Major Histocompatibility Complex (MHC) and other cell receptors

By
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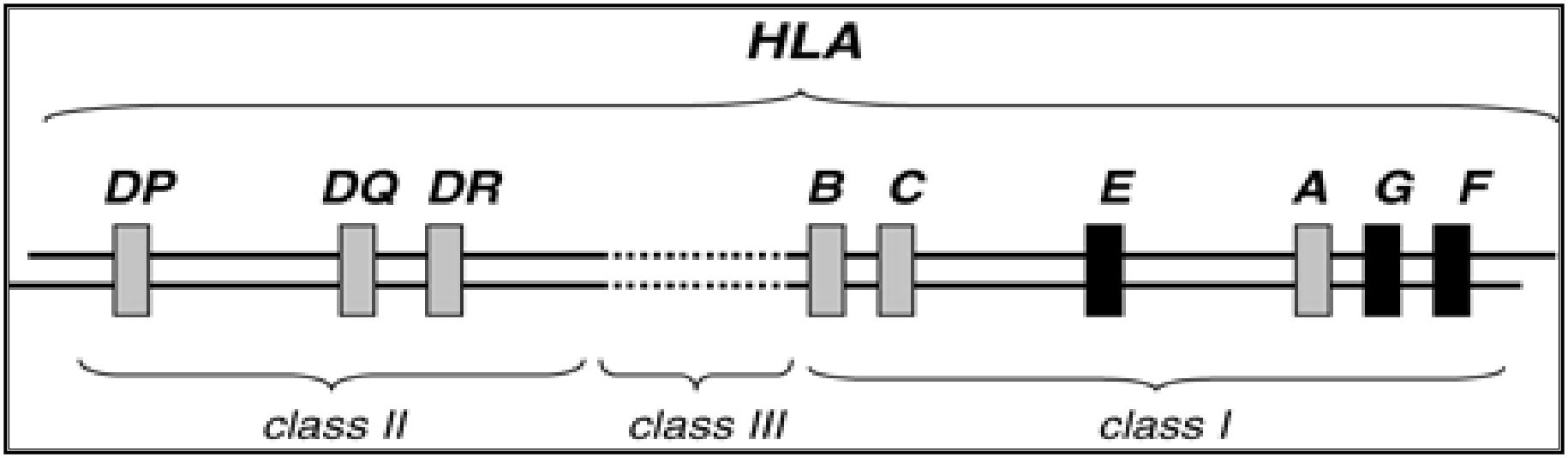
The **major histocompatibility complex** (**MHC**) is a large genomic region or gene family found in most vertebrates. It plays an important role in the immune system, autoimmunity, reproductive success and to determin, whether transplanted tissue is accepted as self (histocompatible) or rejected as foreign (histo**in**compatible).

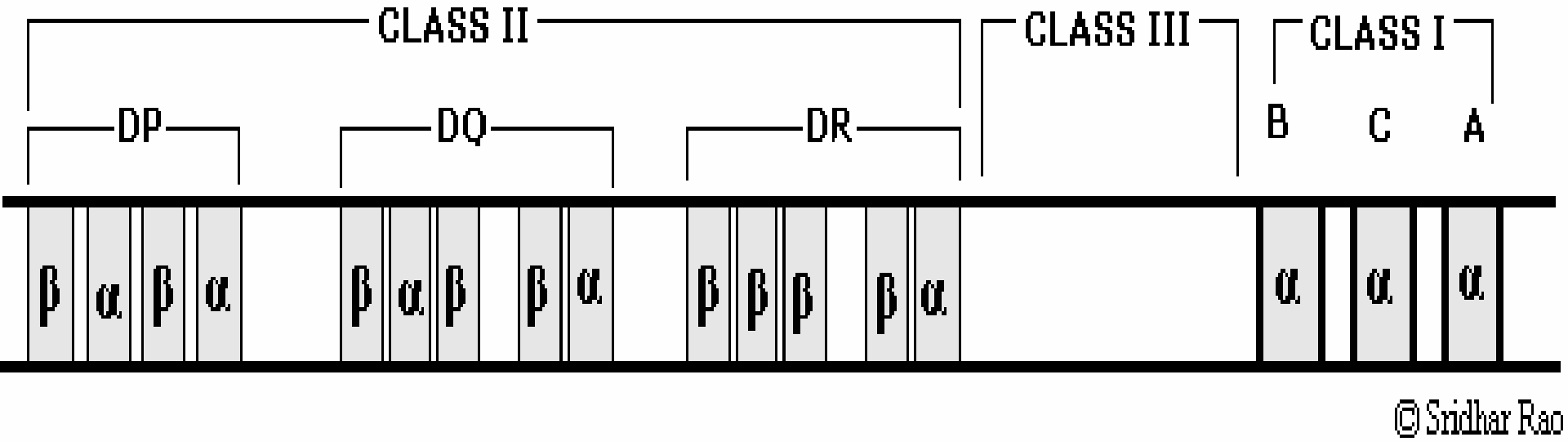
It is resides on chromosome 6 (Each individual expresses two alleles one from the father and one from the mother).

It encode for proteins expressed on the surface of nucleated cells called

Human Leukocyte Antigen (HLA).

MHC region is divided into three subgroups called Class I, II and III.


HLA
DP
DQ
DR
B
C
E
A
G
F
class II
class III
class I


CLASS II
CLASS III
CLASS I
DP
DQ
DR
B
C
A
β
α
β
α
β
α
β
α
β
β
β
β
α
α
α
α

1-MHC class I molecules :- MHC class I molecules are heterodimers, consisting of a single transmembrane glycosylated heavy chain (encode in MHC gene) associated with β2 microglobulin (polypeptide that is found free in serum). The heavy chain consists of three polymorphic domains, α1, α2, α3. Between α1 and α2 is the peptide-binding groove.

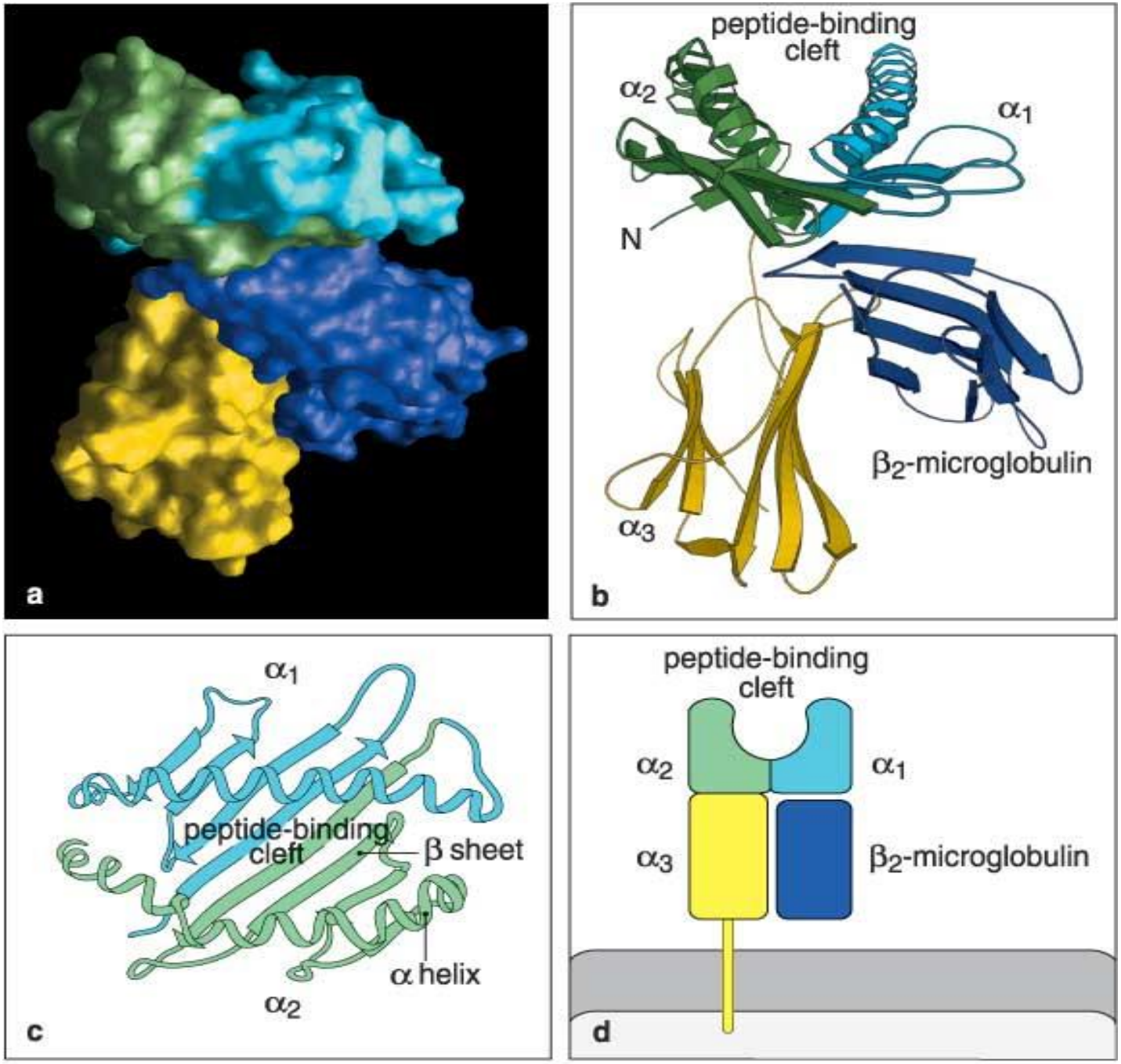


Fig 3.20 © 2001 Garland Science

Human **class I MHC** are coded for proteins known as:-
HLA-A, HLA-B and **HLA-C,……. (some time these form can be called gene)**.

- HLA-A, -B and -C specified proteins are expressed on **all nucleated cells**.

- Class I proteins are the major antigens involved with **graft rejection**. (Many human tumors do not express class I antigens or express them at a very low level , they have a tendency to metastasize)

- **There are 3 major and 3 minor of HLA:**

The major are HLA-A, HLA-B and **HLA-C**

The minor are HLA-E, HLA-F and HLA-G

- **MHC molecules** bind only peptides and not other types of Ags; so that is why MHC- restricted CD4 & CD8 T cells can recognize and respond only to protein Ags the natural source of peptides
- MHC class I molecules are loaded with proteins generated in the cytosol while the MHC II will be generated in intracellular vesicles .
- MHC class I molecules interact with CD8+ ("cytotoxic") T cells (CTLs).

So when the cell are infected with virus (cytosolic antigen) , viruses will use **MHC class I-dependent pathway** to present it to T cells.

- The fate of the virus-infected cell is almost always apoptosis or programmed cell death to reduce the risk of infecting neighboring cells.

2- MHC Class II molecules are

- Heterodimers, consist of two homologous peptides, a α and β chain, both of them are encoded in the MHC.
- Human class II MHC gene are coded for HLA-DP, HLA-DQ (have two chains one for α and β chain) and HLA-DR (have one chain for α and 9 chain for β).
- Unlike class I MHC proteins, class II proteins are **mainly limited to antigen presenting cells (APC); macrophages, dendritic cells and B cells.** These proteins are involved with antigen presentation and cell-cell interaction.

- **Endothelial and epithelial cells can also be induced to produce MHC class II antigens by exposure to interferon-gamma**

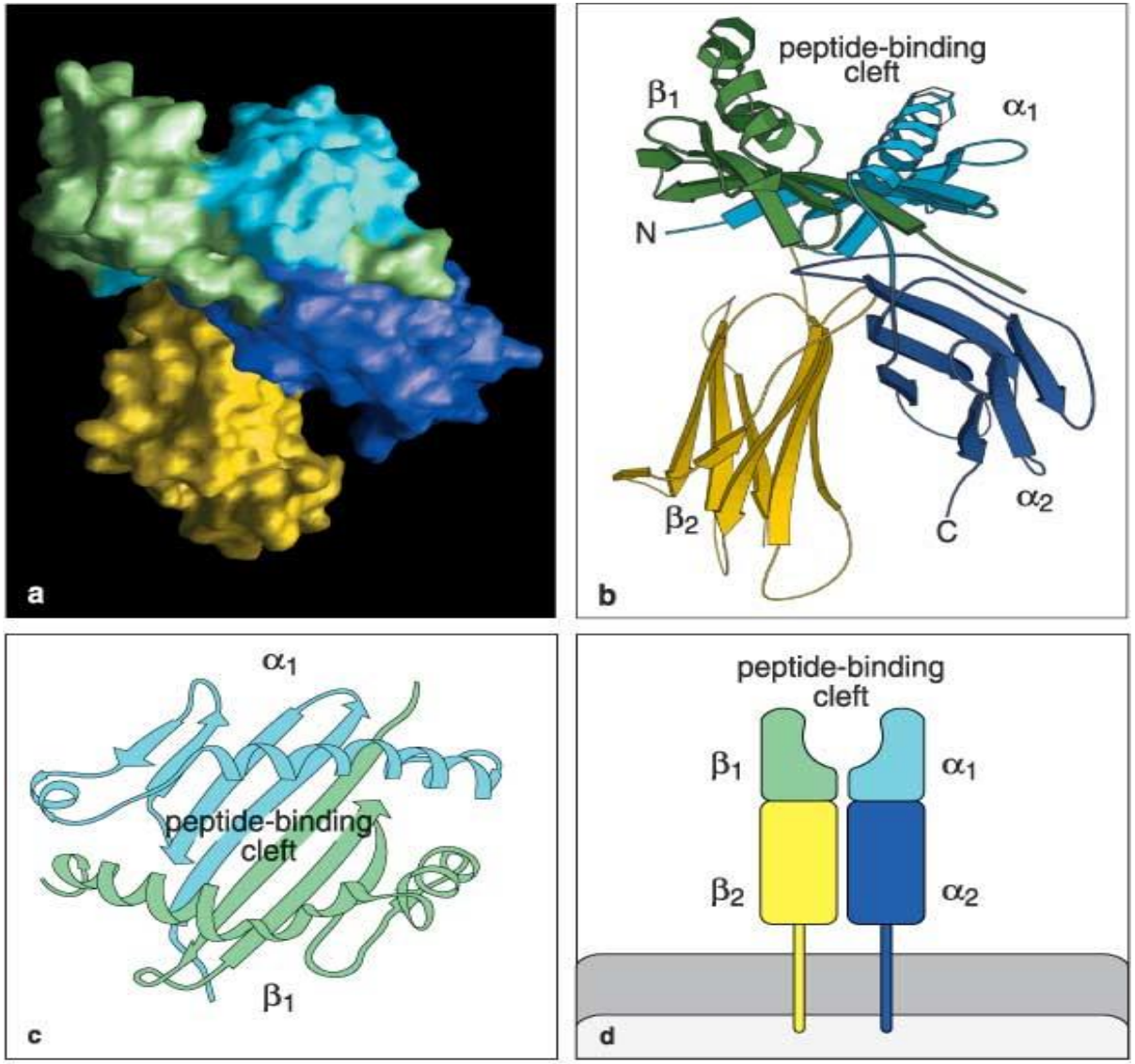


Fig 3.21 © 2001 Garland Science

- The peptides presented by class II molecules are derived from extracellular proteins; (**MHC class II-dependent pathway)**of antigen presentation is called the *endocytic* or *exogenous* pathway .

- Class II molecules interact with CD4+("helper") T cells .

- The helper T cells then help to trigger an appropriate immune response which may include localized inflammation , swelling and activation of B cells to produce Abs.

the antigen-binding groove of MHC class II molecules is open at both ends while the corresponding groove on class I molecules is closed at each end, so the antigens presented by MHC class II molecules are longer, generally between **15** and **24** amino acid residues long while in MHC-I about **9** amino acid

3- class III MHC :-most of genes in this region are encoded for proteins **secreted by the cells**. Examples of class III proteins include **complement components C2, C4 and Factor B** as well as **Tumor Necrosis Factor(TNF) α and β**.

Table 2-1	Comparison of MHC Class I and Class II	
	Class I	Class II
Loci	HLA-A, -B, and -C	HLA-DN, -DO, -DP, -DQ, and -DR
Distribution	Most nucleated cells	B lymphocytes, macrophages, other antigen-presenting cells, activated T lymphocytes
Function	To present endogenous antigen to cytotoxic T lymphocytes	To present endogenous antigen to helper T lymphocytes

The expression of MHC molecules differs between tissues

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Other antigen-presenting cells (eg Langerhans' cells)	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	– †
Non-nucleated cells		
Red blood cells	–	–

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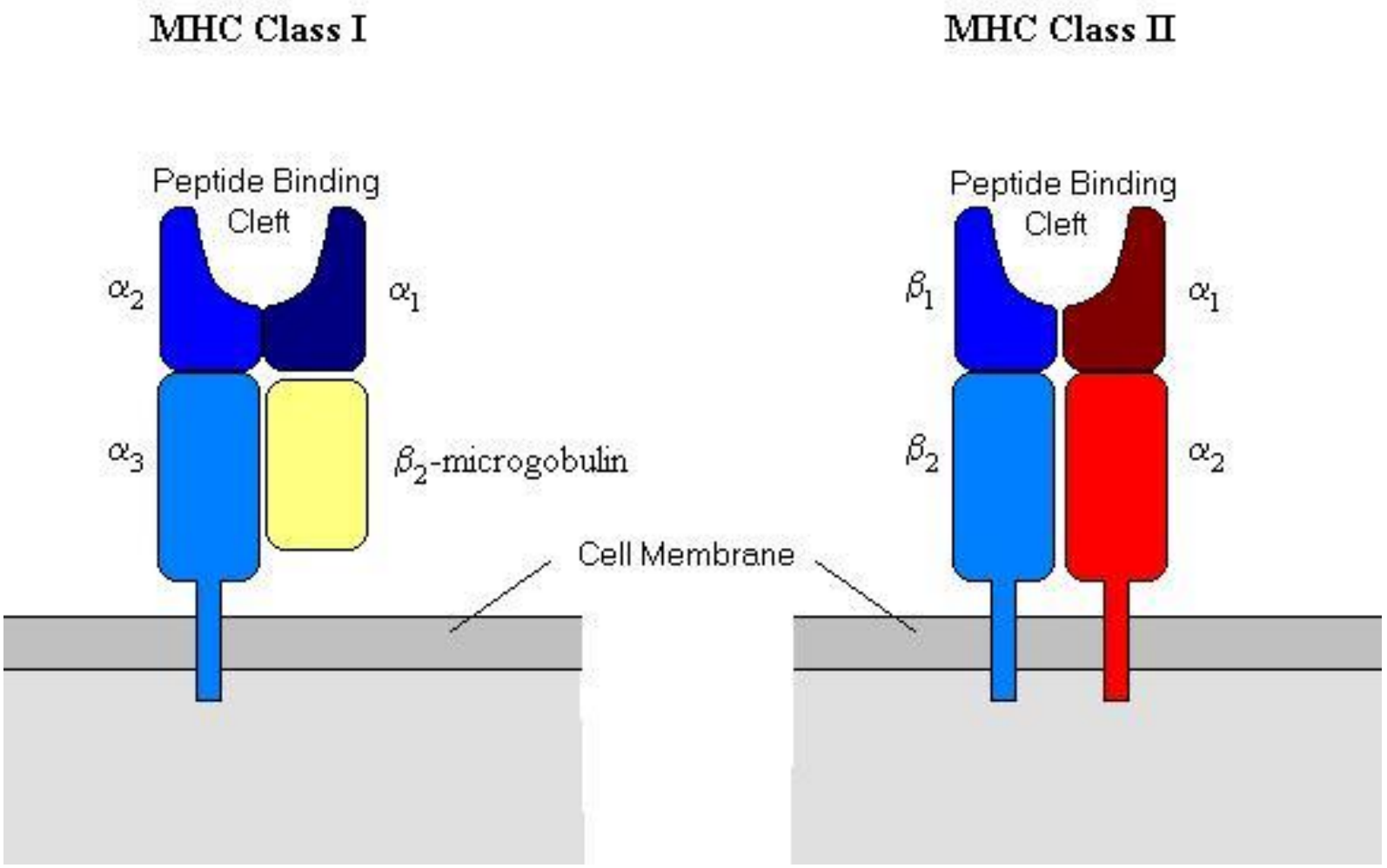
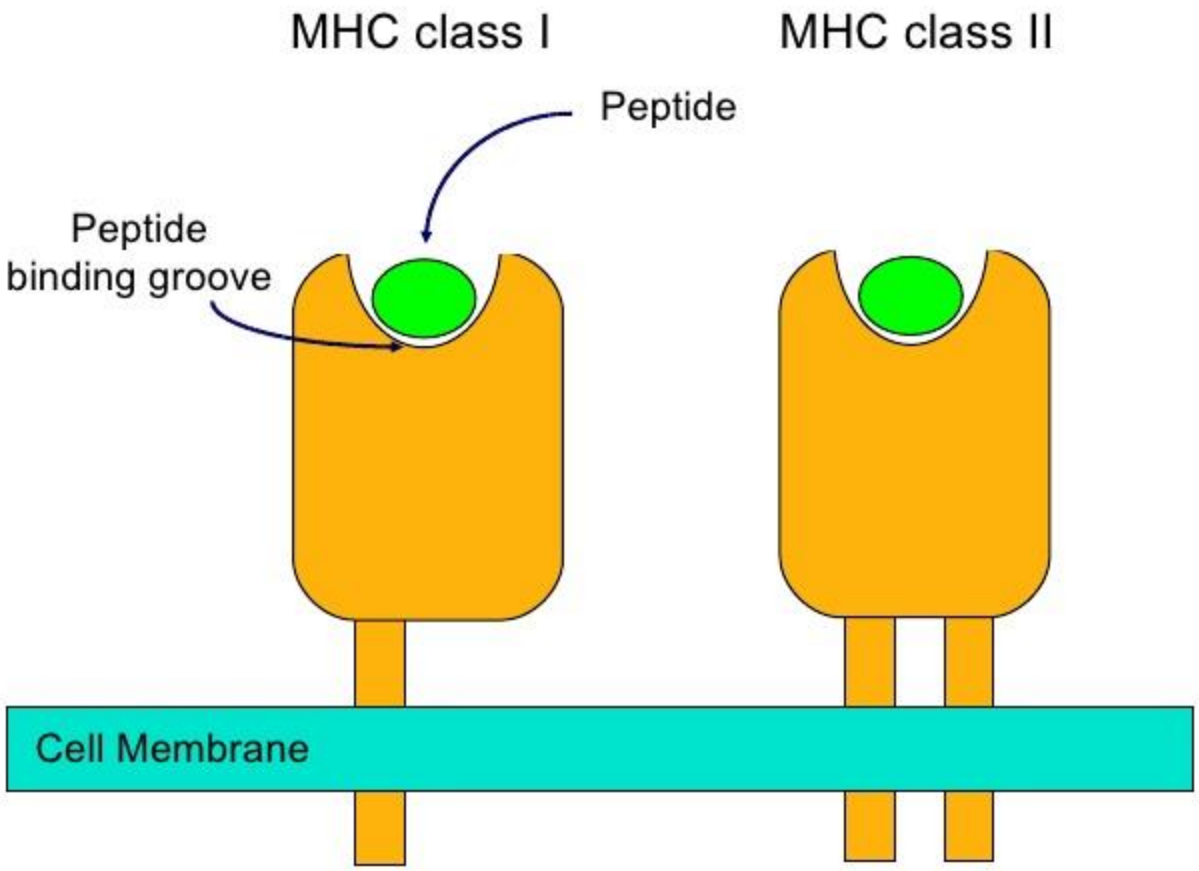
MHC class I:
Expressed on all nucleated cells

MHC class II:
Expressed on surface of APCs
(antigen presenting cells)


MHC Class I
MHC Class II
Peptide Binding Cleft
Peptide Binding Cleft
α_2
α_1
α_3
β_2-microgobulin
β_1
α_1
β_2
α_2
Cell Membrane

MHC molecules

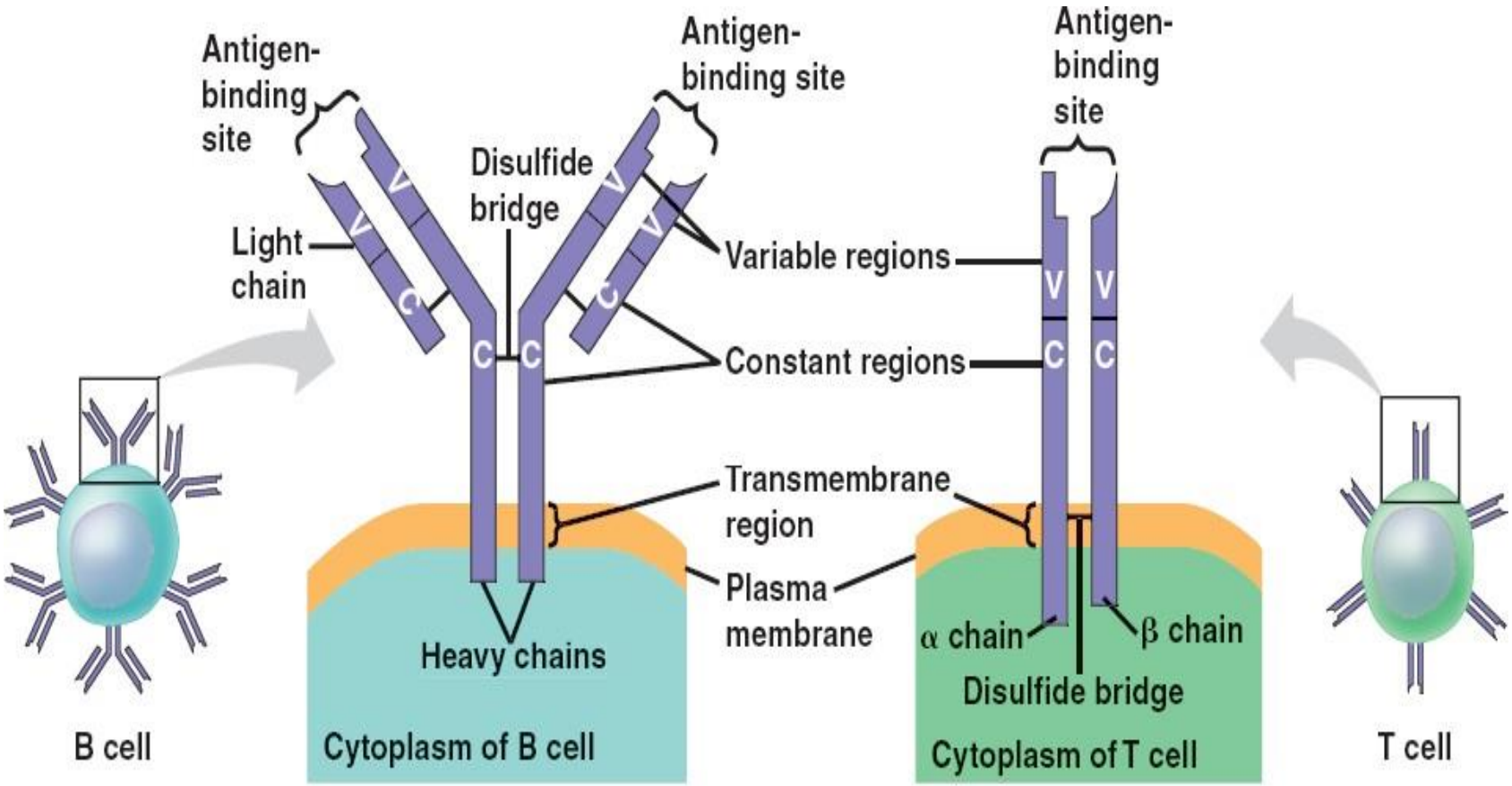


Immune Cell Receptors

In addition to the MHC class I and II receptors , some cells of the immune system also possess specialized, transmembrane receptors. These receptors are involved in antigen recognition and the determination of self/non-self.

1- **B cell receptor (BCR):-** It is the Abs molecules ; Fab or variable portion of this molecule provides the specificity for antigen recognition. Each mature B cell makes only single type of antibody with single specificity for a given antigenic determinant (epitopes)

2- T cell receptor (TCR) is a more complex structure. The TCR is composed of **two polypeptide chains** most **mature T cells** usually **express α and β** chains (about 90%) while 10% express gamma (γ) and delta (δ). This receptors are present on surface of both CD4 & CD8 T cells



(a) A B cell receptor consists of two identical heavy chains and two identical light chains linked by several disulfide bridges.

(b) A T cell receptor consists of one α chain and one β chain linked by a disulfide bridge.

The structure of the TCR is similar to that for antibody; there is a constant region and a variable region that specifies antigen recognition.

TCR will recognize the peptide antigen presented in either MHC I or MHC II

Various types of T cells, T helper (T_H), and T cytotoxic (T_C) have TCRs that differ from each other.

TCR recognises MHC/antigen complex

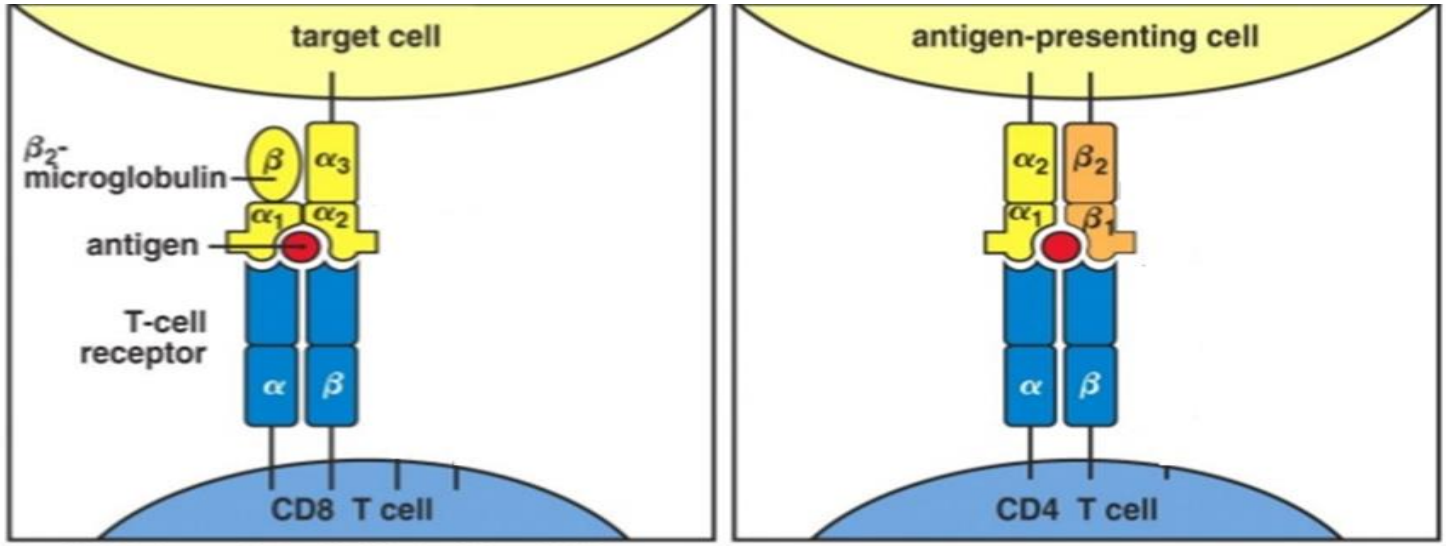


Figure 3-14 The Immune System, 2/e (© Garland Science 2005)

T-cells recognize foreign peptides by interaction of the T cell receptor (TCR) with peptide complex to major histocompatibility complex (MHC-I molecules on the surface of target cells or MHC-II on the surface of APCs).

Interaction of antigen (Ag) with the TCR results in either clonal expansion or unresponsiveness (anergy). This will be depend on the present of signals for activation.

(Co-stimulatory signals) accessory Molecules :-

1- CD4⁺ and **CD8⁺** :- They are present on the surface of T cells

- CD4⁺ on the T –helper cells
- CD8⁺ present on cytotoxic T-cells.

CD4⁺ and CD8⁺ recognize and bind to HLA -I and HLA -II molecules outside of the antigen binding site.

- CD4⁺ and CD8⁺ stabilization the interaction between TCR and HLA molecules **(complete the first signal)**

Signal 1 :TCR recognises MHC/antigen complex+coreceptors

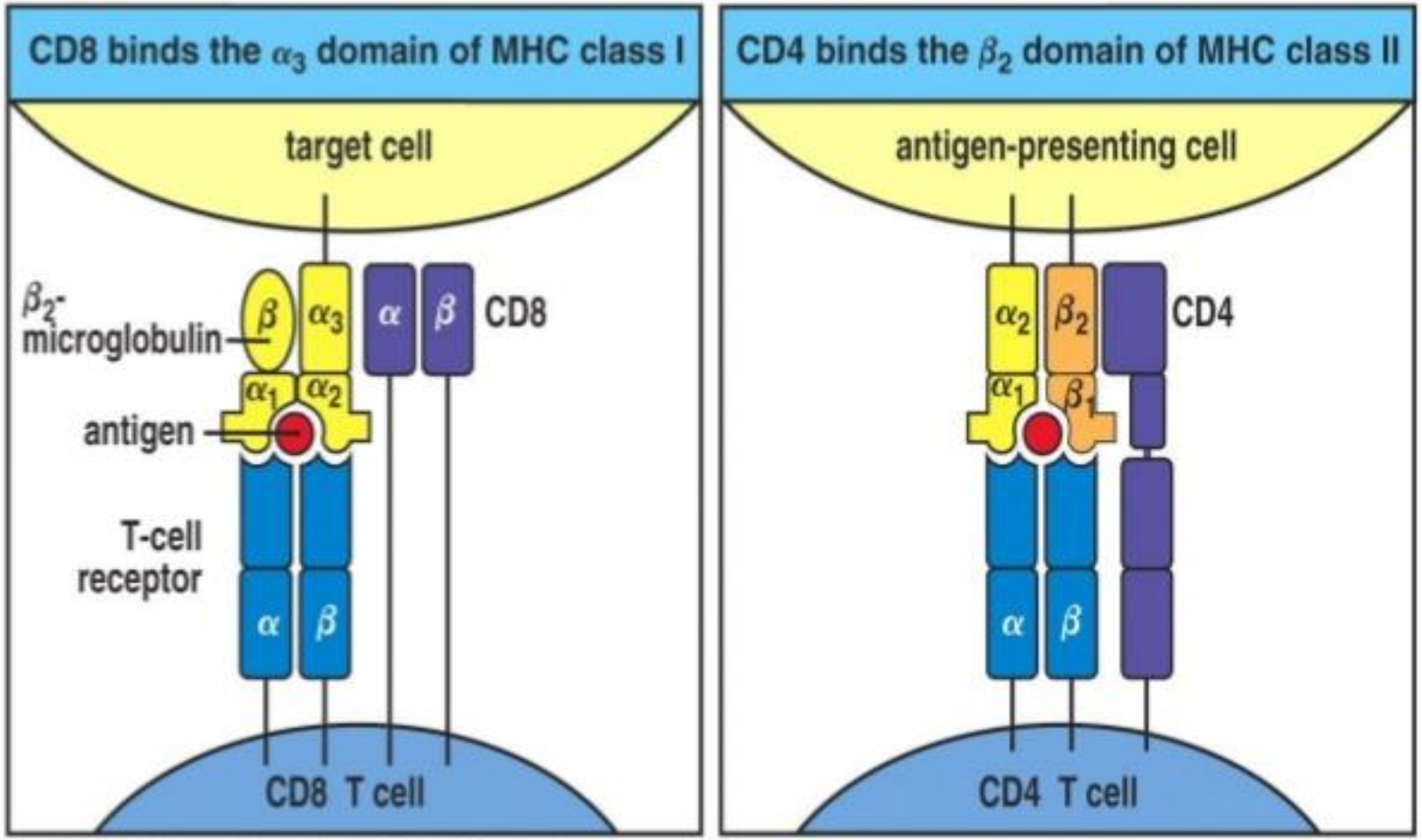


Figure 3-14 The Immune System, 2/e (© Garland Science 2005)

2- B7 / CD28:- It result from the binding of B7 ligand on the antigen-presenting cell with its receptor (CD28) on the T cell
This consider the **second signal .**

- This second 'costimulatory' signal can only be delivered by APC and is required for IL-2 production. In the absence of this costimulatory signal, T cells fail to make IL-2 and may become unresponsive to further stimulation with antigen.

- The B7 family of ligands has two members, B7-1 and B7-2 its now know as (CD80 & CD86)

These co- stimulatory molecules are nonspecific for antigen. If both signals are provided, the T cell will proliferate , differentiate and secrete cytokines.

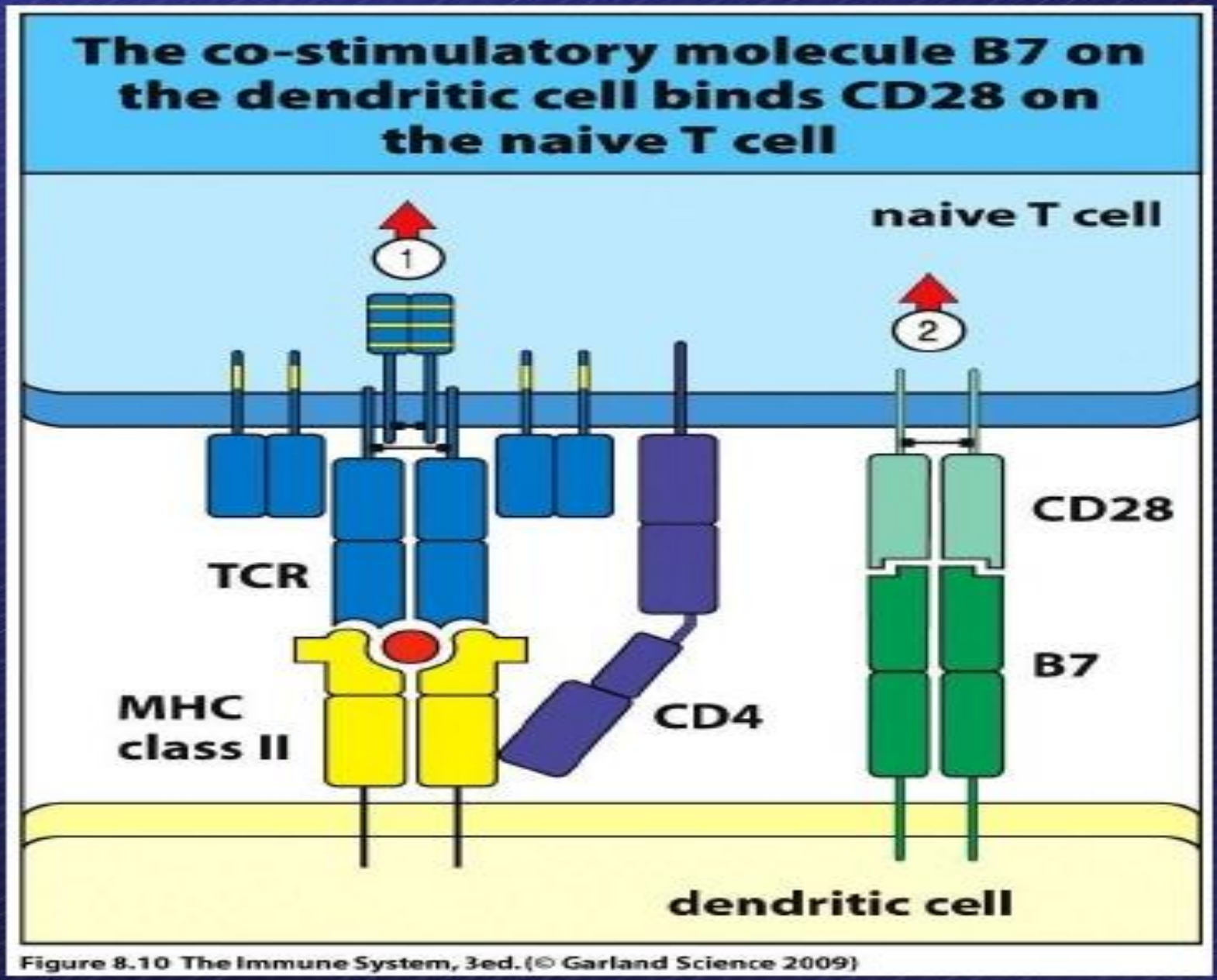


Figure 8.10 The Immune System, 3ed. (© Garland Science 2009)

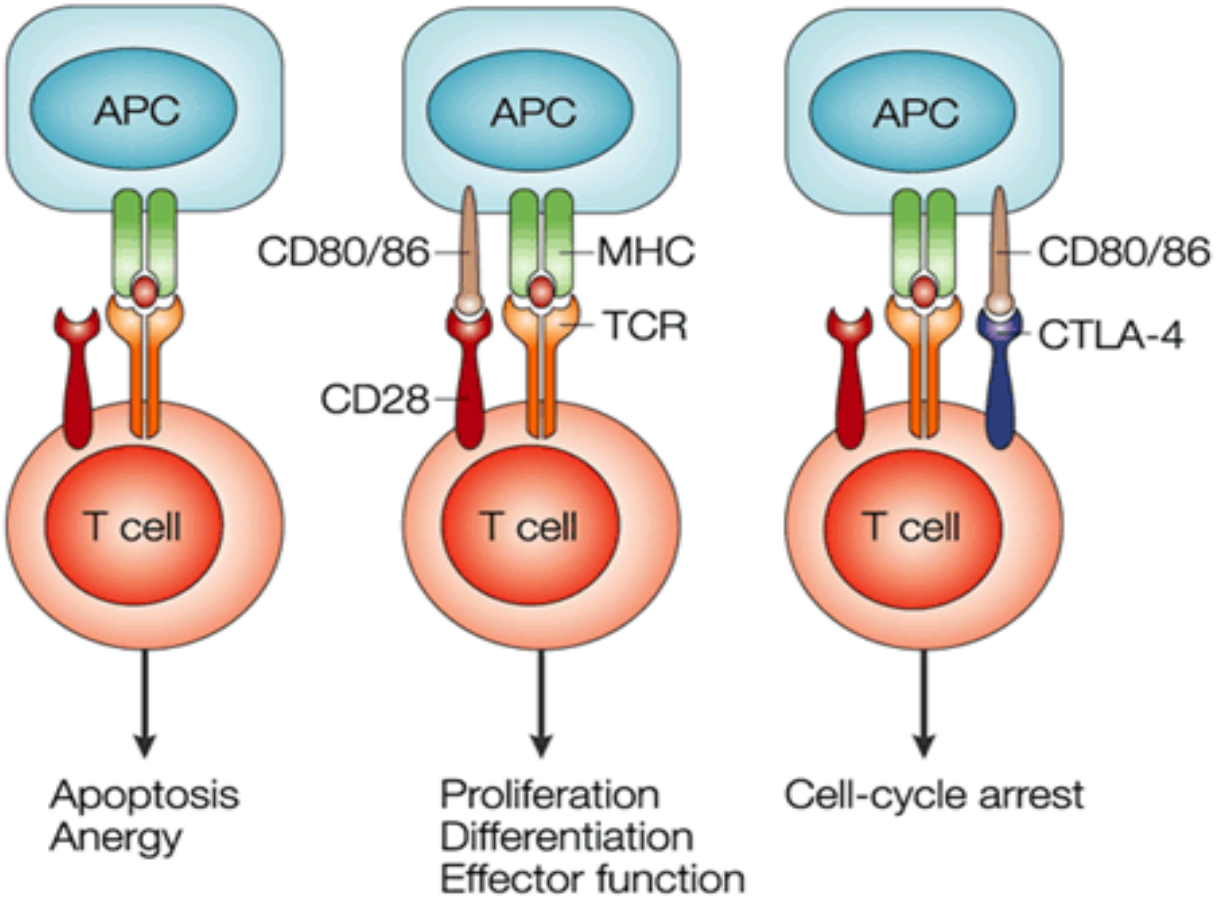
The second receptor on T cells for B7 is called

(**C**ytotoxic **T-L**ymphocyte-**A**ssociated molecule-4) **(CTLA-4)** is thought to negatively regulate T cell responses.

The CTLA-4 molecule is not found on the surface of resting T cells but is up-regulated following T cell activation.

Binding of the B7-CTLA4 pathway results in the down-regulation of the responding T cells.

Thus, the B7/CD28/CTLA4 pathway has the ability to both positively and negatively regulate immune responses **(How???)**



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What are the most important receptors present on the surface of the

1- APCs

2-CD4 -helper T cells

3- CD 8 -cytotoxic T cells