecules on activated T cells. These include spe- cific inhibitory molecules such as CTLA-4 and PD-1 (programmed death 1), which bind specific ligands on target cells or DCs, causing a downregulation of T-cell triggering. Many such inhibitory mol- ecules act through so-called immunoreceptor tyrosine-based in- hibitory motifs (ITIMs) which recruit phosphatases and compete with ITAMs. Blockade of inhibitory molecules by biologic agents ('checkpoint inhibitors') can very effectively augment responses to and tumours, although potentially risk immunopathology. Mechanisms of B-cell tolerance Since B cells do not receive education regarding self in the thymus, a potential self-reactive antibody repertoire is being generated Tetramer 104 103 102 101 100 100 101 102 103 104 CD8 CD8+ T cells specific for a single epitope from CMV Fig. 4.3.7 Direct ex vivo evaluation of human antigen-specific T cells using MHC class I peptide tetramers. The example is a healthy donor with a memory response to CMV. The peptide is derived from pp. 65 and the HLA restriction is A2. Approximately 1% of CD8+ T cells are visible after staining, using a flow cytometer. Courtesy of Alison Turner.

4.3 Adaptive immunity 335 continuously. One important mechanism for containing this is through the requirement for T-cell help for full maturation of anti- body responses—in other words a crucial mechanism for B-cell tol- erance is induction and maintenance of CD4+ T-cell tolerance. The use of transgenic mouse models, where both a model antigen and antigen-specific antibody are expressed (classically hen egg lysozyme, HEL) has shed important light on other mech- anisms of B-cell tolerance. As they mature, B cells encountering self-antigens may be controlled through deletion and anergy, as for T cells, or later suffer exclusion from germinal centres. Unlike T cells, autoreactive B cells get a second chance to rearrange their immunoglobulin genes through a process of receptor editing. This may rescue the B cell and allow further normal maturation. Additionally, B cells can contribute to the control of immune re- sponses generated by other cell types. A cell population termed regulatory B cell (Breg) have been described as preventing immunopathology by inhibiting inflammatory lymphocytes through the production of IL-10 and TGFβ. Regulatory mechanisms and immune responses to pathogens Induction of T-cell tolerance at high levels of viral replication has been observed in murine models and is probably occurring to some extent in chronic hepatitis B (HBV), hepatitis C (HCV), and HIV infection. Functional failure or anergy of T-cell responses under such conditions is termed T-cell exhaustion, and ultimately there may be deletion of such cells. It may be that such mechanisms have evolved to avoid potentially lethal immunopathology (e.g. in brain or liver), especially in noncytopathic virus infections. Induction of PD-1 and associated inhibitory molecules play a crucial role in such regulation. Induction of Tregs may play an important role in persistent in- fection and such populations have been implicated in tubercu- losis, leishmania, HCV, and HIV. To what extent they are a cause or consequence of persistent infection remains to be established. Upregulation of PD-1 and IL-10 have been similarly implicated. Failure of regulation of responses The mechanisms of tolerance outlined here may limit self-reactivity, and also responses against pathogens. However, in all responses to pathogens, some immune-mediated pathology may occur as in acute hepatitis B or C. In most circumstances the benefit of the pro- tective response outweighs the short-term cost of the tissue damage. However, immune-mediated pathology can occur against harmless environmental antigens, where there is no net benefit and here it is termed hypersensitivity, or allergy (in the case of IgE-mediated responses; see Chapter 4.5). The underlying immunological mech- anisms for this (and also for autoimmunity) are identical to those against pathogens.

Classically they are divided into four forms, using the criteria of Coombs. • Type I hypersensitivity describes immediate responses mediated by IgE and mast cells and is clinically the most critical (including anaphylactic responses to insect venom and asthma). Underlying this is a T-cell response predominated by Th2 cells. • Type II responses are based on antibody binding antigen on the cell surface and fixation of complement, for example in red-cell or platelet sensitizing syndromes induced by drugs (e.g. penicillin). • Type III responses involve antibody binding soluble antigen (e.g. drugs or therapeutic anserum) to form complexes. These may again fix complement in tissues leading to an Arthus reaction or lead to a more generalized syndrome described as serum sickness. Both type II and III responses are mediated by IgG antibodies. • Type IV responses are cell mediated, and thus delayed, requiring activation and migration of memory T cells. The best example of this is in the tuberculin test. Harnessing adaptive immune responses Diagnostics B cells The use of antibody induction to track exposure to specific patho- gens relies on the specificity of responses. Early responses induce IgM, which is ultimately switched to IgG, except in the case of carbo- hydrate antigens. Direct detection of antibody-secreting or memory B cells may be performed using specific B-cell ELISpot analysis, but these populations are very rare in blood, boosted transiently by vac- cination. Affinity maturation of B-cell responses leads to increased antibody avidity over time, which may be used to date the onset of IgG responses. Antibody detection in patient sera using immuno- assays such ELISA and Western blot forms the basis of many clinical tests. In addition, antibodies specific for multiple molecules have been developed in animals as diagnostic reagents, expanding diag- nostics for many infectious and noninfectious diseases using tech- nologies such as flow cytometry. T cells In the past, detection of antigen-specific T cells usually required cul- ture in vitro and was cumbersome and poorly quantitative. However, techniques such as ex vivo ELISpot, intracellular cytokine staining, and MHC–peptide tetramer analysis have revolutionized the ability to measure T-cell responses in human disease. ELISpot and intracellular cytokine staining rely on detection of cytokine (typically IFN-γ) after exposure to antigen, and subsequent capture of these single cell events on plates, or using a flow cytometer. Alternatively total IFNg can be captured using an ELISA. Direct ex vivo analysis of such populations has been used clinically to evaluate the T-cell response against tuberculosis, in a manner similar to the tuberculin skin test (interferon-γ-release assay or IGRA). Tetramer analysis relies on in vitro synthesis of fluorescently la- belled MHC–peptide complexes. These bind specifically to the T- cell populations of interest, which may be identified using a flow cytometer (Fig. 4.3.7). Such analyses may be of value in tracking the immune responses to infection or vaccines, or during immuno- suppression. Novel technologies based on cytometer coupled with mass-spectrometry (CyTOF) or coupled to a microscope can define multiple functional and phenotypic parameters per cell. Prophylaxis Clearly the most successful clinical harnessing of the adaptive im- mune response is in the form of immunization, which relies on the antigen specificity and memory induction just described. This is dealt with in detail in Chapter 8.3. Overall, vaccines that induce neutralizing antibodies and provide sterilizing immunity have been

 the most successful. CD4+ T-cell-based vaccines already exist for tuberculosis in the form of bacille Calmette–Guérin (BCG) and may be relevant in other settings. The ability to generate specific CD8+ T responses may be needed for complex infections such as HIV and HCV, where antibody responses are insufficient or are confounded by strain variation. Experimental vaccines, especially based on re- combinant virus technology such as adenoviruses to deliver viral antigens, are in trial in such settings. Therapy B cells Transfusion of serum enriched for particular antibodies has been used for many years (e.g. in postexposure prophylaxis of herpes zoster, ra- bies, and hepatitis B). Such antibodies are polyclonal (i.e. derived

from a range of B cells). Fusion of antibody-secreting B cells with myeloma partners in vitro, followed by selection of specific hybridomas al- lows the generation of highly potent and specific monoclonal anti- bodies. This technology was first developed by Milstein and Kohler in 1975 and has in recent years led to the generation of a large range of ‘biologics’ antibodies with therapeutic potential (e.g. targeting cytokines/receptors, adhesion molecules, and tumour receptors). ‘Humanization’ of murine monoclonal antibodies by subsequent mo- lecular modifications may be required for optimization. T cells In contrast with B-cell based interventions, transfusion of specific T cells has been limited by the inability to grow such cells in vitro, and problems of MHC restriction and rejection. However, the ability to detect and isolate specific T cells has allowed some intervention in specific cases, such as cytomegalovirus disease after bone marrow transplantation. In vivo expansion of donor-derived transfused T cells may be observed after bone marrow transplantation and clinical effects even against established EBV-driven lymphomas have been reported. Augmentation of pre-existing T-cell responses through use of ‘checkpoint inhibitors’ can liberate a marked antitumour ef- fect in cancers such as melanoma. In addition, in vitro expanded tumour-specific T lymphocytes can form the basis of the adoptive T-cell therapies such as prostate cancer while chimeric antigen re- ceptor (CAR) T cells with modified and targeted receptors have been successfully used to treat several haematological malignancies. Possible future developments The molecular dissection of the adaptive immune response has re- cently allowed a clearer view of the basis for antigenic diversity and the mechanisms involved in induction and maintenance of func- tional responses. This has allowed improved diagnostics and tar- geted therapies to enhance or suppress specific responses. Further developments in this area leading to rationally designed immuno- suppressant or adjuvant approaches are to be expected. The use of monoclonal antibodies or small molecules to interrupt or target spe- cific pathways has been greatly expanded recently, although there is caution since severe reactions can occur, as in the case of a trial anti- body to CD28. Further complexity of the cellular components of im- mune responses is likely to be revealed, including defining further the role for novel ‘bridging subsets’ (see Fig. 4.3.8) and integration of innate and adaptive responses. Finally, pathogens are by far the best immunologists. Learning from them could lead us to novel and successful immunotherapy strategies. While their ability to manipu- late host responses will remain a challenge to vaccine development, their ingenuity may be fruitfully harnessed further to provide novel immunization strategies. FURTHER READING Beck A, et al. (2010). Strategies and challenges for the next generation of therapeutic antibodies. Nat Rev Immunol, 10, 345–52. Blum J, et al. (2013). Pathways of antigen processing. Ann Rev Immunol, 31, 443–73. Davis SJ, van der Merwe PA (2006). The kinetic-segregation model: TCR triggering and beyond. Nat Immunol, 7, 803–9. Guedan S, Ruella M, June CH (2018). Emerging cellular therapies for cancer. Annu Rev Immunol, doi: 10.1146/annurev-immunol-042718-041407. Horton R, et al. (2004). Gene map of the extended human MHC. Nat Rev Genet, 5, 889–99. Kurosaki T, et al. (2015). Memory B cells. Nat Rev Immunol, 15, 140–50. Mueller SN, Mackay LK (2016). Tissue-resident memory T cells: local specialists in immune defence. Nat Rev Immunol, 16, 79–89. Natoli G, Ostuni R (2019). Adaptation and memory in immune re- sponses. Nat Immunol, 20, 983–92. Qi H, et al. (2015). Spatiotemporal basis of innate and adaptive immunity in secondary lymphoid tissue. Annu Rev Cell Dev Biol, 30, 141–67. Rammensee H, et al. (1999). SYFPEITHI: database for MHC ligands and peptide motifs. Immunogenetics, 50, 213–9. Rosser E, Mauri C (2015). Regulatory B cells: origin, phenotype and function. Immunity, 42, 607–12. Sallusto F, et al. (2010). From vaccines to memory and back. Immunity, 33, 451–63. Sharma P, Allison JP (2015). The future of immune checkpoint therapy. Science, 348, 56–61. Virgin HW, Wherry EJ, Ahmed R (2009). Redefining chronic viral in- fection. Cell, 138, 30–50. Xing Y, Hogquist KA (2012). T-cell tolerance: central and peripheral. Cold Spring Harb Perspect Biol, 4, a006957. Zinkernagel

RM (1996). Immunology taught by viruses. Science, 271, 173–8. Innate Adaptive B cell CD4+ T cell CD8+ T cell DCs Granulocytes MAIT cell NKT cell γδ T cell ILCs NK cells MZ B cell Fig. 4.3.8 Innate, adaptive, and ‘bridging’ immune cell subsets. From left to right are depicted components of the immune response with a transition from ‘innate’ to adaptive. The innate lymphoid cells, and NK cells show broadly innate behaviour, although share many phenotypic and functional features with T and B cells, while MAIT, NKT, and γδ T cells are T-cell subsets which show significant innate responsiveness, as do marginal zone and B1 B cells.

Revision #1
Created 2026-01-22 16:44:22 UTC by Omar Ayman
Updated 2026-01-22 16:44:22 UTC by Omar Ayman