Critical roles of dendritic cells in the initiation of the adaptive immune responses

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Outlines

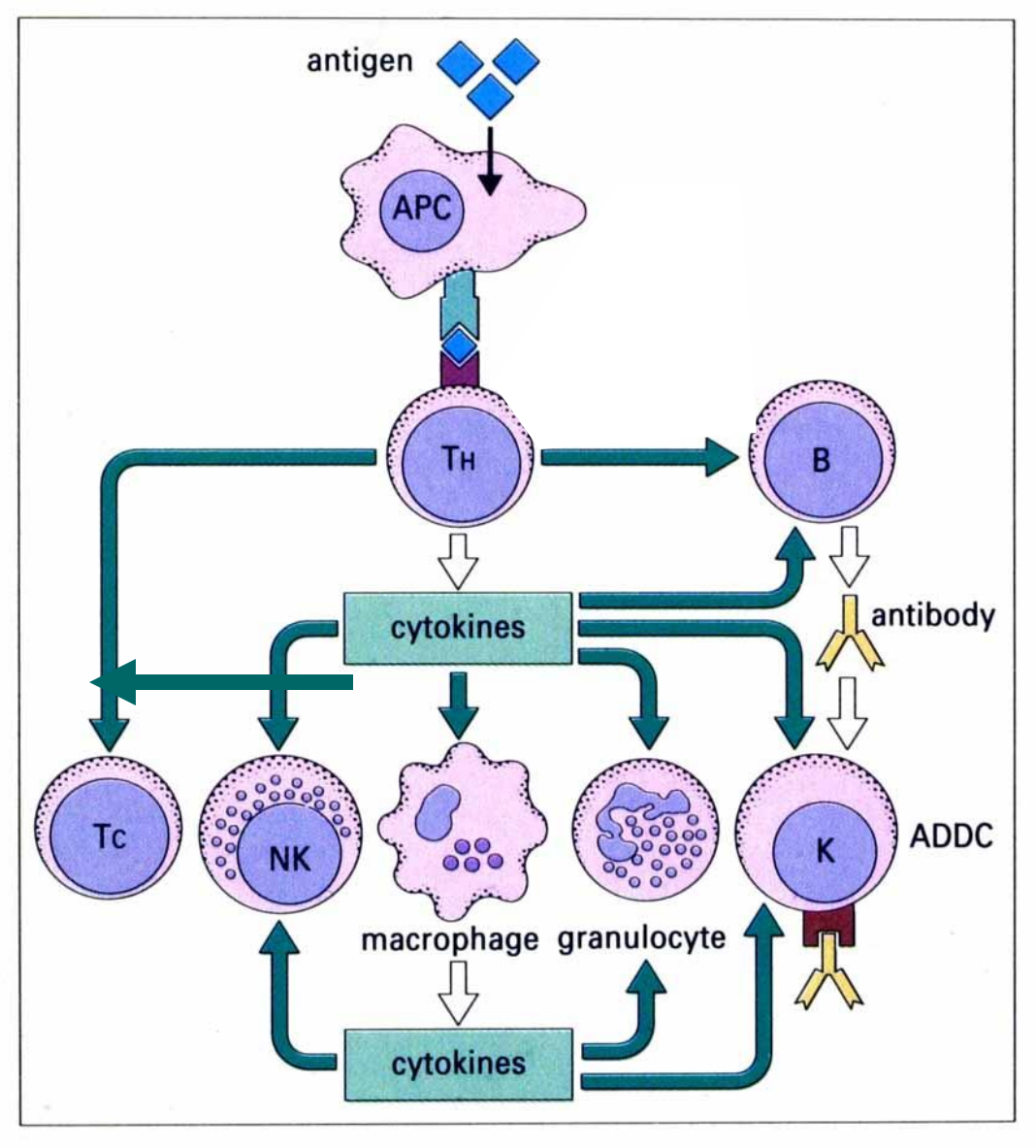
- **Signals required for initiating the adaptive immunity**
  - *Ag recognition (Signal 1)*
  - *Co-stimulations (Signal 2…)*
- **Models of T-B cell cooperation**
  - *The 'original' model*
  - *The 'modified' model*
  - *The 'contemporary' model*
- ***DC – Initiator of the adaptive immune responses***
  - *Basic & uniquely combined immunobiological properties*
  - *A link between the innate & the adaptive immune systems*
  - *The activator of naïve T cells*

Types of immunity
- Speed, Strength, Specificity & Memory

- *Innate (natural)*
  - ***Features:*** *early, rapid but limited in strength, 'non-specific'*
  - ***Players:*** *Macrophages, polymorphs, mast cells, NK cells etc*

- *Adaptive (acquired)*
  - ***Features:***
    - *Specificity & memory*
    - *Take time but powerful once initiated*
  - ***Players:***
    - ***B cells:*** *humoral immunity (Ab production)*
    - ***Cytotoxic T cells ($CD8^+$):*** *Cell-mediated immunity (CMI)*
    - ***Helper T cells ($CD4^+$):*** *Central roles in immune responses*

T_H Cells Play a Central Role in Immune Responses



("Immunobiology", by Janeway, Travers, Walport & Capra)

Question 1:

How is an adaptive immune response initiated?

Ag recognition alone (Signal 1) is not sufficient to initiate an immune response (e.g. Ab response)

→ "Signal 2…" is needed

T-dependent Ab responses – *early findings*

- Importance of thymus in immune responses
  - *Miller JF (1961)*
- Importance of circulating lymphocytes in Ab responses
  - *Gowans J (1963)*
- Phenomenon of T-B cell co-operation
  - *Davies AJS (1964)*
  - *Claman HN (1966)*
  - *Miller JF & Mitchell GF (1967)*
- *'Hapten-carrier effect'* → *The 'Linked recognition'*
  - *Landsteiner K (1868-1943)*
  - *Mitchison NA (1971)*

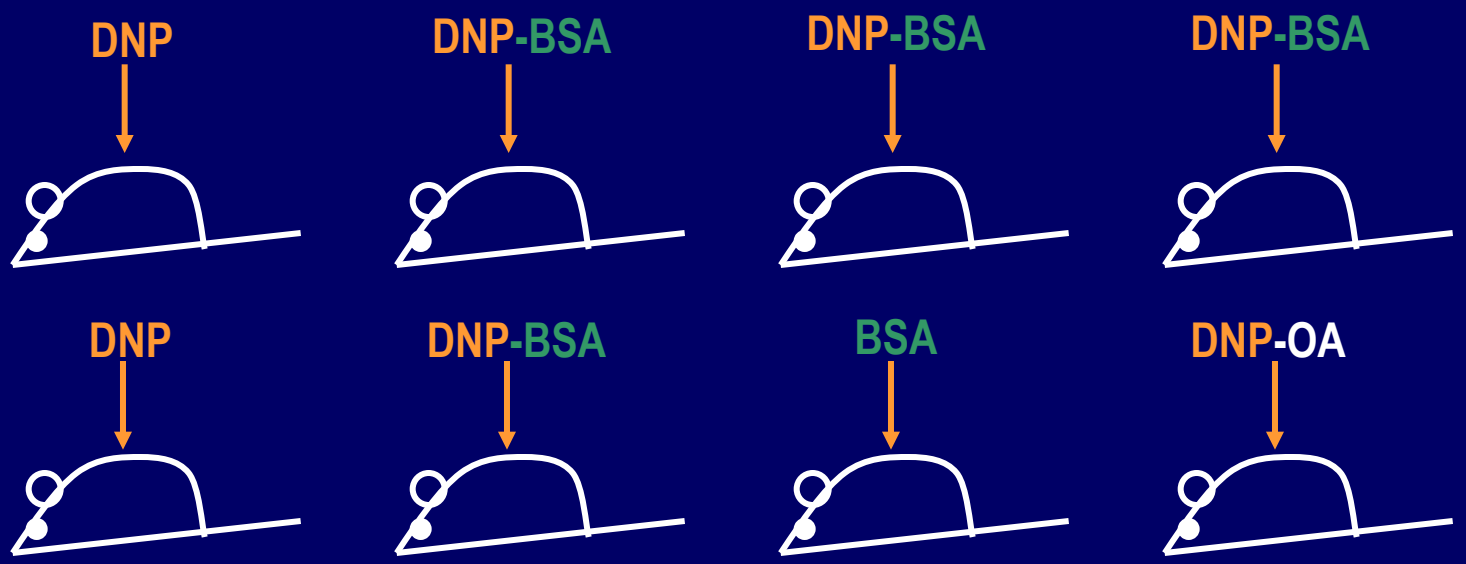
T-B cell cooperation

The Ab response to a thymus-dependent Ag requires two different cell populations

Cells injected	None	T (thymocytes)	B (bone marrow)	T & B
X-irrad. recipient injected with Ag				
Ab response	-	-	+	+++

The "Hapten-carrier effect"

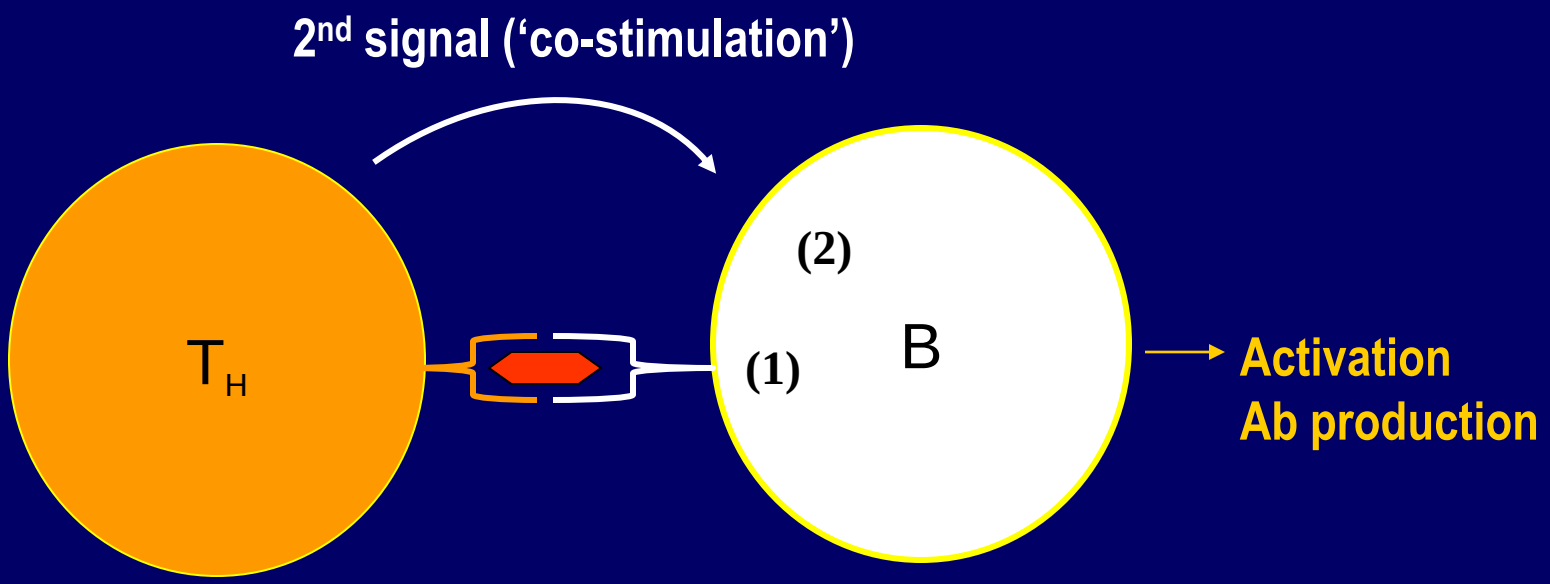
(late 60/70s)



DNP: A hapten of di-nitrophenyl group
BSA: Bovine serum albumin
OA: Ovalbumin

The "original" 2-signal model

(Bretscher P & Cohn N, 1970)



Finding:

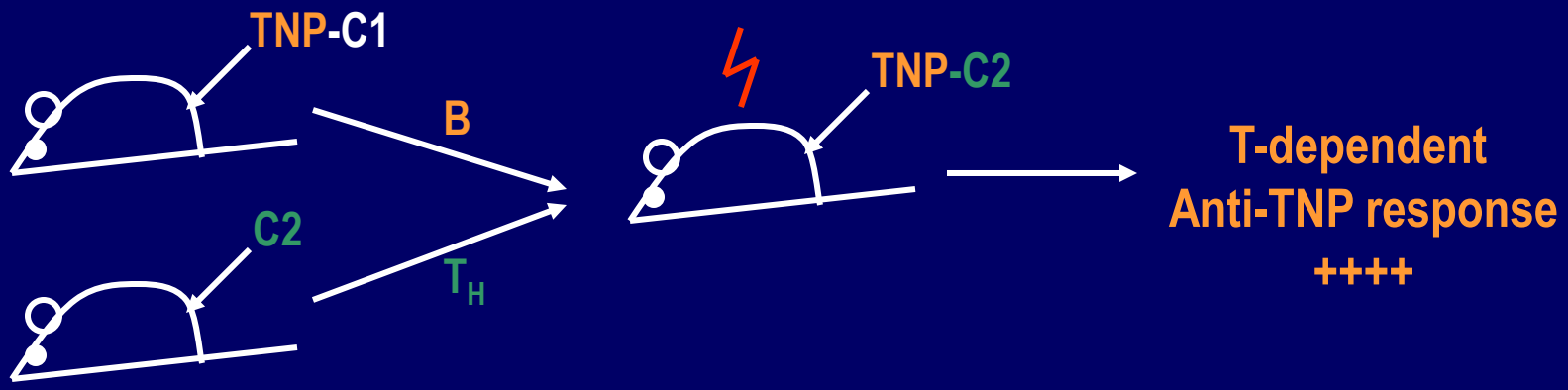
T cell Ag recognition is MHC-restricted

(Doherty PC & Zinkernagel RM, 1974/5)

Question 2

How could T and B cells recognize the same Ag if T cells recognized only processed Ag (small peptide) presented by MHC?

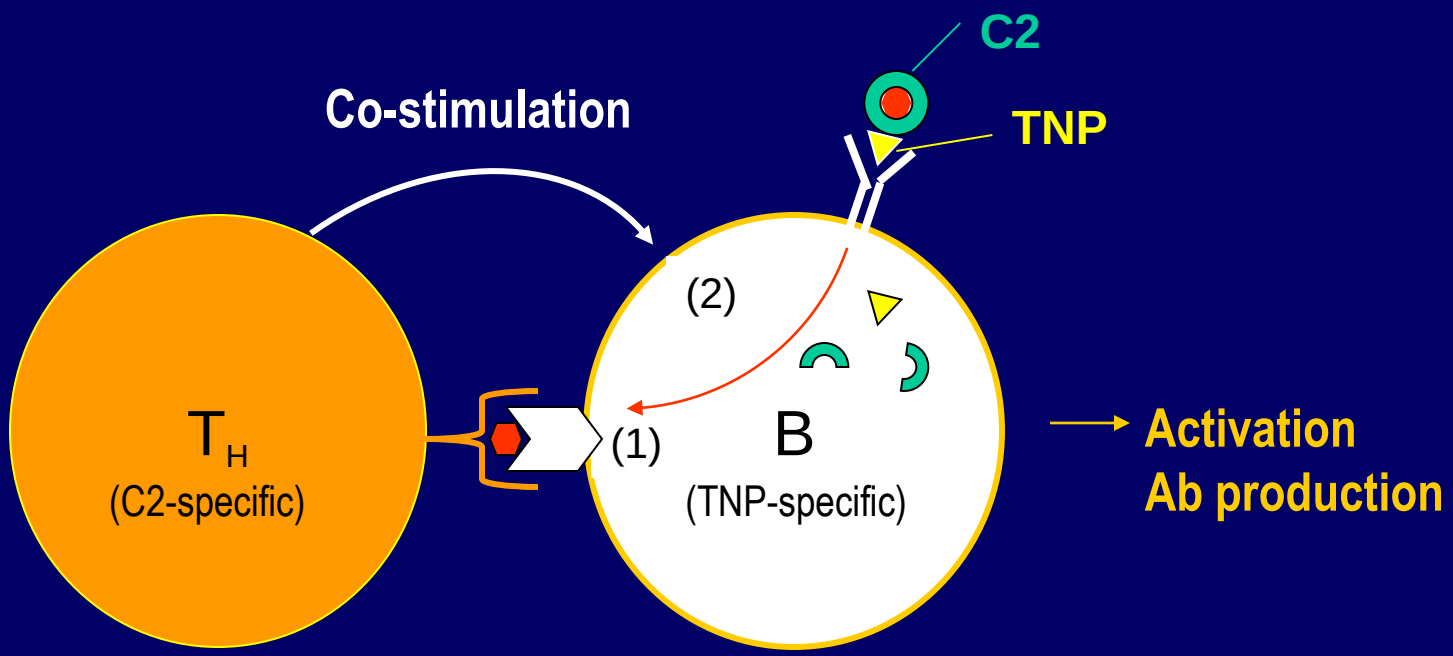
Linked recognition
- The ‘Carrier-priming’ experiment



TNP: A hapten of tri-nitrophenyl group

(Mitchison NA. Eur J Immunol. 1971)

The "modified" model



Another problem:

Resting B cells can not activate naïve T cells, or vice versa

Question 3

How is a naive T cell activated?

- Naïve lymphocyte

  Lymphocyte that has not encountered its specific antigen

- Armed effector lymphocyte

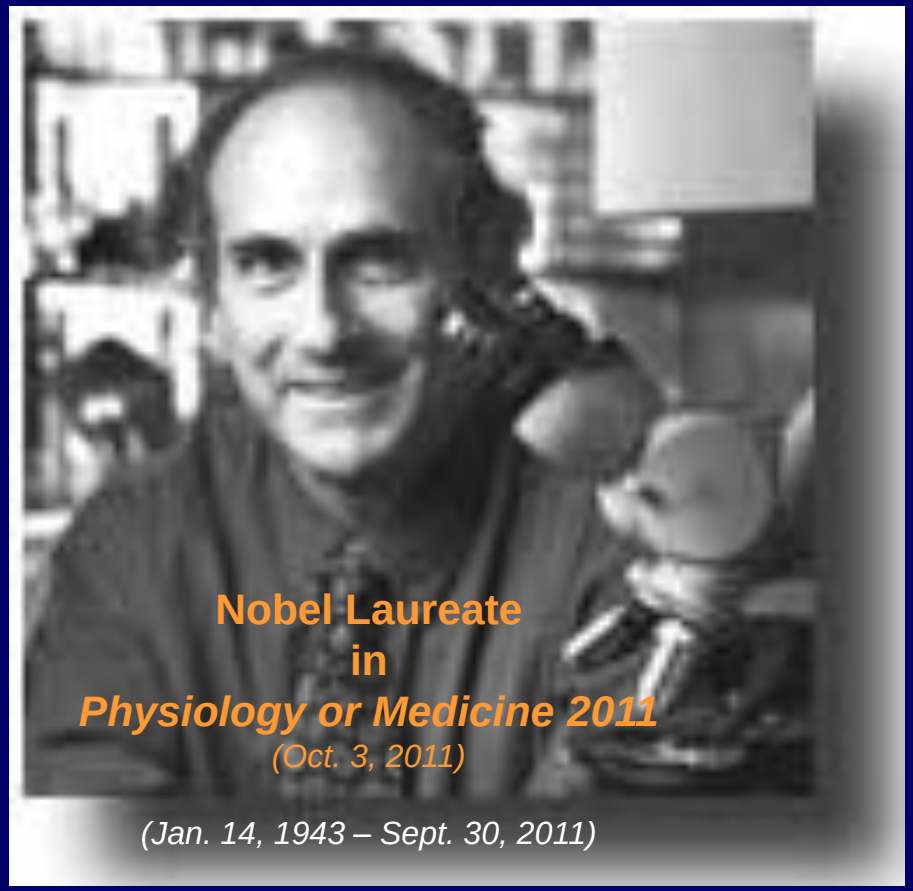
  Activated & differentiated lymphocyte that may respond to antigen binding alone to produce effector functions

- Memory lymphocyte

  Lymphocyte that has experienced specific antigen previously but needs to be triggered to differentiate again to become effector cell

Dendritic cell: Initiator of the adaptive immunity

Ralph M Steinman & Zanvil A Cohn (Rockefeller, 1973)



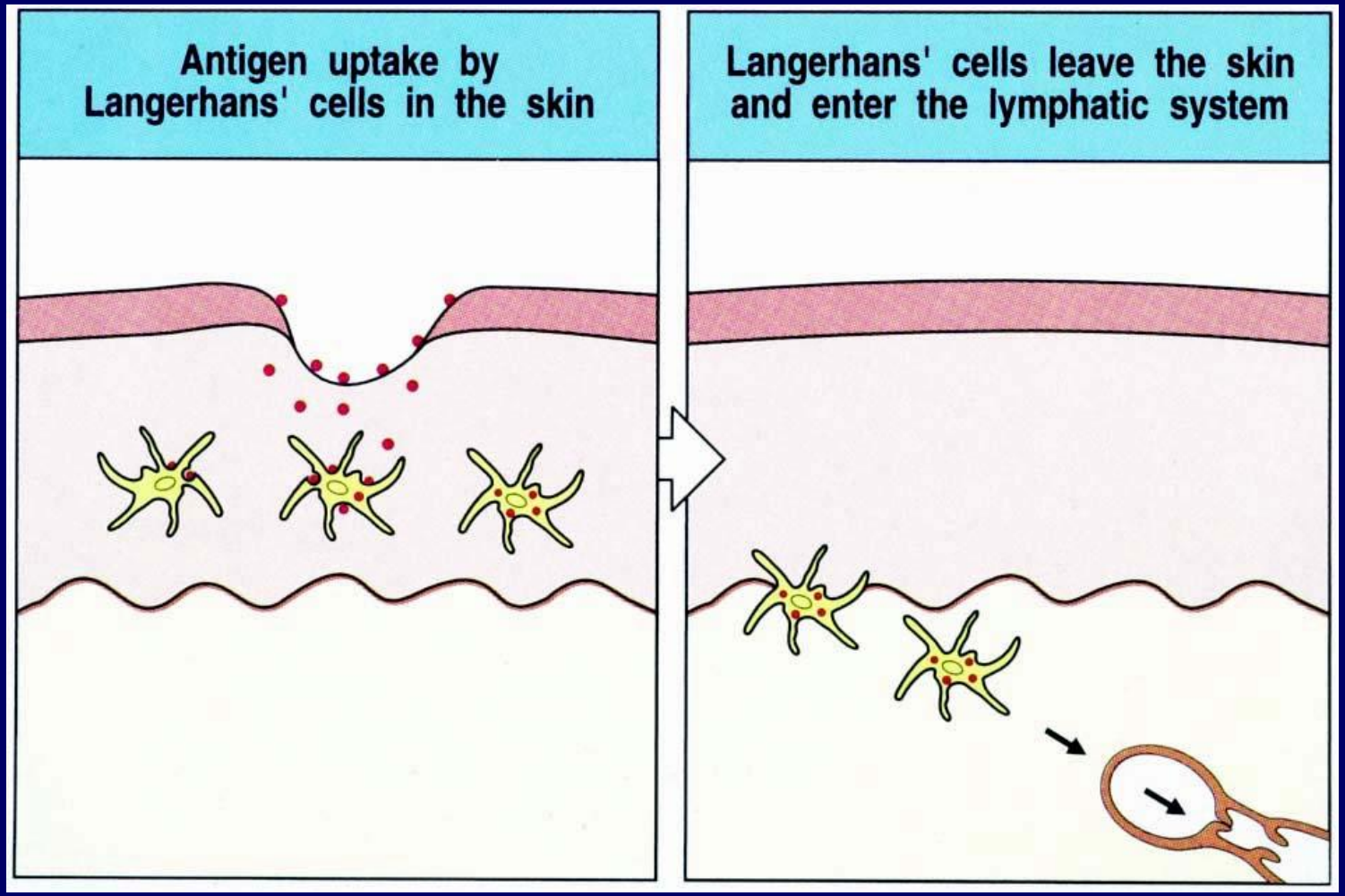
J Exp Med. 1973 May 1;137(5):1142-62.
J Exp Med. 1974 Feb 1;139(2):380-97.
J Exp Med. 1974 Jun 1;139(6):1431-45.
J Exp Med. 1975 Apr 1;141(4):804-20.
J Exp Med. 1979 Jan 1;149(1):1-16.

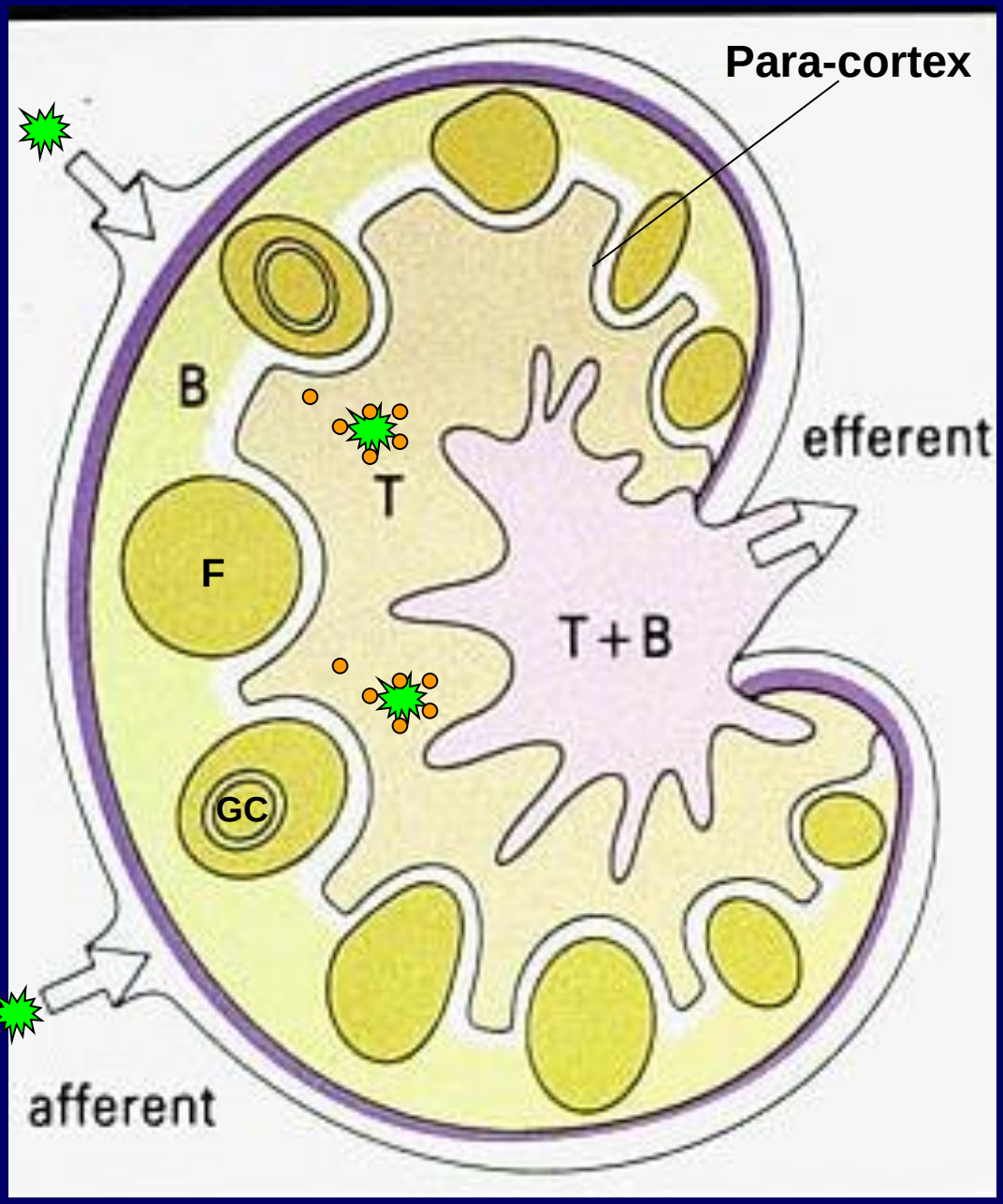
DC immunobiology
(basic properties)

- Sentinel position: ***Constant surveillance***
  - *Distribution throughout peripheral tissues*
- Endocytic activities: ***Ag uptake***
  - *Micro/Macro-pinocytosis (soluble Ags)*
  - *Phagocytosis (pathogens, dying cells, ICs etc)*
  - *Receptor-mediated endocytosis*
    - *C-type lectins (DEC205, Mannose receptor, DC-SIGN etc)*
    - *Fc receptors*
    - *Complement receptors*
    - *Scavenger receptors*
- Migratory property: ***Ag transport***
  - *from peripheral tissues to secondary lymphoid organs*

Skin DC

- The Langerhans' cells (Paul Langerhans, 1868)





Secondary lymphoid organs where DC & naïve T cells meet:

- Highly organized cellular distribution

- Site of naïve T cell activation

B: B cell area
T: T cell area

F: B cell follicle
GC: germinal centre

DC migrating in the lymph

A model of authentic DC generation:

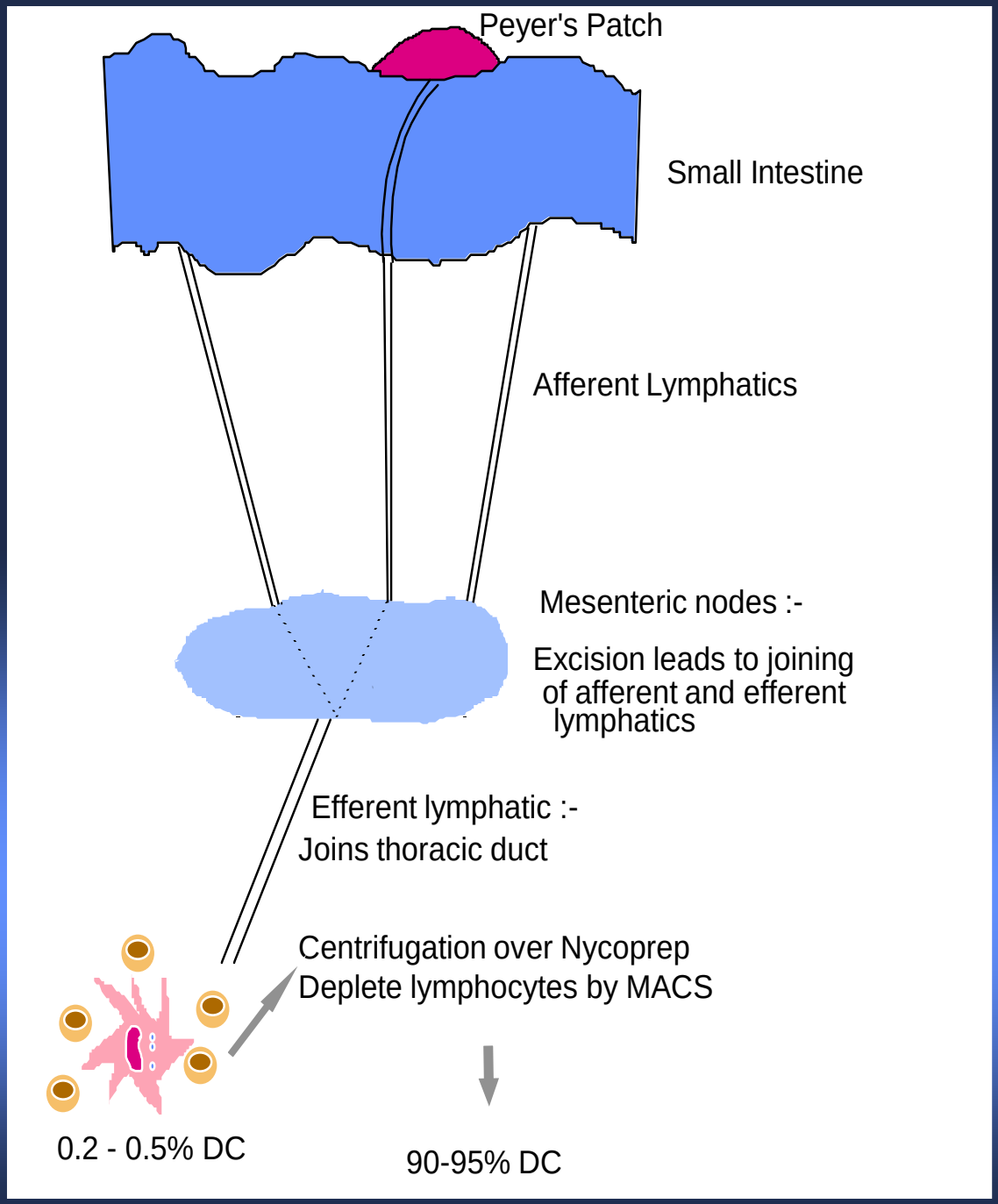
(*2 steps*)

(1) Mesenteric lymphadenectomy

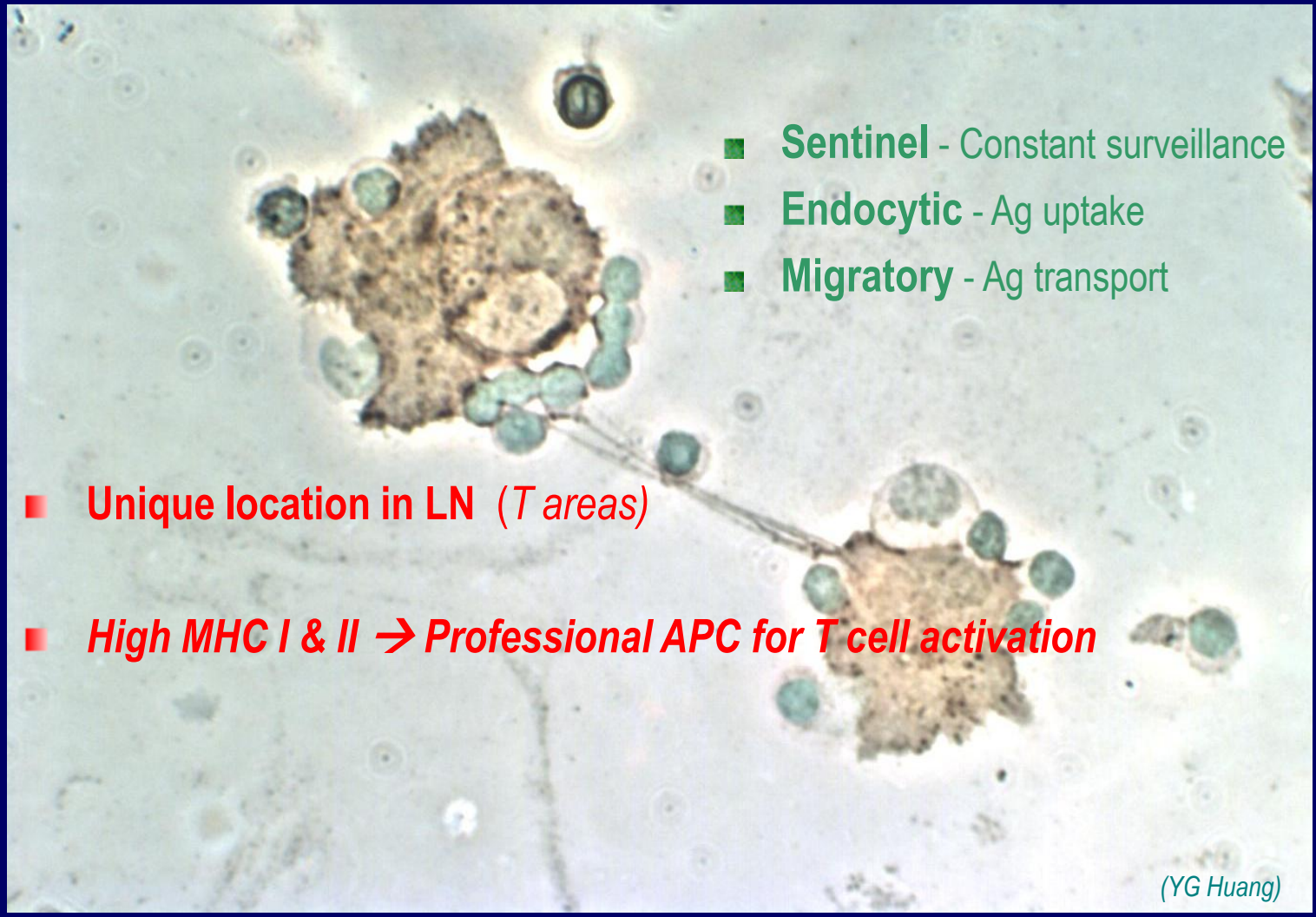
(2) Thoracic duct cannulation

(J Exp Med. 1983 Jun 1;157(6):1758-79.)

Photograph copyright:
G.G. MacPherson
(Oxford, 1997)



DC - a link between the innate-adaptive immune systems



Antigen presenting cells

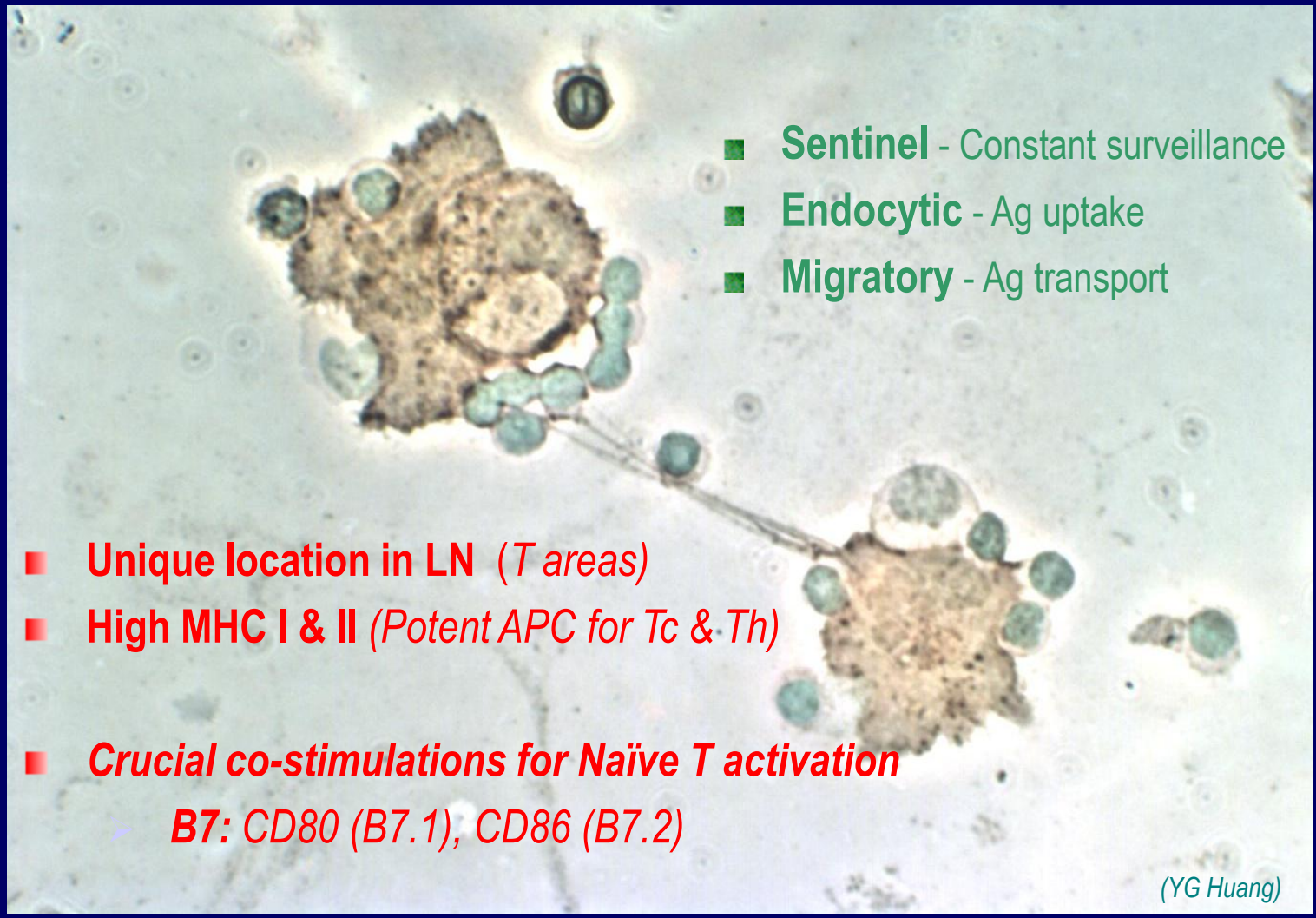
- *Broad sense:*
  - *Virtually all cells (nucleated) can be "APC" (MHC Class I)*
- *More specific:*
  - *APC: cells present antigen to activate (or inactivate) T cells*
  - *Target cells: infected or tumor cells to be killed by T cells*
- *"Professional" APC (MHC Class I & II):*
  - *B cell*
  - *Macrophage*
  - ***DC***

MHC class I & class II expression

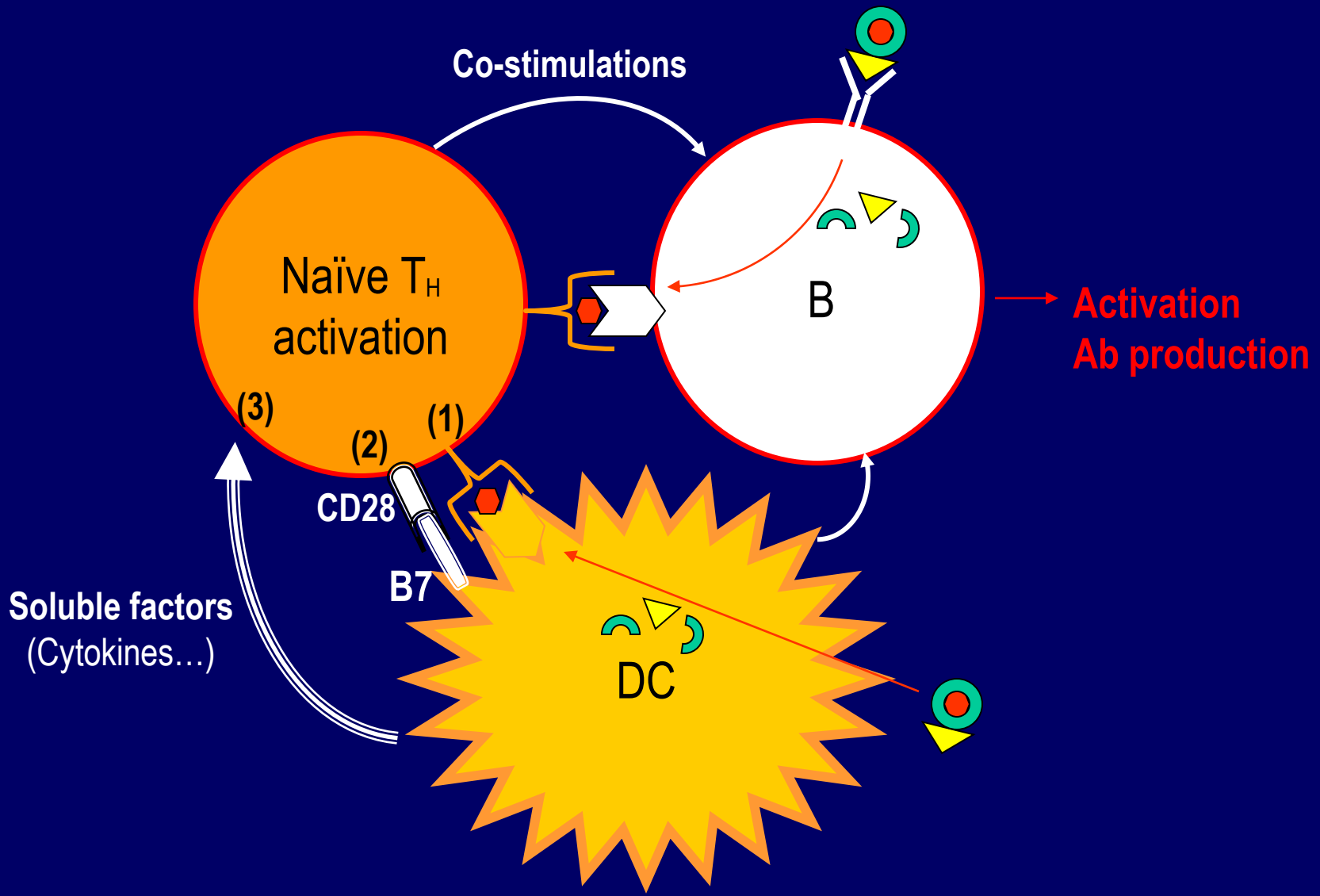
Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Other antigen-presenting cells (eg Langerhans' cells)	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	—
Hepatocytes	+	—
Kidney	+	—
Brain	+	—†
Non-nucleated cells	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

DC: The TRUE professional APC

- Only cell type capable of activating naïve T cells *in vivo*



The contemporary model



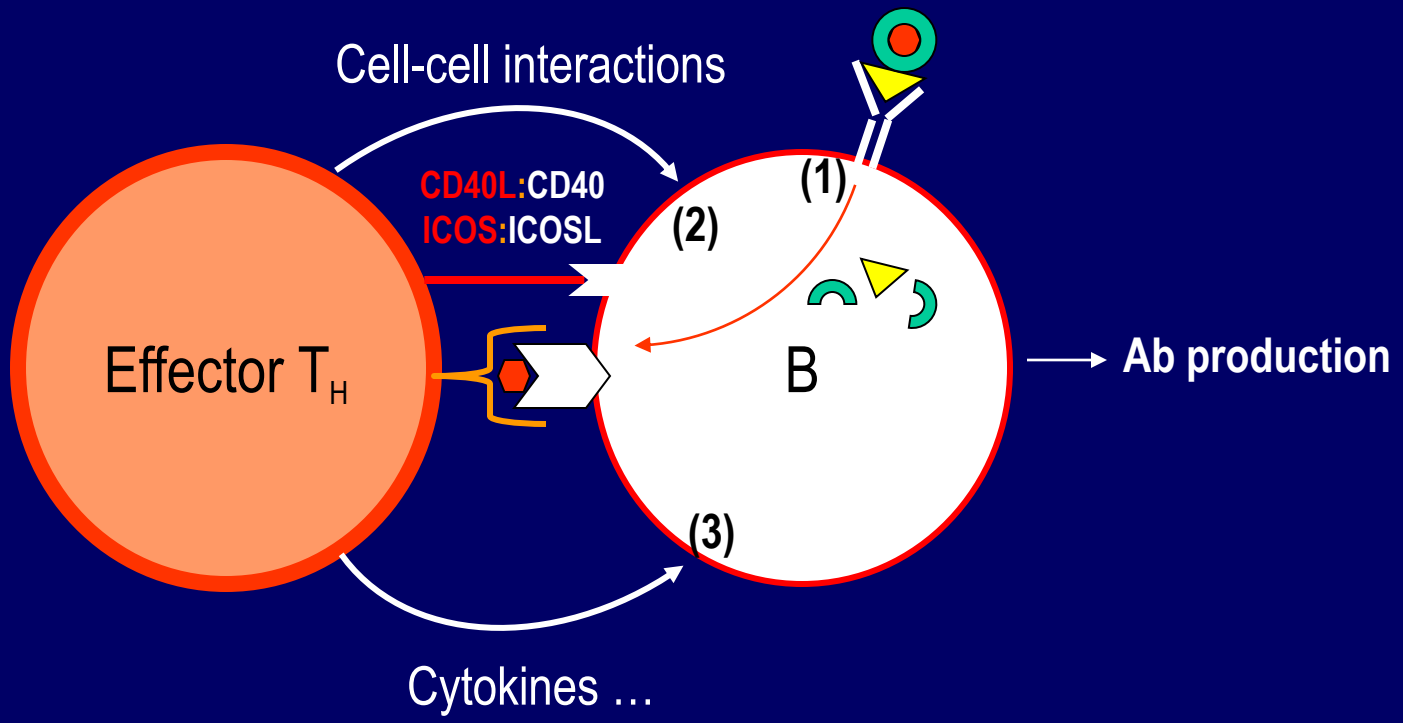
Cytokines

- **Small pharmacologically active products of cells**

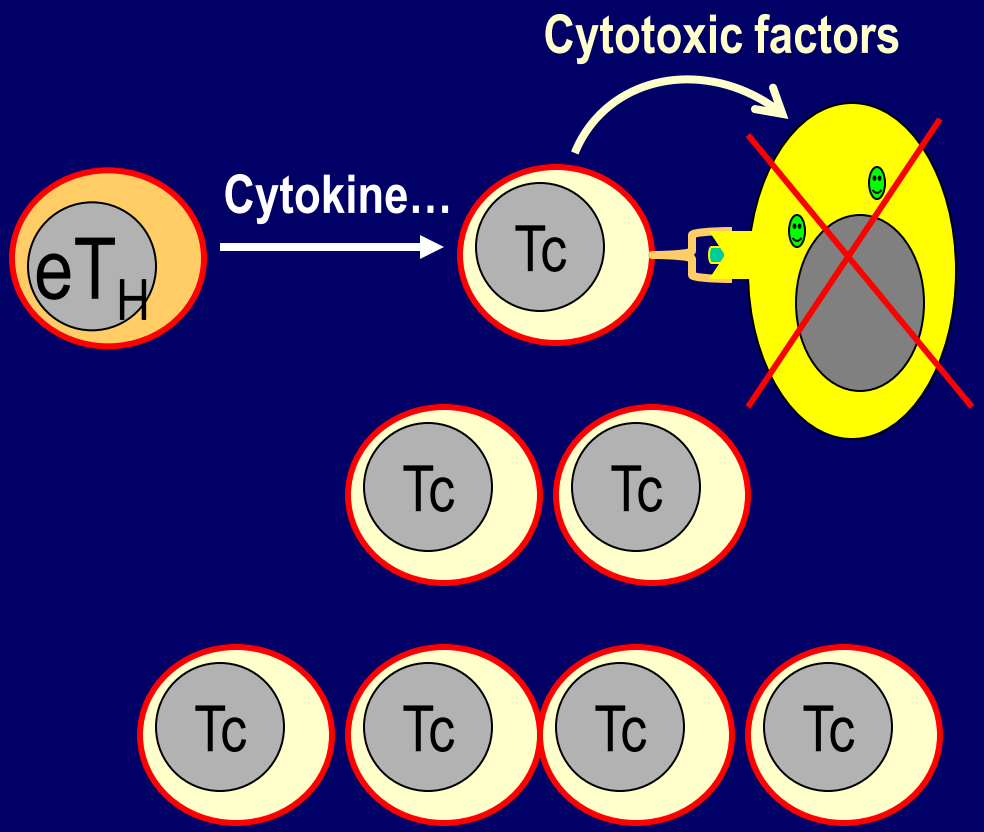
- **Nomenclature & classification**

  - **Interleukins:** interleukin 1 - 37 (IL-1 – IL-37)
    interferons, TNF etc.
  - *Lymphokines:* *produced by lymphocytes*
  - *Monokines:* *produced by monocytic/phagocytes*
  - **Chemokines:** CXC (IL-8), CC (**DC-CK**, MDC), CX3C (Fractalkine)

T-B cell cooperation



T-T cell cooperation

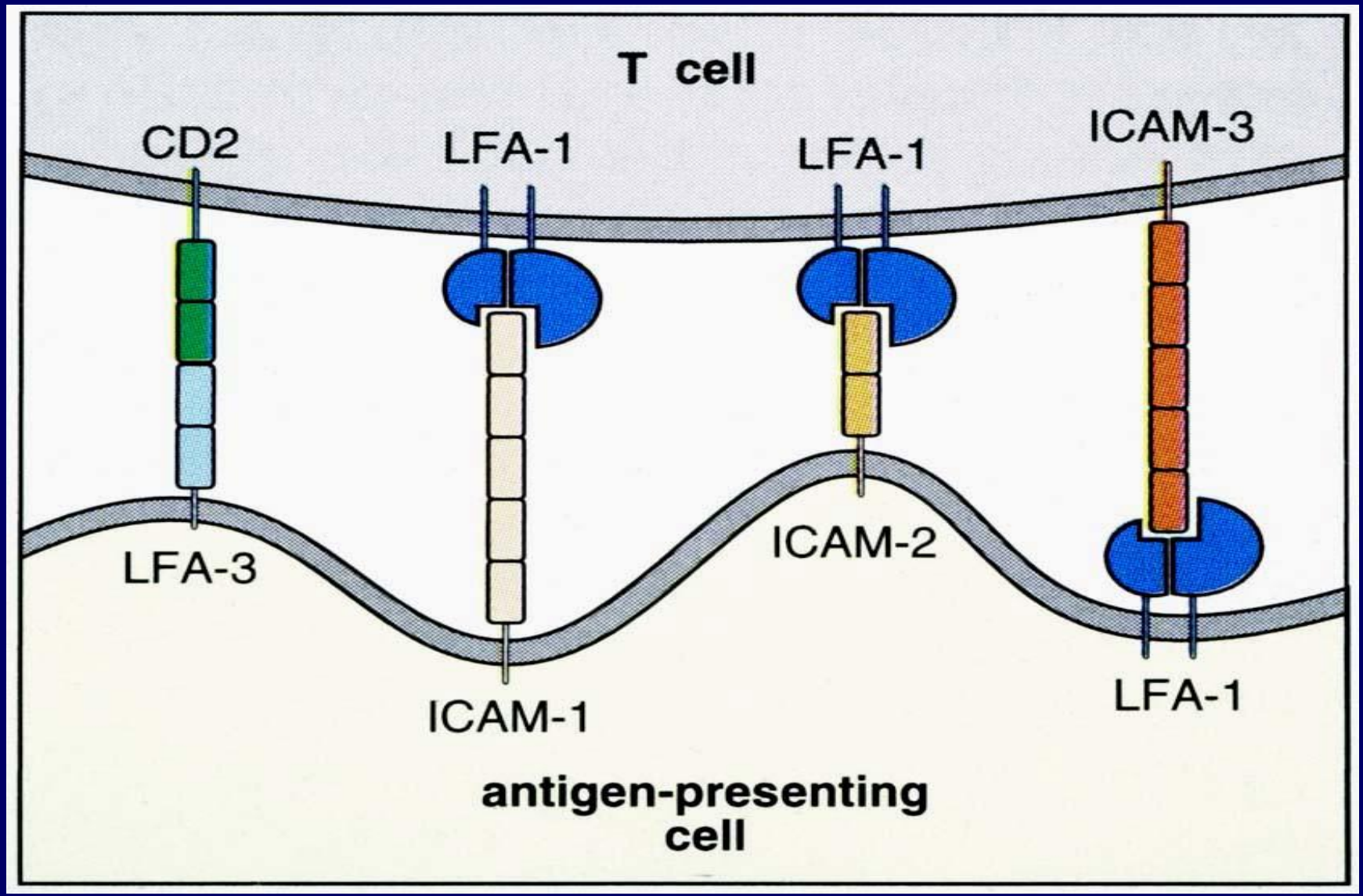


Co-stimulations

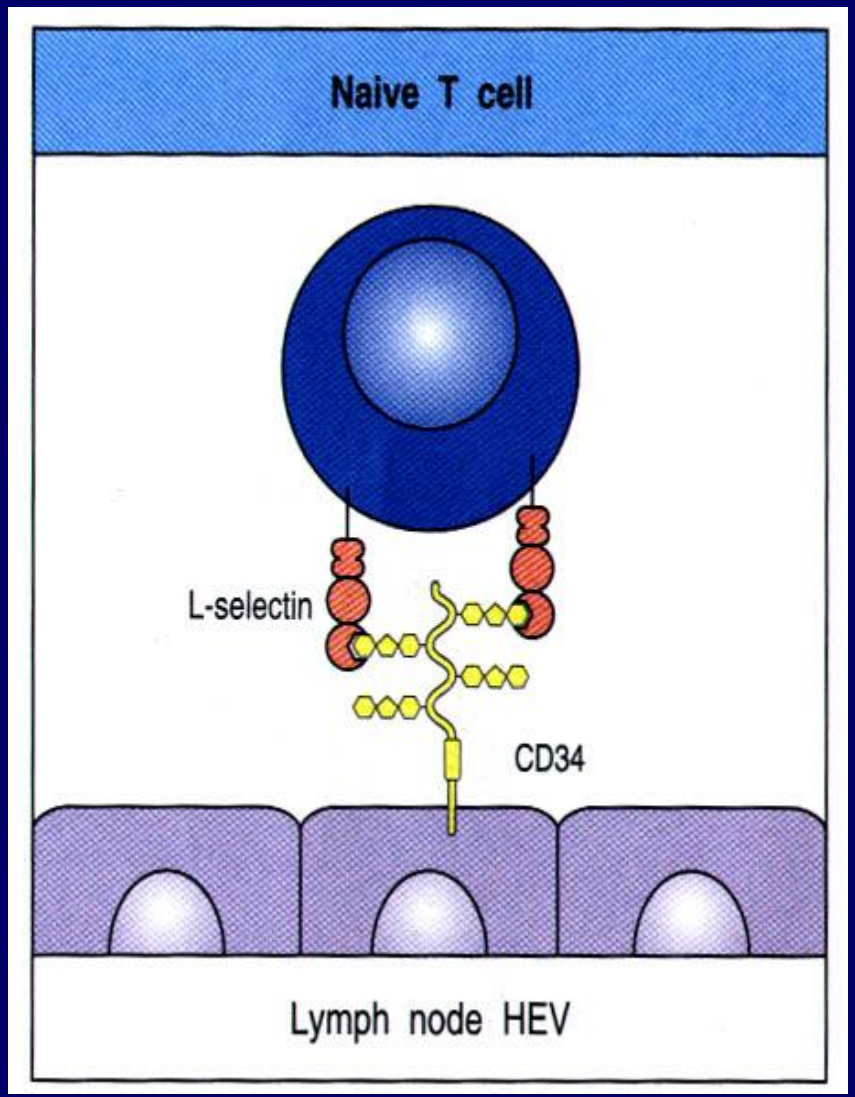
- Cellular interactions/triggering other than Ag-specific stimulation

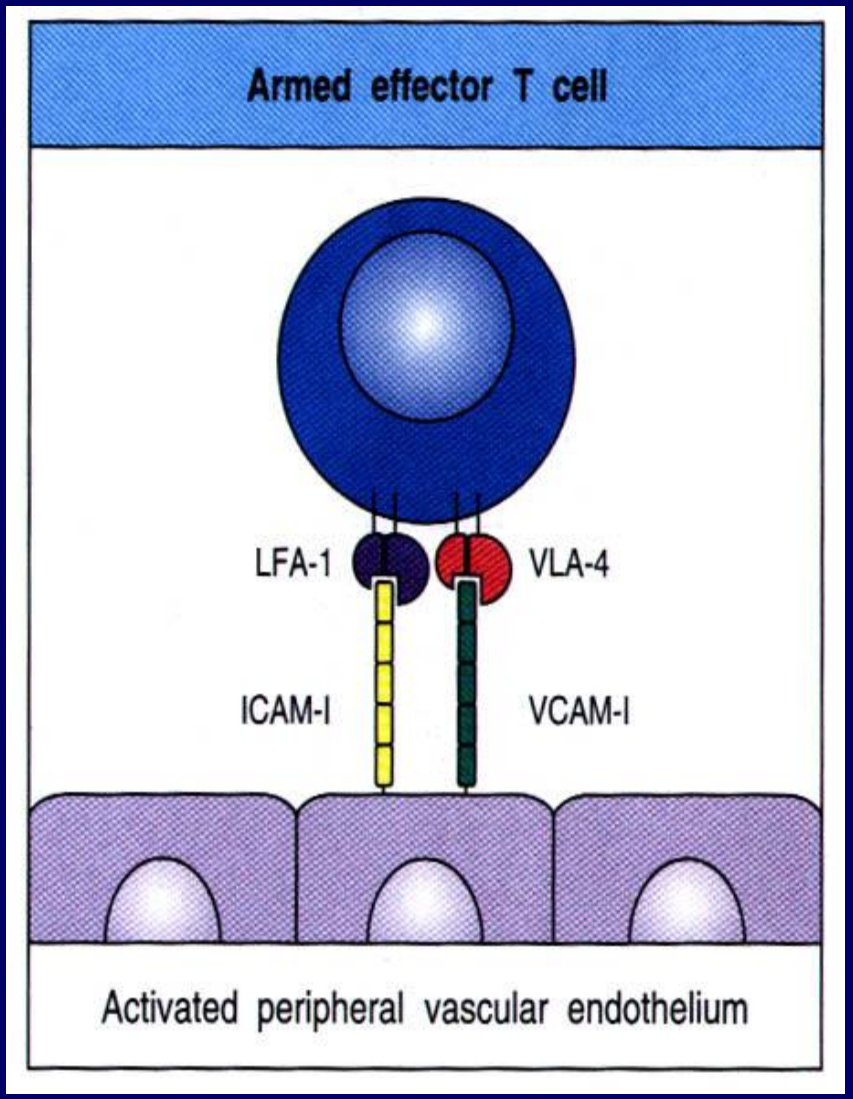
- **B7:CD28** *- Naïve T cell activation*
- **CD40:CD40L** *- B cell growth & differentiation*
- **ICOS:ICOS-L** *– Effector T & B cell functions*
- **Cytokines & the receptors** *– Immune cell functions*
- ***Adhesion molecules …***

T cell:APC interactions



Naïve & activated T cells expressed different types of adhesion molecules





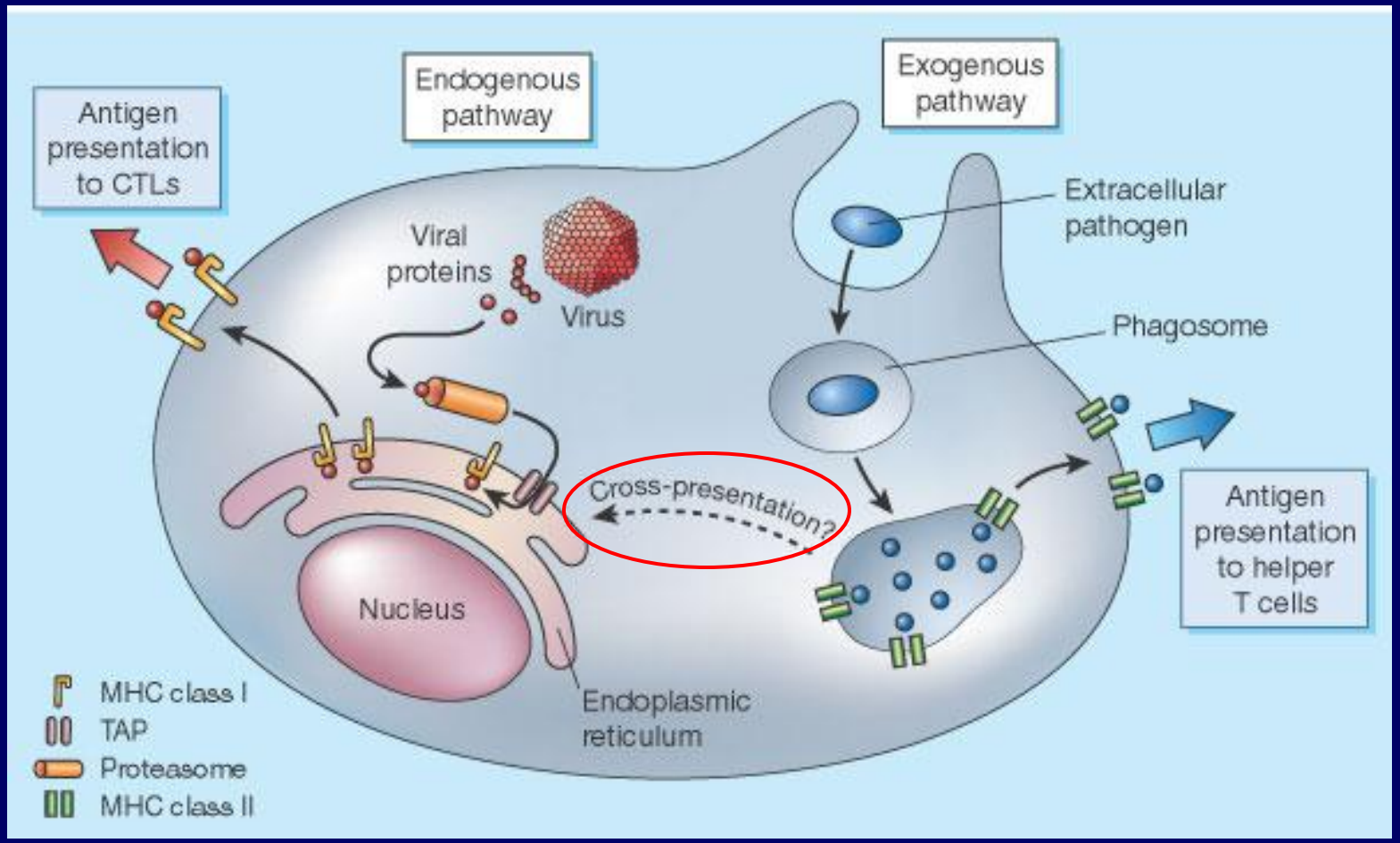
DC: an unique Ag processing & presenting machine

In immature DC:

- Attenuated lysosomal potential for Ag degradation
  - Ag sequestered from lysosome for extended period
- Regulated cathepsin S activity by Cystatin C
  - delaying the cleavage of MHC II- associated Ii chain
  - favouring MHC II transport to lysosome

(Mellman I & Steinman RM, Cell. 2001; 106:255-8)

Ag ‘cross-presentation’ - DC breaks the rules

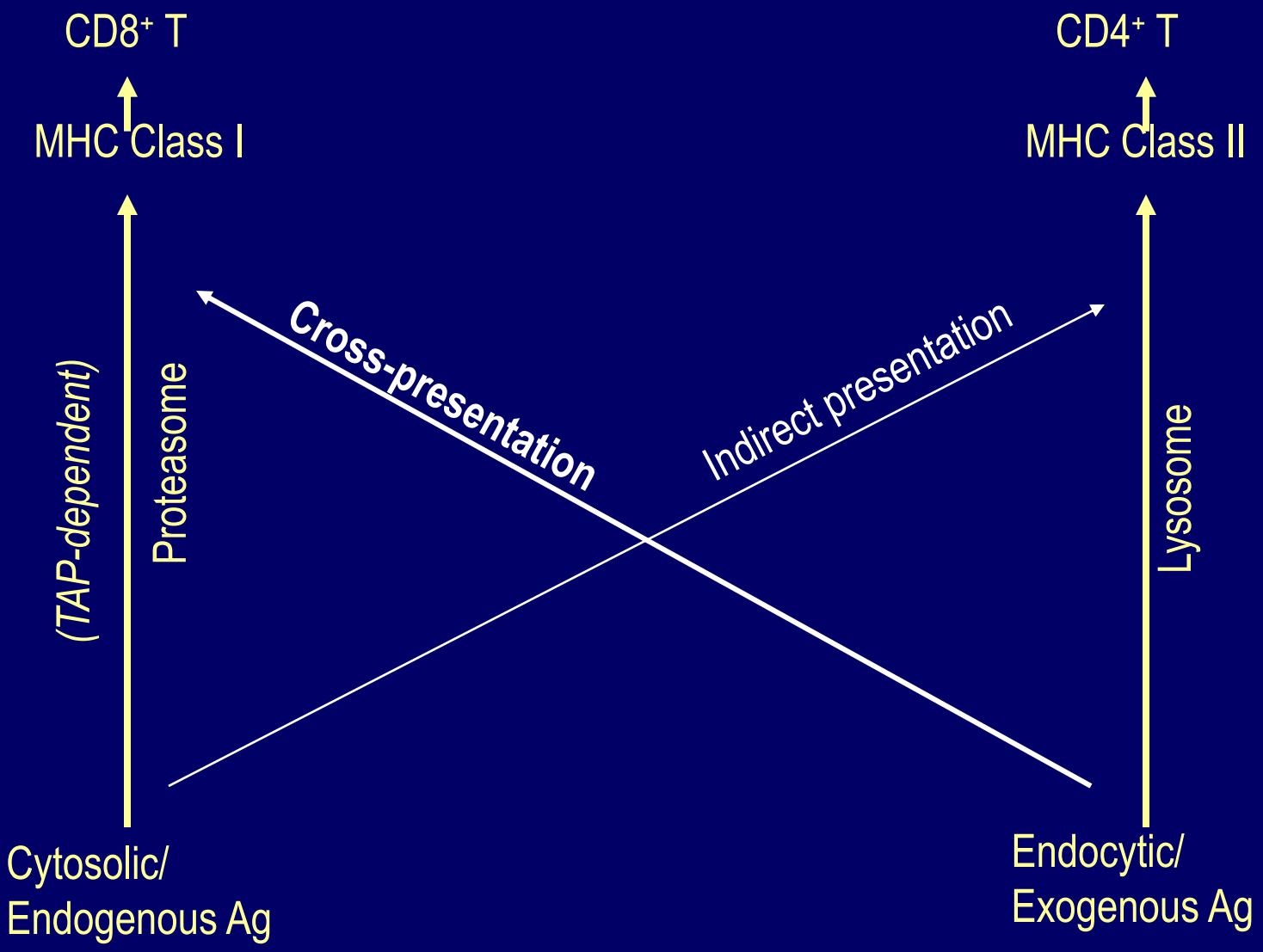


Craig RR. Nature **425**, 351-52 (2003)

Two CLASSICAL pathways for Ag processing & presentation

- **"MHC class I pathway" → $CD8^+$ T cells**
  (Endogenous/cytosolic/TAP-dependent pathway)
- **"MHC class II pathway" → $CD4^+$ T cells**
  (Exogenous/endocytic/TAP-independent pathway)

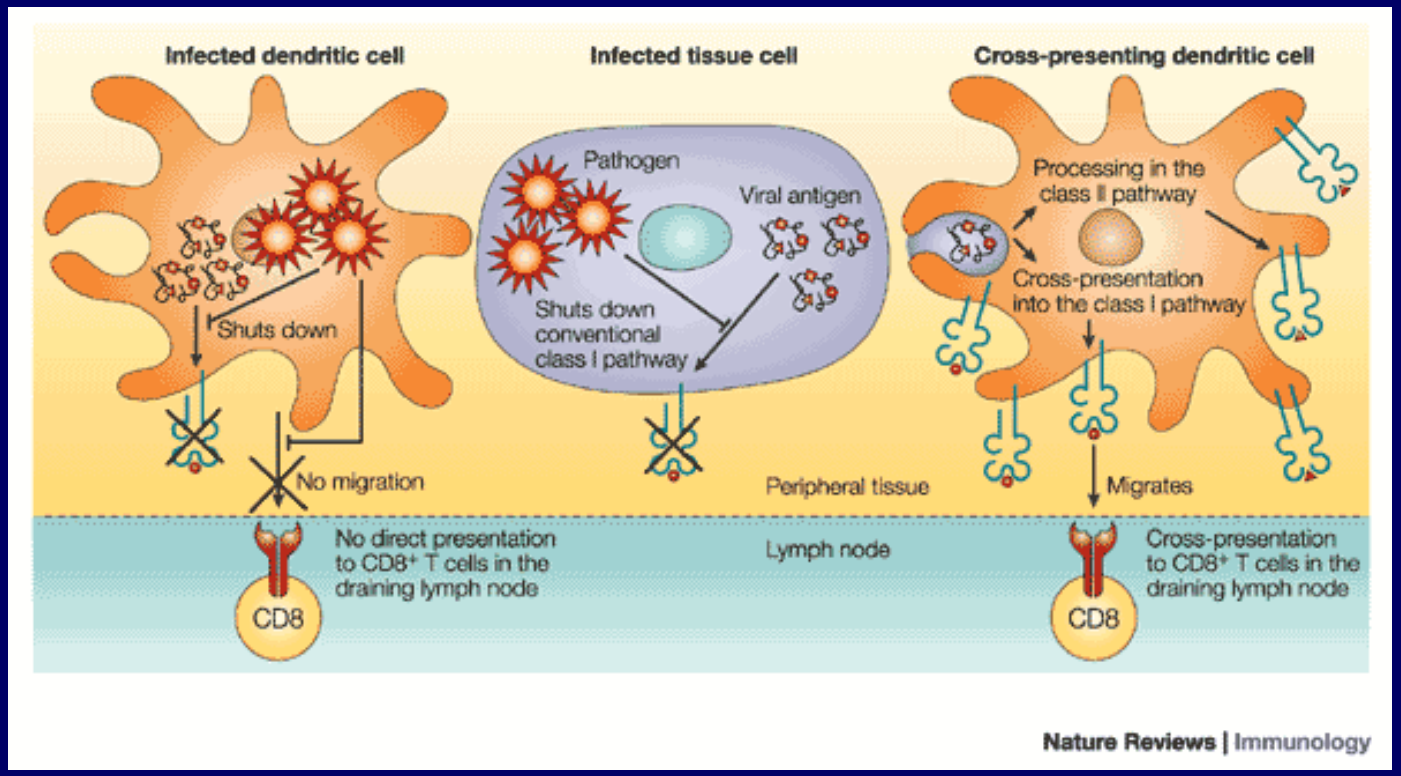
The alternative pathways of Ag presentation by DC



Antigens cross-presented

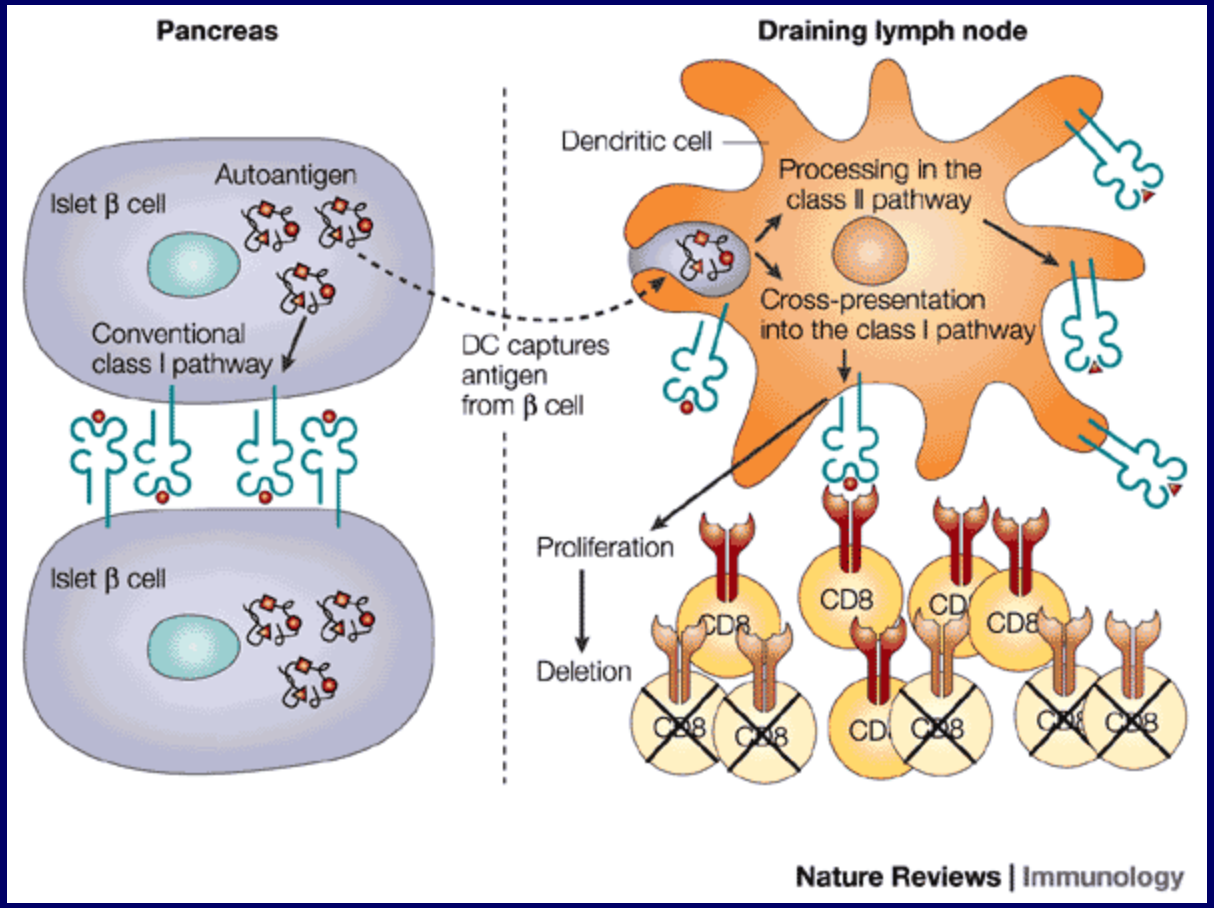
- Virus-infected apoptotic cells
- Cell death due to normal cell turnover
- Apoptotic tumour cells
- Transplantation Ags
- Endocytosed Ag: small fragments (3-12 KD)

Cross-priming for inducing effective CTL immunity



(Heath WR & Carbone FR. Nat Rev Immunol, 2001)

Cross-presentation of self-antigens leads to induction of CTL tolerance to peripheral tissues



(Heath WR & Carbone FR. Nat Rev Immunol, 2001)

Further questions:

DC heterogeneity?

How DC may induce immunity, & tolerance?

Summary I

DC – Initiator of the adaptive immunity

(The TRUE professional APC)

Basic properties:

- **Sentinel position** *(Constant surveillance)*
- **Endocytic** *(Ag uptake)*
- **Migratory** *(Ag transport)*

Unique features:

- **Unique location in the secondary lymphoid organs** *(T area)*
- **High surface MHC Class I, Class II** *(Ag presentation)*
- **Constitutive expression of B7** *(Co-stimulations)*
- **Special Ag processing machine** *(Unique Ag processing capacity)*
- **Ag cross presentation** *(Th, Tc)*

- ***A link between the innate & the adaptive immune systems***

Summary II

Co-stimulations

Definition:

- **Cellular interactions/triggering other than Ag-specific stimulations.**

Types:

- **CD28:B7 (CD80, CD86)** – *Naïve T cell activation*
- **ICOS:ICOSL** – *Effector T & B cell functions*
- **CD40:CD40L** – *B cell growth & differentiation*
- **Adhesion molecules** – *Cellular interactions*

- **Chemokines & receptors** – *Cell migration & homing*
- **Interleukins & receptors** – *Effector functional molecules*
- *etc…*