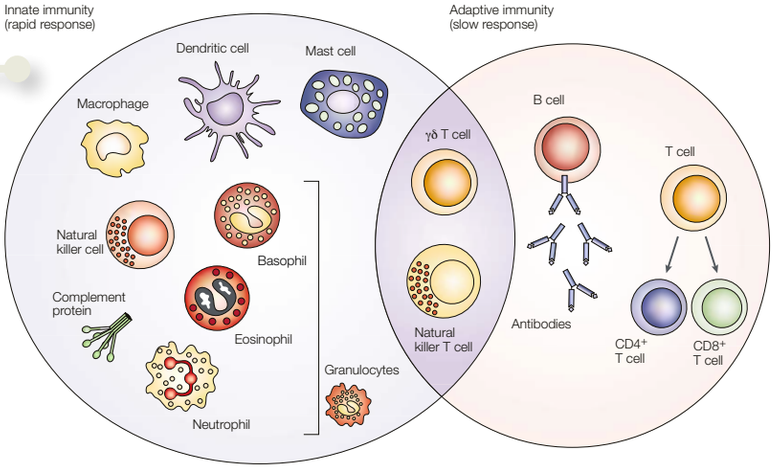
1 The immune system

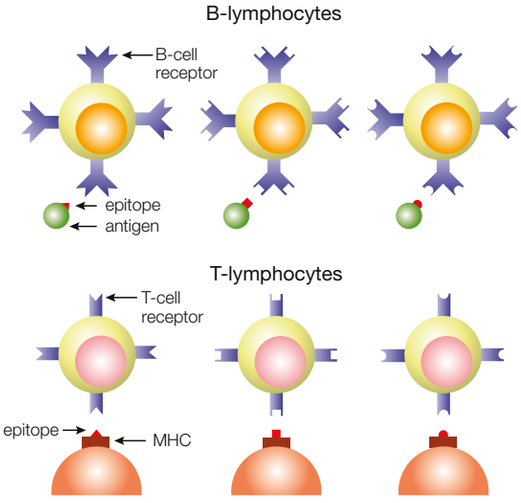
The immune response

The immune system comprises two arms functioning cooperatively to provide a comprehensive protective response: the innate and the adaptive immune system.

The innate immune system is primitive, does not require the presentation of an antigen, and does not lead to immunological memory.

Its effector cells are neutrophils, macrophages, and mast cells, reacting within minutes to hours with the help of complement activation and cytokines (CK).





The adaptive immune response is provided by the lymphocytes, which precisely recognise unique antigens (Ag) through cell-surface receptors.

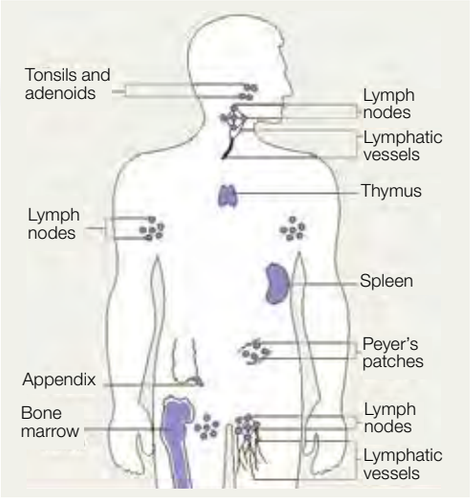
Receptors are obtained in billions of variations through cut and splicing of genes and subsequent negative selection: self-recognising lymphocytes are eradicated.

Immunological memory after an Ag encounter permits a faster and heightened state of response on a subsequent exposure.

Lymphocytes develop in primary lymphoid tissue (bone marrow [BM], thymus) and circulate towards secondary lymphoid tissue (lymph nodes [LN], spleen, MALT).

The Ag reach the LN carried by lymphocytes or by dendritic cells. Lymphocytes enter the LN from blood transiting through specialised endothelial cells.

The Ag is processed within the LN by lymphocytes, macrophages, and other immune cells in order to mount a specific immune response.



REVISION QUESTIONS

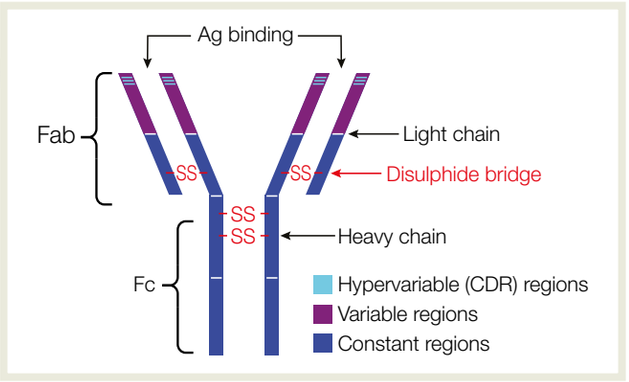
1. What are the effector cells of the innate immune system?
2. Which cells are responsible for immune memory?
3. In which anatomical structure are the antigens processed by lymphocytes?

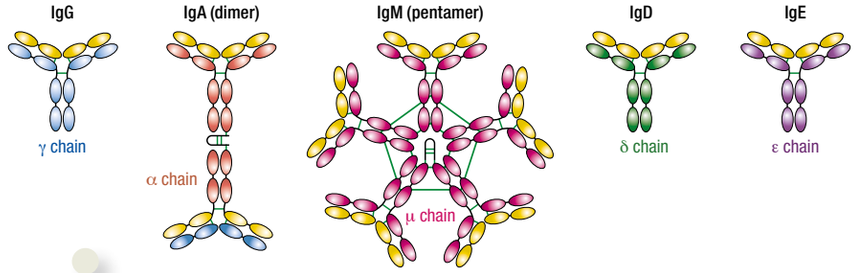
Immunoglobulins and B-cell development

The lymphocytes developed in the BM (B cells) have as their final task the production of Ag-specific immunoglobulins (Ig), which function as antibodies (Ab).

Ig are proteins secreted by or present on the surface of B cells, assembled from identical couples of heavy (H) and light (L) chains.

The highly variable N terminal regions are the Ag-binding portion (Fab fragment). The constant domains interact with the Fc receptors on the effector cells.





There are 5 classes of Ig: M, G, A, E, and D, distinguished by different heavy chains. B cells can change the class of Ig produced: class switch.

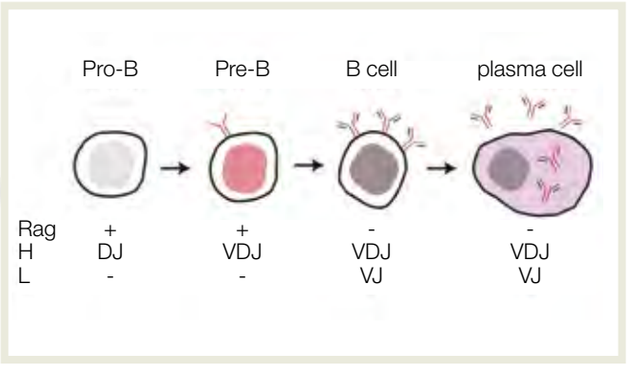
Before being capable of producing Ag-specific Ig, B cells must undergo a number of transformations, first in the BM and subsequently in the LNs.

In the rest of the cells in the body (not B cells), the genes encoding for the H and L chains of the Ig are distributed in many segments so that they cannot be expressed.

These gene segments must be rearranged within the chromosome in the B cells so the final gene structure allows the expression of a functional protein.

The first stages of B-cell development occur in the BM, where pro-B cells first rearrange the Ig H chain gene to become a pre-B cell.

Pre-B cells continue this somatic recombination process by rearranging the L chain to become an immature B cell, expressing IgM on their surface.



REVISION QUESTIONS

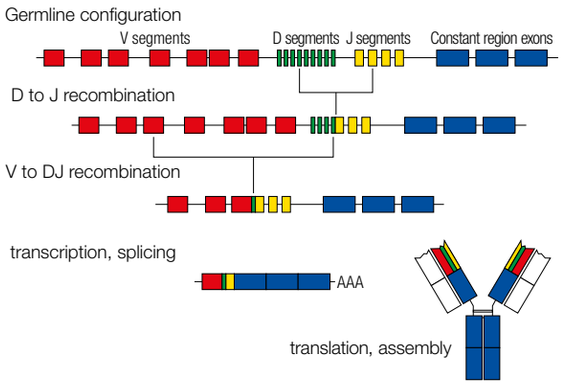
1. What are the Fab and the Fc portions of an immunoglobulin?
2. What distinguishes a pre-B from a pro-B from an immature B cell?
3. What is meant with the term “somatic recombination”?

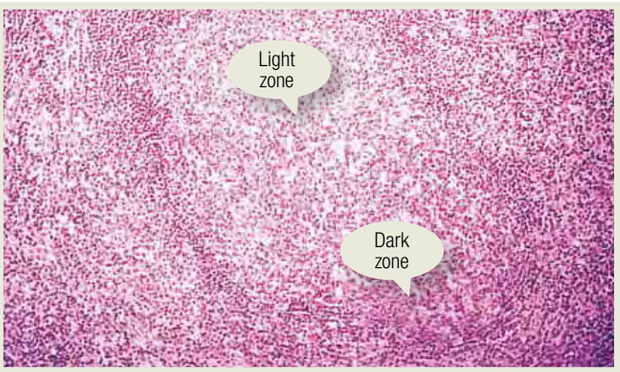
B-cell diversity

In B cells the variable regions of the Ig L chains are encoded by the random joining of one of many variable (V) and joining (J) segment genes.

In addition to the above, for the H chain gene, a diversity (D) gene must also be rearranged.

The result of this random process is the expression on any individual naive B-cell surface of a unique Ig with Ag specificity: the B-cell receptor (BCR).





Naive B cells exit the BM and circulate between blood, LN, and secondary lymphoid tissue in search of an Ag that will match the randomly determined BCR.

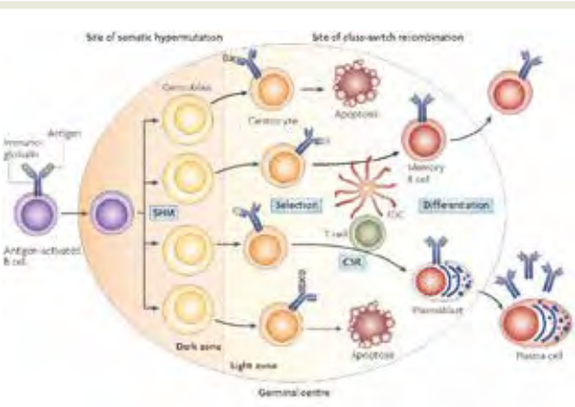
When naive B cells encounter an antigen within the germinal centre (GC) of a LN they undergo further variation and selection.

Binding of an Ag to the BCR, with the help of T cells and antigen-presenting cells (APC), initiates Ag-dependent germinal centre reaction.

In the peripheral dark zone of the GC, rapidly dividing B cells (centroblasts, CB) introduce random mutations in the H and L chains (somatic hypermutation).

In the central light zone, CBs mature to centrocytes (CC) and are selected for affinity with the help of follicular helper T cells and dendritic cells.

High-affinity CC mature to either plasma cells or memory B cells and leave the GC. They may undergo Ig class switch by changing the Ig H chain.



REVISION QUESTIONS

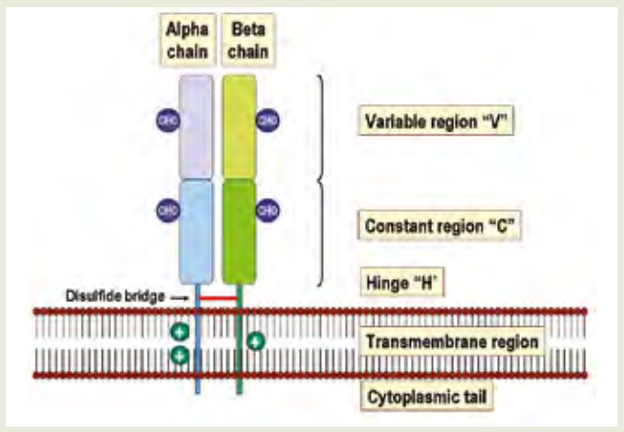
1. What are the phases of B-cell development and where do they take place?
2. How is the diversity of immunoglobulin specificity derived?
3. What is meant by “somatic hypermutation”?

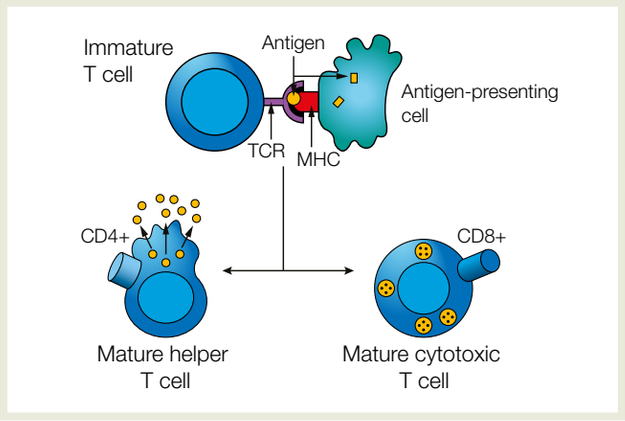
T cells and NK cells

T lymphocytes arise in the BM but soon migrate to the thymus, where they mature to express the Ag-binding T-cell receptor (TCR) on their membrane.

The TCR is a dimer composed of 2 chains, usually α and β. Similar to the BCR, each one of these chains includes a variable and a constant domain.

T cells are able to recognise Ag (through their TCR) only when the Ag is bound to a major histocompatibility complex (MHC) molecule.





After migrating to the secondary lymphoid organs, naive T cells are exposed to Ag which bind to the TCR. TCR activation induces proliferation and differentiation.

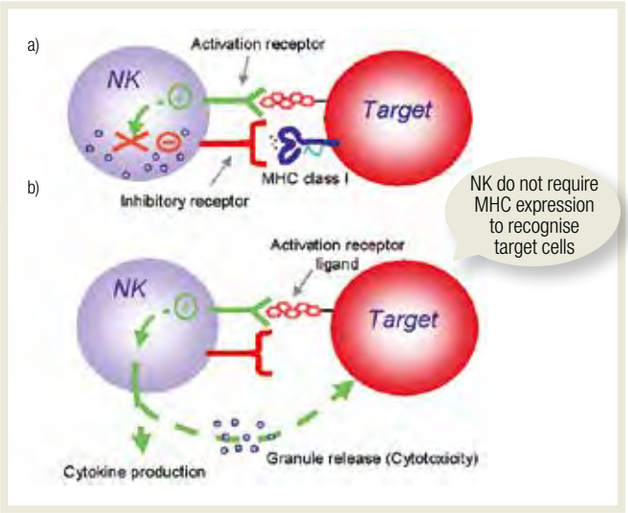
T cells mature to distinct T-helper (Th) and T-cytotoxic (Tc) populations characterised by expression of CD4 and CD8, respectively.

There are 2 classes of MHC molecules: class I and class II. Th recognises Ag in the context of class II MHC, whereas Tc recognises Ag bound to class I MHC.

Activated Th cells divide and produce a clone of effector cells, which in turn secrete CK, activating other components of the immune response.

Once activated, Tc induce apoptosis of dysfunctional cells (i.e. infected) by enzymatic or signalling processes. Natural killer (NK) cells have a similar function.

Memory T cells are produced after Ag exposure. They remain quiescent and provide an enhanced response after repeated exposure to the Ag.



REVISION QUESTIONS

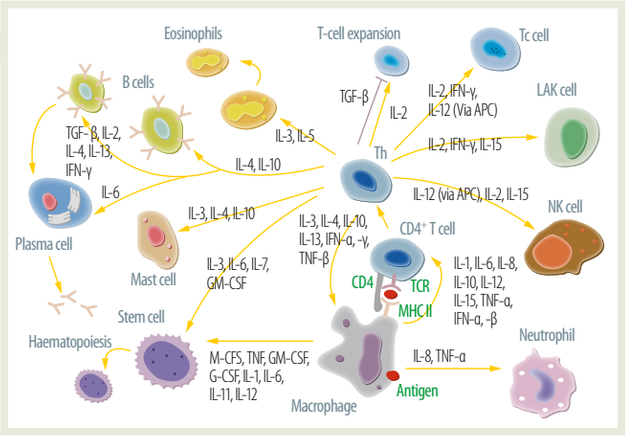
1. What is the structure of the T-cell receptor?
2. How can T-helper and T-cytotoxic cells be easily distinguished?
3. What is the main function of cytotoxic T cells?

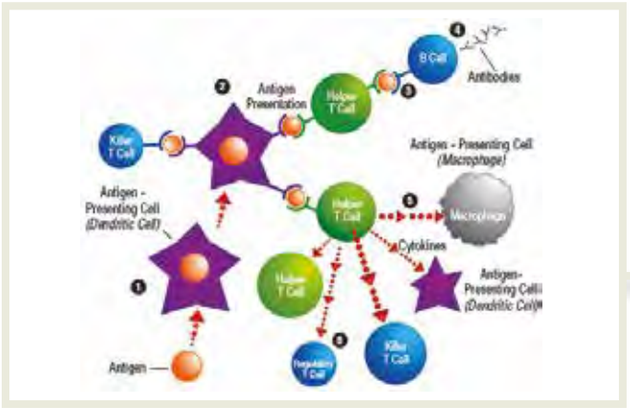
Immune system activity

CK are low molecular weight proteins that play a key role in the induction and regulation of the immune response.

Produced by a variety of cells, their actions are mediated through their respective receptors; they exert autocrine, paracrine, and endocrine effects.

CK regulate the intensity and duration of both the innate and adaptive immune response.





The various individual facets of the immune response interact in a complex fashion to result in a coordinated response.

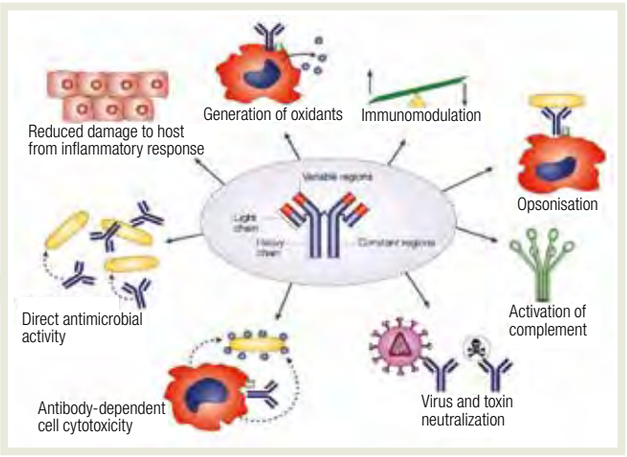
Following a rapid response by the cells of the innate system, the cells of the adaptive immune system recognise Ag, expanding and activating effectors.

APC, present throughout the body, internalise and process Ag, displaying part of it on their surface bound to a class II MHC molecule.

This way APC carry cargos of foreign Ag to lymphoid organs, where they are recognised by Th cells which initiate the adaptive response.

All aspects of the adaptive response are initiated and controlled by T cells. They recruit immunological effector mechanisms by direct contact or through CK.

Antibodies may cause direct cytotoxicity by activation of the complement cascade or by recruiting effector cells (NK, macrophages, etc.) that cause cell death.



REVISION QUESTIONS

1. What are cytokines and how do they exert their function?
2. What is the role of the antigen-presenting cells?
3. What mechanisms are employed by antibodies to result in dysfunctional cell death?

Summary: The immune system

- Cells of the primitive innate immune system and the antigen-specific adaptive immune system act as a cooperative network to bring about a coordinated and tightly regulated immune response to foreign antigens
- The former uses a limited pattern of recognition molecules and, although it retains no memory, is able to mount a rapid response
- The latter recognises a huge diversity of different specific antigens and elicits a response that is highly specific and retains memory
- Diversity and antigen specificity in both the TCR and BCR result from somatic recombination and the random splicing of a selected number of gene segments
- When naive B cells encounter an antigen, further antigen specificity is added by somatic hypermutation in the germinal centre of secondary lymphoid organs
- Only the most avidly antigen-binding cells mature to become either antibody-producing plasma cells or memory B cells
- Antibodies may switch to different classes with differing effector functions and tissue locations while retaining the same antigen specificity in their variable regions
- In response to antigen, T cells differentiate to effector T cells that may augment the immune response, cytotoxic T cells that destroy altered self-cells, or regulatory T cells
- Cytokines regulate the immune response by autocrine, paracrine, and endocrine mechanisms
- Cooperative interactions of both facets of the immune response result in efficient effector mechanisms that clear foreign antigen with residual immunological memory

Further Reading

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