Adaptive (acquired) immunity

Learning objectives

To be able to:
1) Name the major types of T lymphocyte
2) Discuss how T lymphocytes carry out their functions
3) List the similarities and differences between T and B lymphocytes
4) Explain the concept of clonal selection
5) Describe how dendritic cells are key to the activation of the adaptive immune Response

Adaptive immune responses rely on **lymphocytes**. These are the only cells in the immune response that (a) are **highly antigen-specific** and (b) exhibit **immunological memory** – the two defining characteristics that distinguish adaptive responses from innate responses. There are 2 main types of lymphocyte: **T-cells** and **B-cells**.

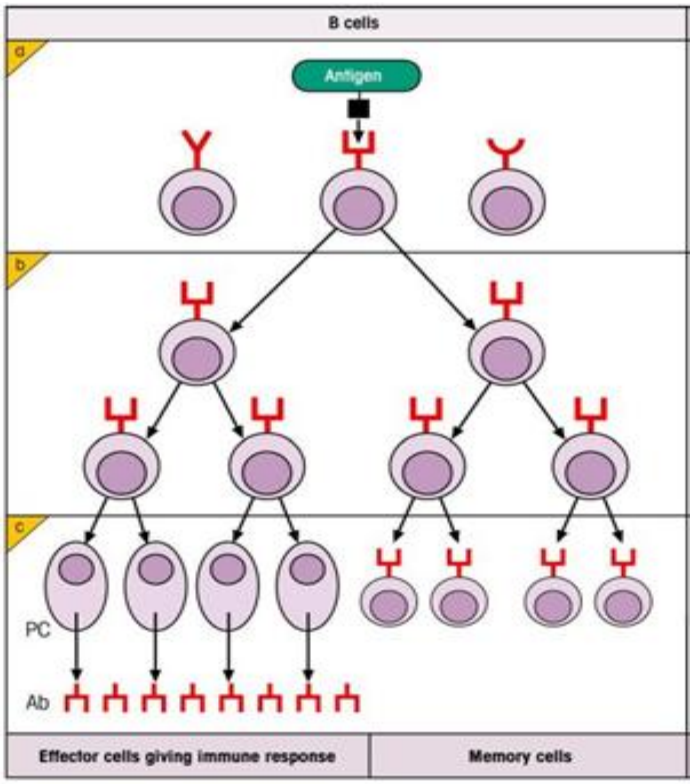
B-cells use **surface immunoglobulin** molecules as their B-cell receptor (**BCR**). Prior to encounter with antigen, i.e. as **naive B-cells**, they coexpress **IgM** and **IgD** antibodies on their cell surface. Possession of transmembrane surface immunoglobulin defines a cell as being a B-cell. Other molecules typically present on the surface of the B-cell include **CD19** and **CD20**. The surface immunoglobulin of the BCR is associated with 2 signal transduction molecules termed **Igα** and **Igβ**.

B-cells recognise antigen in its natural form (**native antigen**) and, following antigenic stimulation, they divide and develop into specific **effector** cells. Each lymphocyte gives rise to a '**clone**' of effector cells. Since most antigens have many different **epitopes** several clones of B-cells are normally selected (**clonal selection**) to participate in a polyclonal immune response and will secrete **polyclonal antibody**.

The B-cell response to most antigens requires **T-cell help** ('T-dependent antigen') although the response to some antigens, e.g. certain carbohydrate antigens, is T-cell independent. The 'help' for responses to T-dependent antigens is provided by

‘**costimulation’** of the B-cell by T-cell derived **cytokines** and **CD40/CD40L** interactions.

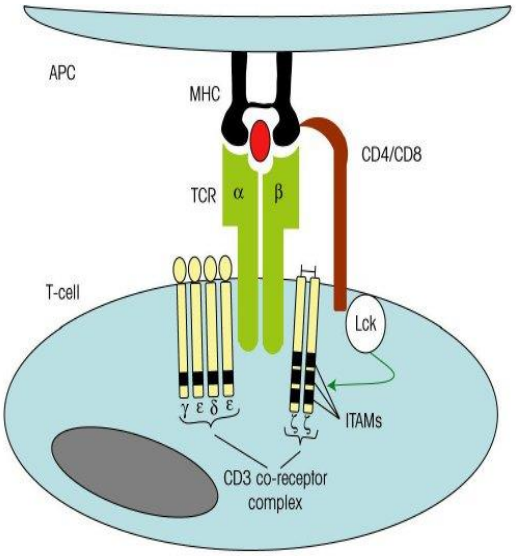
Within anatomical structures called **germinal centres** in spleen and lymph node B-cells undergo **class switch recombination (CSR)** to produce **IgG**, **IgA** or **IgE** antibodies, and **somatic hypermutation** of the antibody genes leads to **affinity maturation**. The generation of **memory cells** and of plasma cell precursors also occurs in the germinal centres. The final stages of differentiation into antibody-secreting **plasma cells** occurs within the secondary lymphoid tissues but outside the germinal centres. Although generally short-lived with a half-life of only a few days, some plasma cells survive for periods of weeks or longer, especially within the bone marrow.



Delves *et al. Roitt’s Essential Immunology,*

T-cells: The precursors of T-cells originate in the bone marrow but must mature in the **thymus** before they become functional T-cells. The T-cells recognise antigen using the T cell receptor (**TCR**, most commonly an $\alpha\beta$ heterodimer but alternatively

a γδ heterodimer) and, like B-cells, show a high degree of **antigen specificity**. For recognition by αβ T-cells protein antigens are first **processed** into **peptides** by proteases and the peptides **presented** to the TCR by **MHC** molecules.



Delves *et al. Roitt's Essential Immunology, 12th ed.*
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As with B-cells, following antigenic stimulation individual T-cells **proliferate** and develop into specific **effector** cells. Functionally, αβ T-cells can be roughly divided into three populations; (1) **helper T-cells** (**Th**) and (2) **regulatory T-cells** (**Tregs**), most of which express the **CD4** cell surface molecule, and (3) **cytotoxic T-cells** (**Tc** or cytotoxic T lymphocytes, **CTL**) most of which express the **CD8** cell surface molecule. All T cells express surface **CD3** molecules which transduce the signal from the TCR into the T-cell. Helper T-cells 'help' other cells of the immune system to carry out their functions. The **T helper cells** can be divided into subpopulations such as **Th1**, **Th2**, **Th17**, etc. depending on which cytokines they secrete. **Th1** cells characteristically secrete **IFNγ**, **Th2** cells characteristically secrete **IL-4**, and **Th17** cells characteristically secrete **IL-17** (note that all 3 types also secrete many other cytokines). In general **Th1** cells help **cell-mediated immunity** (CMI, which refers to cytotoxic T-cells and macrophages), **Th2** cells help **humoral immunity** (antibody production by B-cells) and **Th17** cells promote **inflammation**. In addition to providing the cytokines necessary for B-cell activation and differentiation, Th2 cells provide additional costimulatory signals to the B-cell when the **CD40 ligand** (**CD40L**) on the T-cell surface engages **CD40** on the B-cell surface.

Regulatory T-cells suppress immune responses. They do this by secreting cytokines such as **IL-10** and **TGFβ** which can mediate immunosuppressive functions, and also by a not fully defined cell contact dependent mechanism.

Cytotoxic T-cells trigger **apoptosis** in virally-infected cells, either by inserting the pore-forming molecule **perforin** into the target cell membrane and then injecting apoptosis-inducing **granzymes** into the cell, or by the **Fas ligand** (FasL) on the activated cytotoxic T-cell engaging the **Fas** (**CD95**) death receptor on the target cell.

In addition to development of effector function, individual T cells (just like B-cells) can develop into **memory cells** which are responsible for mounting enhanced immune responses against antigens previously encountered by the organism.

The **innate and adaptive responses** very much **work together** to defeat the pathogen. Although **dendritic cells** are generally classified as cells of the innate response, being neither antigen-specific nor exhibiting immunological memory, they are **key cells in the initiation of the adaptive response**. The interdigitating dendritic cells (DC), which include the **Langerhans cells** in skin, constantly sample extracellular antigens by endocytosis. They become activated to an antigen-presenting cell mode when **pattern recognition receptors** (**PRR**s) on their cell surface recognize **pathogen-associated molecular patterns** (**PAMP**s) on the surface of microorganisms. Following activation, the dendritic cells upregulate their cell surface **B7 costimulatory molecules** (B7.1 and B7.2, also known as **CD80** and **CD86**) which, by binding to **CD28** on the T-cell, will contribute to the activation of T-cells. The activated dendritic cells migrate via the lymphatic vessels to the local draining lymph node where they **present antigen to T-cells**. The antigen is intracellularly processed by proteolytic cleavage into short **peptides** prior to presentation by **major histocompatibility complex (MHC) class II** molecules on the dendritic cell surface. These MHC molecules present the peptides to the T-cell antigen receptor (TCR) on the surface of **$CD4^+$ helper T-cells**. Because they can express high levels of costimulatory molecules, dendritic cells are particularly efficient at **priming** (initiating) immune responses for which immunological memory has not previously been established, i.e. they **can activate naive T-cells**.

Follicular dendritic cells in the germinal centres of lymph nodes and spleen constitute an **entirely different cell type**. They do not possess MHC class II molecules and are not therefore involved in antigen presentation to $CD4^+$ helper T-cells. They do, however, have **Fc receptors** for IgG (**FcγR**) and **complement receptors** on their cell surface. This allows them to pick up **immune complexes** (antibody-antigen complexes, which can additionally have complement bound to them) and to **present the native antigen** in these complexes directly to **B-cells**. They are involved in stimulating B cell survival, proliferation, and differentiation into memory cells.