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 systems.

The innate immune system is primitive, does not require the presentation of an antigen (Ag) 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 (CKs).

Innate and adaptive immunity

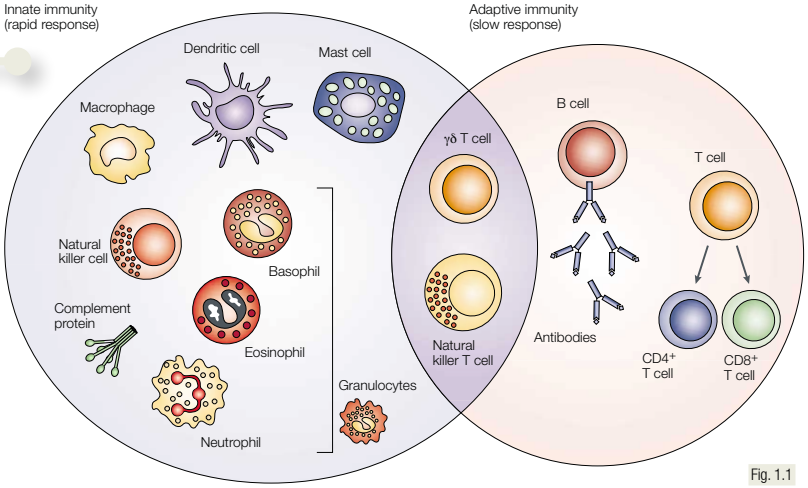
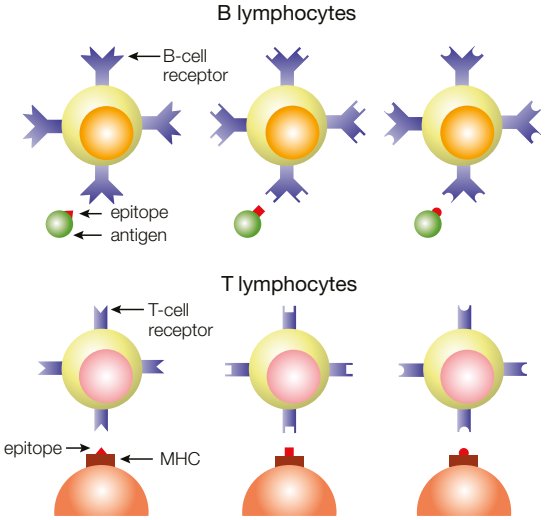


Fig. 1.1

B and T lymphocytes



MHC, major histocompatibility complex.

Fig. 1.2

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

Receptors are produced in billions of variations through cut and splicing of genes and subsequent negative selection: thus, 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 [LNs], spleen, mucosa-associated lymphoid tissue [MALT]).

The Ag reaches the LN carried by lymphocytes or 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.

Primary and secondary lymphoid tissues

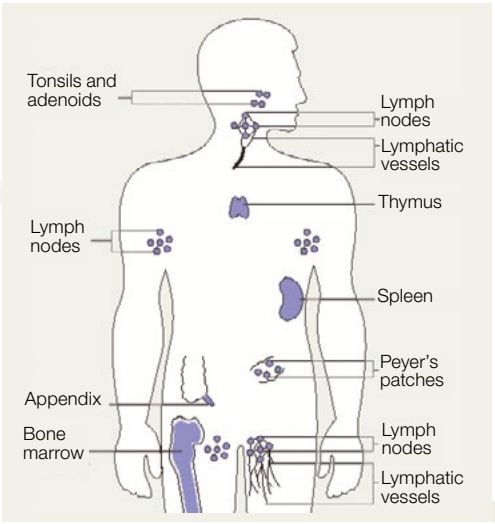


Fig. 1.3

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 Ags processed by lymphocytes?

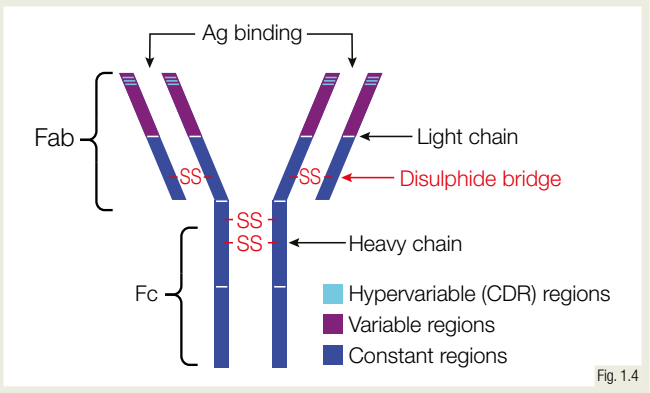
Immunoglobulins (Igs) and B-cell development

The final task of the lymphocytes (B cells) developed in the BM is the production of Ag-specific Igs, which function as antibodies (Abs).

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

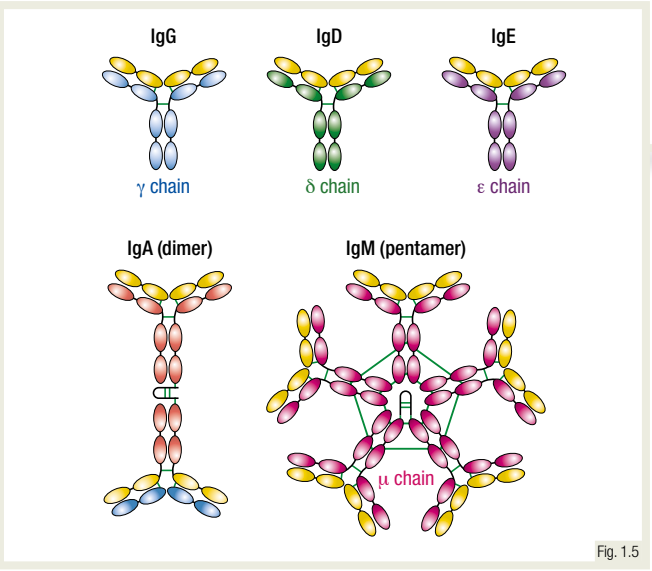
The highly variable N-terminal regions are the fragment antigen-binding (Fab) portion. The constant domains interact with the fragment crystallisable (Fc) receptors on the effector cells.

Antibody structure



Ag, antigen; CDR, complementary-determining region; Fab, fragment antigen-binding; Fc, fragment crystallisable.

Immunoglobulin classes



Ig, immunoglobulin.

There are five classes of Igs: M, G, A, E and D, distinguished by different H chains. B cells can change the class of Ig produced: class switching.

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.

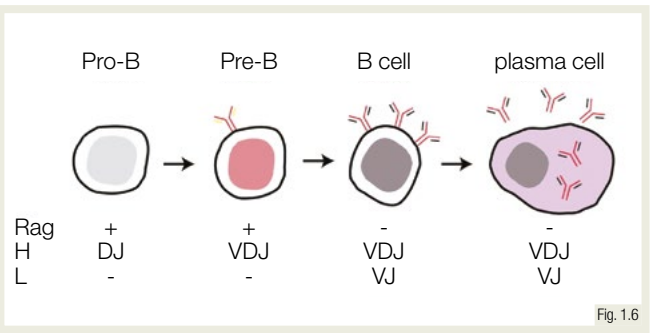
In the rest of the cells in the body (not B cells), the genes encoding the H and L chains of the Ig are distributed in many segments, thus they cannot be expressed.

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 pre-B cells.

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

B-cell development



D, diversity; H, heavy; L, light; J, joining; Rag, recombinase activating gene; V, variable.

REVISION QUESTIONS

1. What are the Fab and the Fc portions of an Ig?
2. What distinguishes a pre-B from a pro-B from an immature B cell?
3. What is meant by 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 naïve B-cell surface of a unique Ig with Ag specificity: the B-cell receptor (BCR).

V(D)J recombination

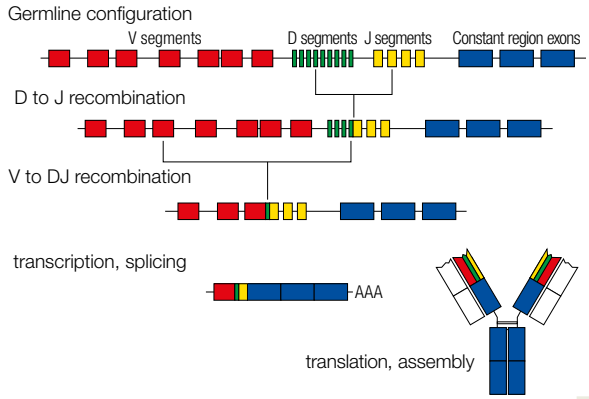


Fig. 1.7

VDJ, variability, diversity and joining.

Germinal centre

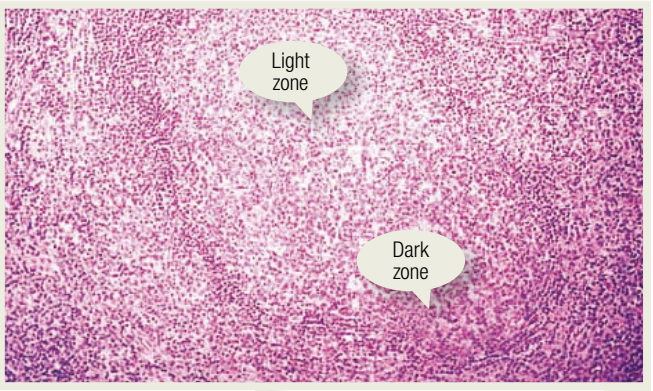


Fig. 1.8

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

When naïve B cells encounter an Ag 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 (APCs), initiates Ag-dependent GC reaction.

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

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

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

Somatic hypermutation and class-switch recombination

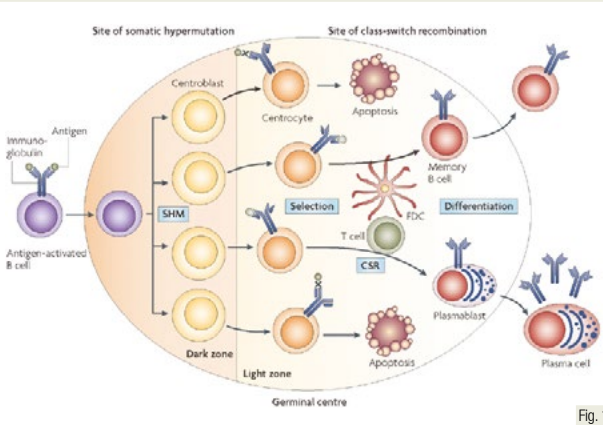


Fig. 1.9

CSR, class-switch recombination; FDC, follicular dendritic cell; SHM, somatic hypermutation.

REVISION QUESTIONS

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

T cells and natural killer (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 two 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 Ags (through their TCR) only when the Ag is bound to a major histocompatibility complex (MHC) molecule.

T-cell receptor structure

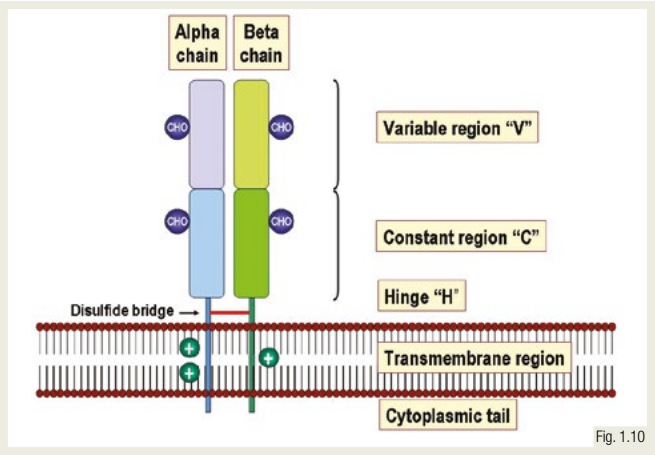


Fig. 1.10

T-cell maturation

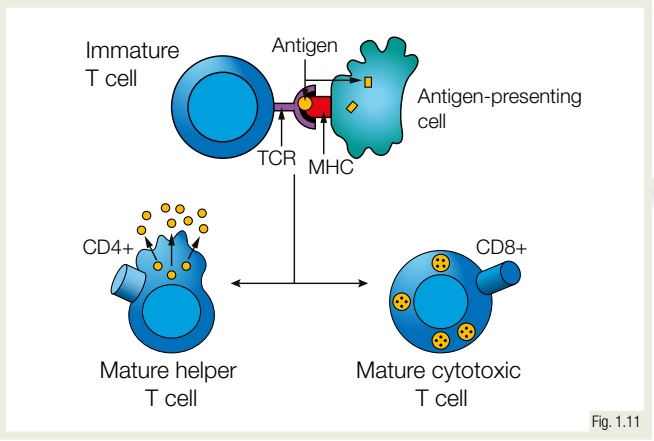


Fig. 1.11

MHC, major histocompatibility complex; TCR, T-cell receptor.

After migrating to the secondary lymphoid organs, naïve T cells are exposed to Ags 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 two classes of MHC molecules: class I and class II. Th cells recognise Ags in the context of class II MHC, whereas Tc cells recognise Ags bound to class I MHC.

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

Once activated, Tc cells induce apoptosis of dysfunctional cells (i.e. infected) by enzymatic or signalling processes. 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 Ags.

Natural killer cell activation

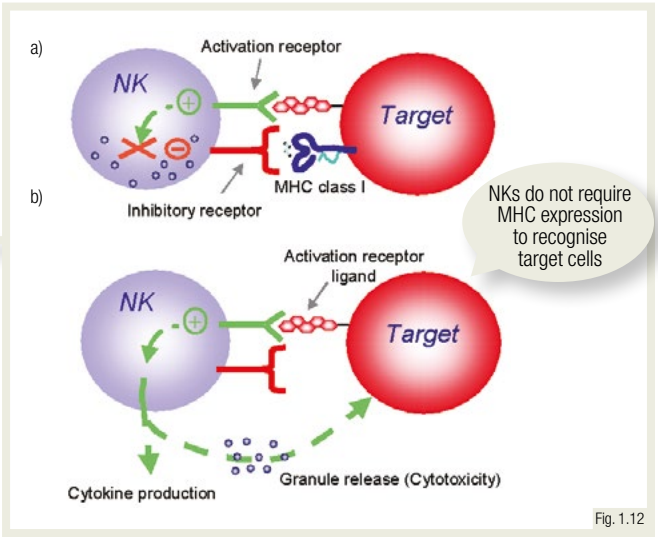


Fig. 1.12

MHC, major histocompatibility complex; NK, natural killer.

REVISION QUESTIONS

1. What is the structure of the TCR?
2. How can Th and Tc cells be easily distinguished from one another?
3. What is the main function of Tc cells?

Immune system activity

CKs 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 receptive receptors; they exert autocrine, paracrine and endocrine effects.

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

Cytokines

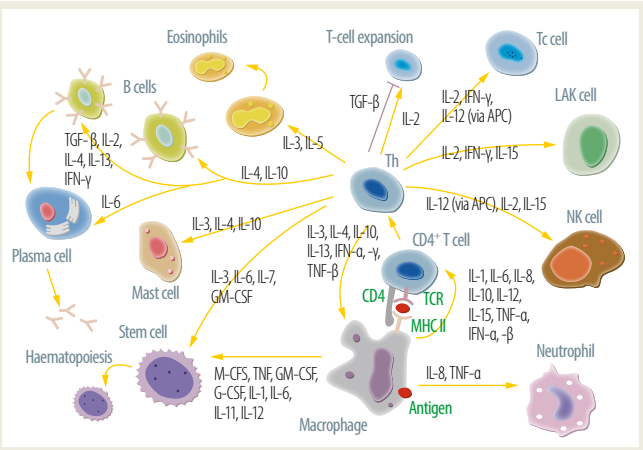


Fig. 1.13

APC, antigen-presenting cell; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; M-CFS, macrophage colony-stimulating factor; MHC, major histocompatibility complex; NK, natural killer; Tc, T cytotoxic; TCR, T-cell receptor; TGF, transforming growth factor; TNF, tumour necrosis factor.

Antigen processing and presentation

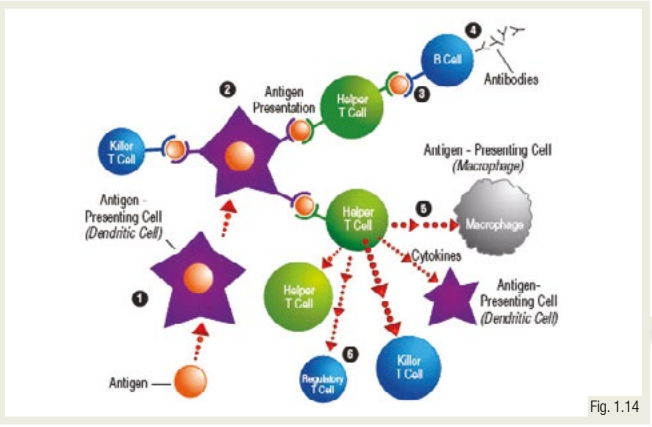


Fig. 1.14

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 Ags, expanding and activating effectors.

APCs, present throughout the body, internalise and process Ags, displaying part of them on their surface bound to a class II MHC molecule.

This way APCs carry cargos of foreign Ags to lymphoid organs, where they are recognised by Th cells that 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 CKs.

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

Antibody-mediated cytotoxicity

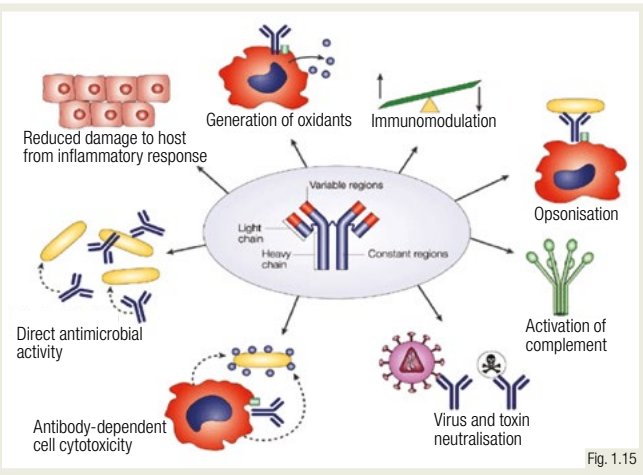


Fig. 1.15

REVISION QUESTIONS

1. What are CKs and how do they exert their function?
2. What is the role of APCs?
3. Which mechanisms are employed by Abs to cause dysfunctional cell death?

Summary: The immune system

- Cells of the primitive innate immune system and the Ag-specific adaptive immune system act as a cooperative network to bring about a coordinated and tightly regulated immune response to foreign Ags
- The primitive innate immune system uses a limited pattern of recognition molecules and, although it retains no memory, is able to mount a rapid response
- The Ag-specific adaptive immune system recognises a huge diversity of different specific Ags and elicits a response that is highly specific and retains memory
- Diversity and Ag specificity in both the TCR and BCR result from somatic recombination and the random splicing of a selected number of gene segments
- When naïve B cells encounter an Ag, further Ag specificity is added by somatic hypermutation in the GC of secondary lymphoid organs
- Only the most avid Ag-binding cells mature to become either Ab-producing plasma cells or memory B cells
- Abs may switch to different classes with differing effector functions and tissue locations while retaining the same Ag specificity in their variable regions
- In response to Ags, 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
- CKs 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 Ags with residual immunological memory

Further Reading

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Image sources: **Fig. 1.1.** Dranoff G. Nat Rev Cancer 2004;4:11-22; **1.2.** Kaiser G. Microbiology (https://bio.libretexts.org/Bookshelves/Microbiology/Microbiology_(Kaiser); **1.4.** Fix D, Professor at Southern Illinois University (https://myplace.frontier.com/~dffix/medmicro/igs.htm); **1.7.** http://www.talkdesign.org/faqs/Evolving_Immunity.html; **1.8.** Levy N, Dartmouth College; **1.9.** Klein U, Dalla-Favera R. Nat Rev Immunol 2008;8:22-33; **1.10.** Hunt R. www.microbiologybook.org; **1.11.** https://en.wikipedia.org/wiki/File:Antigen_presentation.jpg; **1.12.** French AR, Yokoyama WM. Arthritis Res Ther 2003;2004:6:8-14; **1.15**. Casadevall A, et al. Nat Rev Microbiol 2004;2:695-703.