HLA, tra immunità innata e adattativa

Emanuele Cozzi

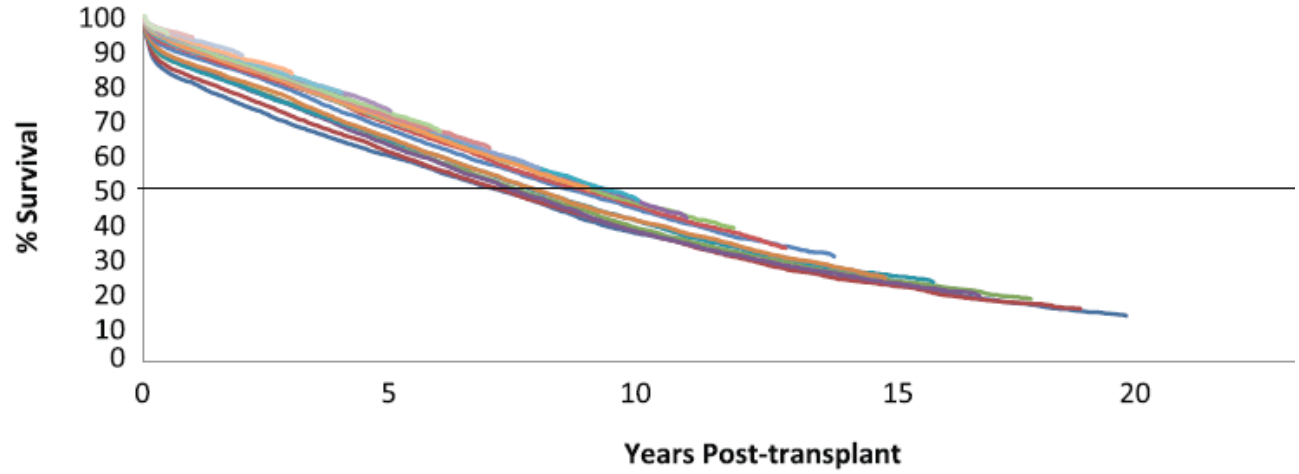
S.S.D. Immunologia dei Trapianti
Azienda Ospedaliera di Padova

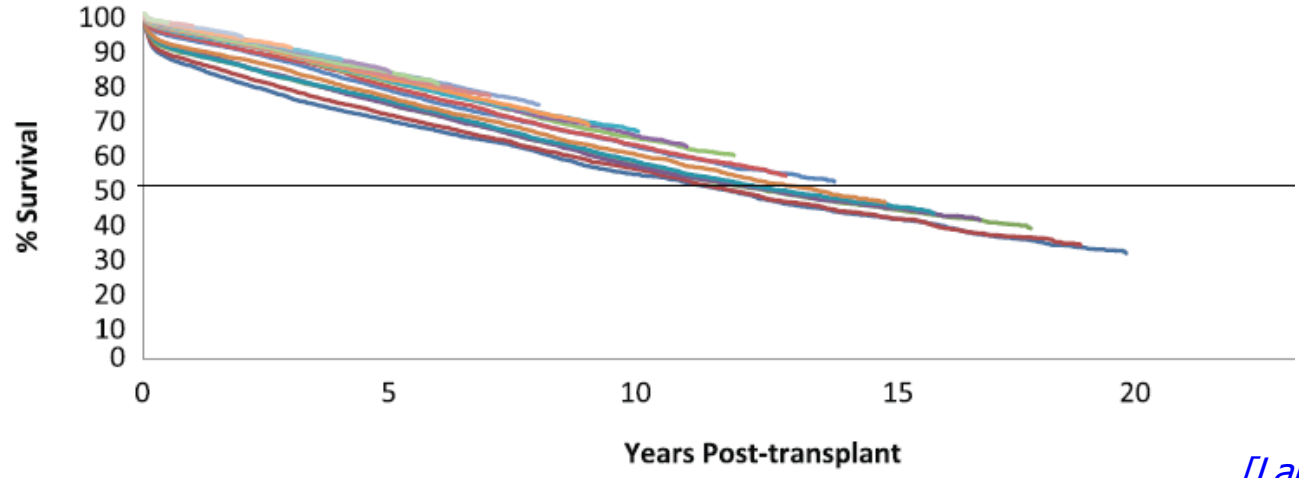
Punti della presentazione

- Risultati attuali del trapianto e problematiche aperte
- Immunità innata ed adattativa
- Il ruolo centrale della molecola HLA
- Aspetti di sinergia tra immunità innata ed adattativa

A central issue in transplantation: how long will the graft survive?

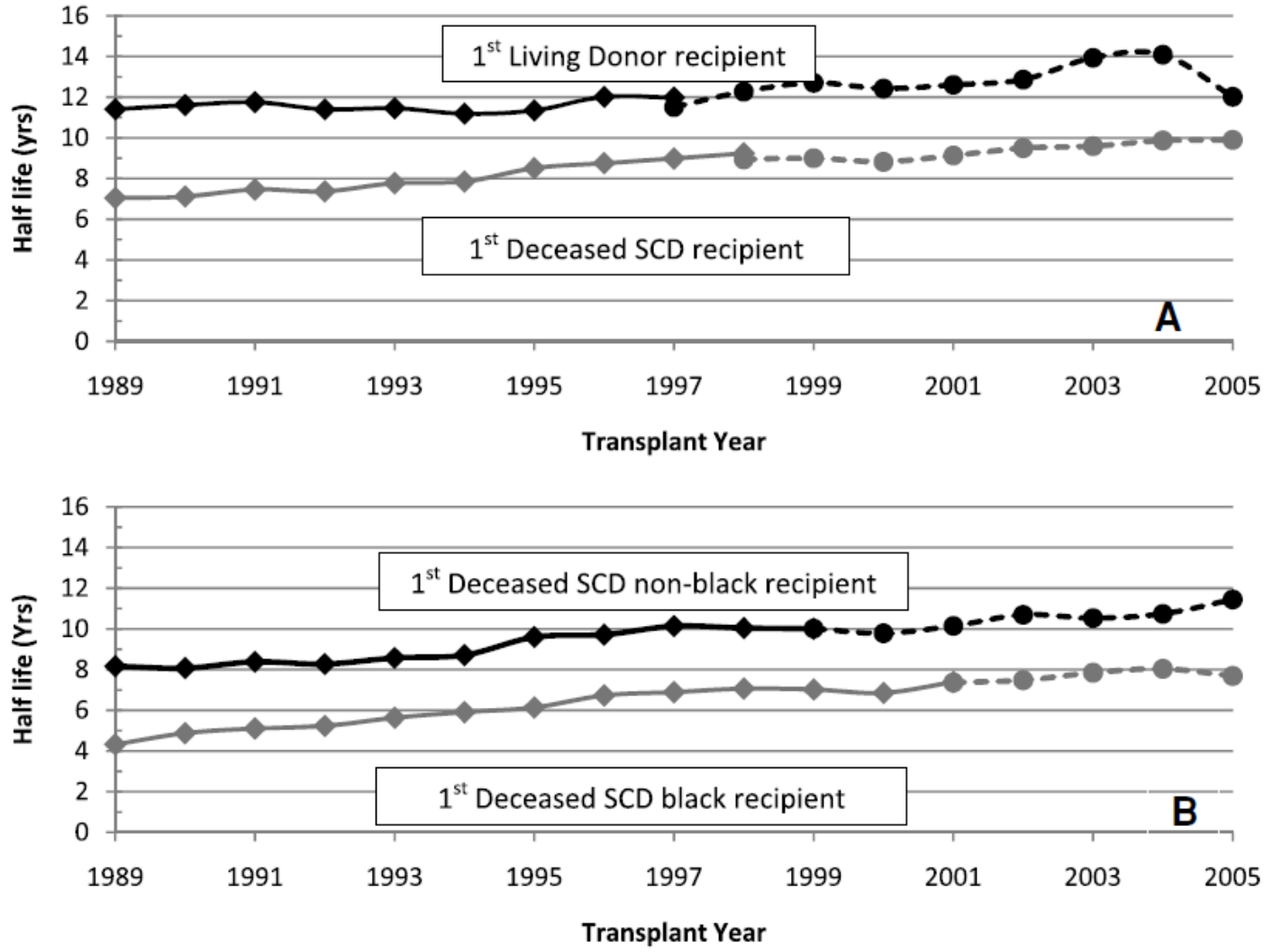
Graft survival following transplantation





[Lamb et al, AJT, 2011]

Graft survival following transplantation



[Lamb et al, AJT, 2011]

Why is the graft not lasting longer? Insults related to transplantation

- Immediate: **Trauma of transplantation**
  - IRI upregulation of proinflammatory cytokines and adhesion molecules; recruitment of inflammatory cells
  - also observed in syngeneic grafts
  - Its importance on acute and chronic rejection is still unclear
- After surgery**: Rejection**

Factors involved in transplant «rejection» [premature graft loss]

Immunological factors

- Cells (innate and specific immunity)
- Antibodies
- Complement

Non immunological factors

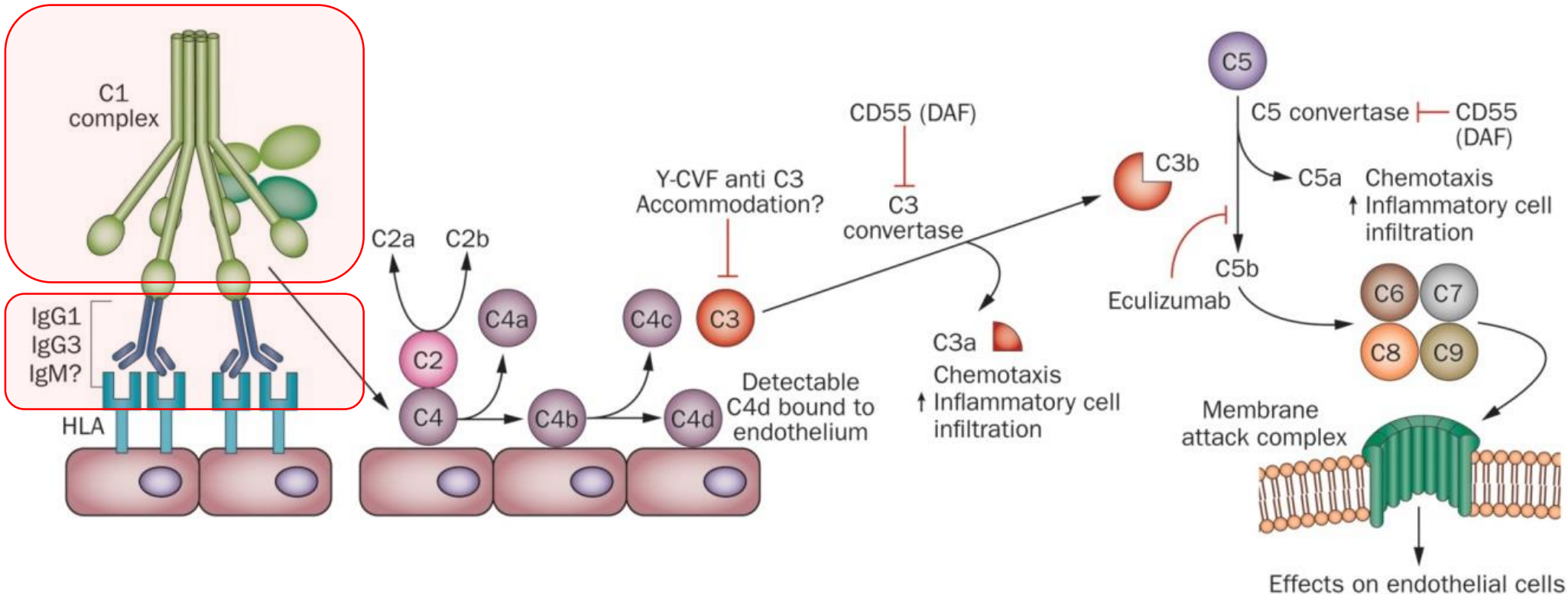
- coagulation
- ischemia/riperfusion
- Infection
- [Hypertension]
- [Dyslipidemia]

Types of **Immunity**

	INNATE (natural, native)	**ACQUIRED** (adaptive, specific)
Specificity	Against microbes + damaged host cells	Against any type of antigen
Diversity	Limited	Very large
Memory	No	Yes
Reactivity against self	No	No
Cellular and chemical barriers	Skin, mucosa	Lympocytes and antibodies
Blood proteins	Complement	Antibodies
Cells involved	MΦ, Neutrophils, NK	Lymphocytes

Risposta alla terapia I.S. usata nel trapianto	Generalmente scarsa	Generalmente Buona

Stretta sinergia tra immunità innata e adattativa



[Stegall et al, Nat Rev Nephrol 2012]

Types of **Immunity**

	INNATE (natural, native)	**ACQUIRED** (adaptive, specific)
Specificity	Against microbes + damaged host cells	Against any type of antigen
Diversity	Limited	Very large
Memory	No	Yes
Reactivity against self	No	No
Cellular and chemical barriers	Skin, mucosa	Lympocytes and antibodies
Blood proteins	Complement	Antibodies
Cells involved	MΦ, Neutrophils, NK	Lymphocytes

Key immunological effectors of the **specific** Immune Response that mediate allograft rejection

Cell type	Effector function
• T lymphocytes	
▪ CD4+	⇒ DTH-type response (activation of other cells such as M and Bcells
▪ CD8+	⇒ Cytotoxicity (defence against intracell microbes)
• B lymphocytes	⇒ Ab production

The central role of the Major Histocompatibility Complex and the MHC molecules

Discovery of the MHC

Two critical observations

1. Transplantation between different inbred strains leads to rejection

   ➡ **Histocompatibility Ag**

2. The antibody response to antigens varies between different inbred strains

   ➡ **Genes of the immune reponse** (IR genes)

Discovery of the MHC

Two critical observations

1. Transplantation between different inbr… leads to rejection

   ➡ **Histocompatibility Ag…**

2. The antibody respons… varies between different inbred strains

   ➡ **Genes of the …mune reponse** (IR genes)

They are the same set of genes: genes of the MHC

The immune-response following organ transplantation

- The immune response is [*predominantly*] directed against the “non-self” in the transplanted organ

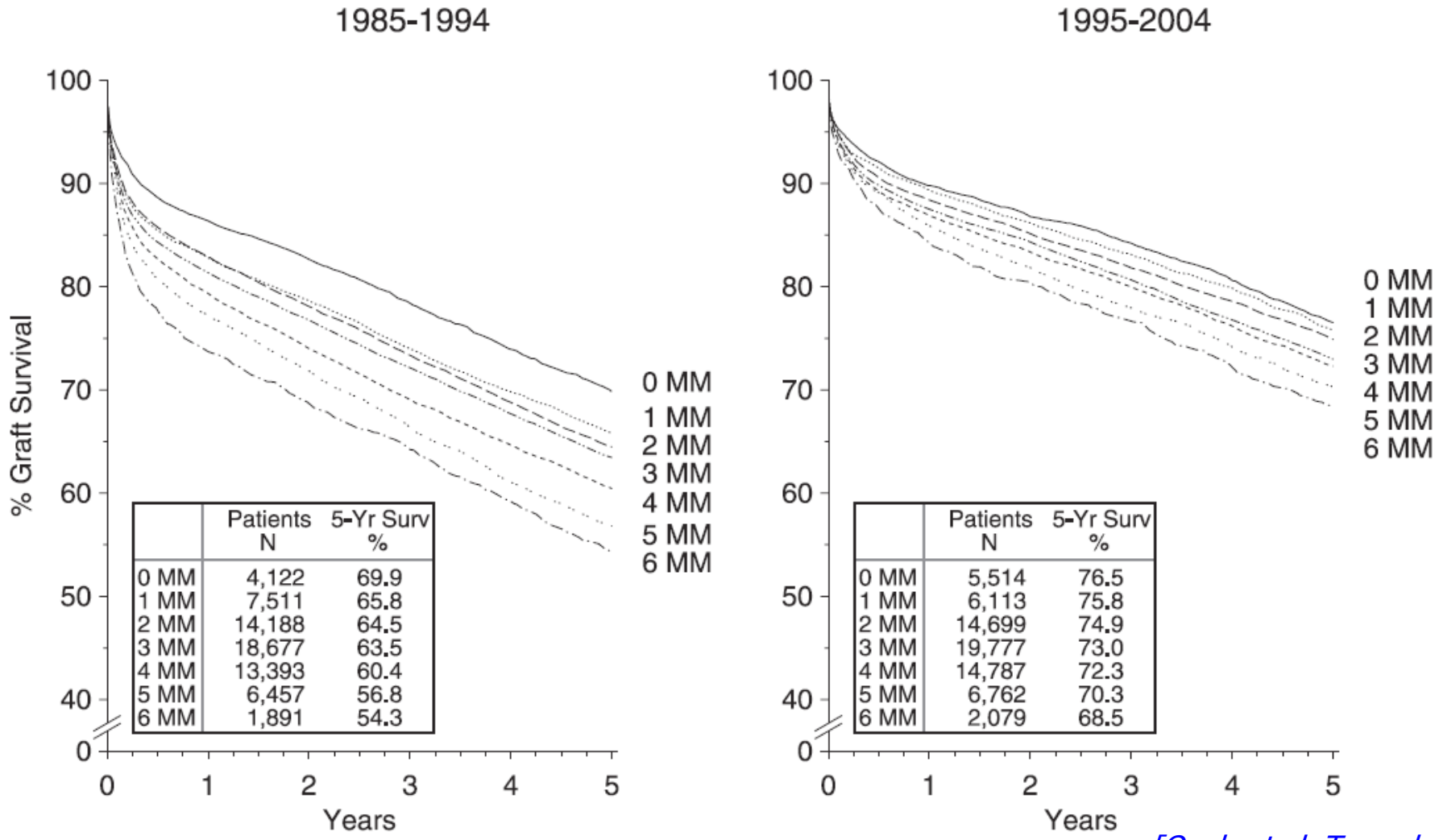
- The key target of the immune response are the MHC antigens (**HLA** in man)

The dual role of the MHC molecules

1. They are the principal target of the immune response directed against the "non-self" expressed by transplanted organs

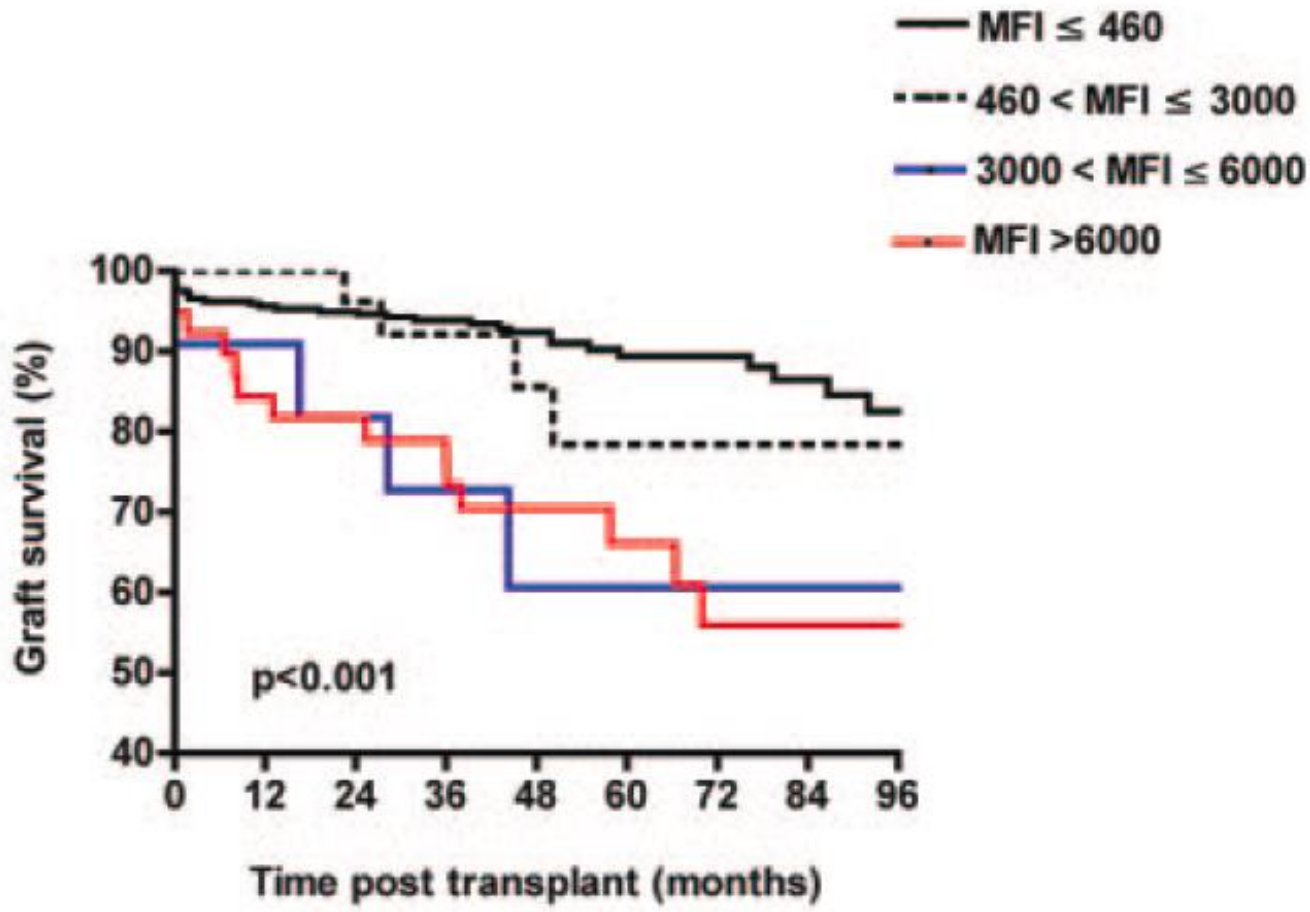
2. They enable antigen presentation to the T cells of the adaptive immune system

HLA as a principal target of the immune response: donor-recipient compatibility and graft survival



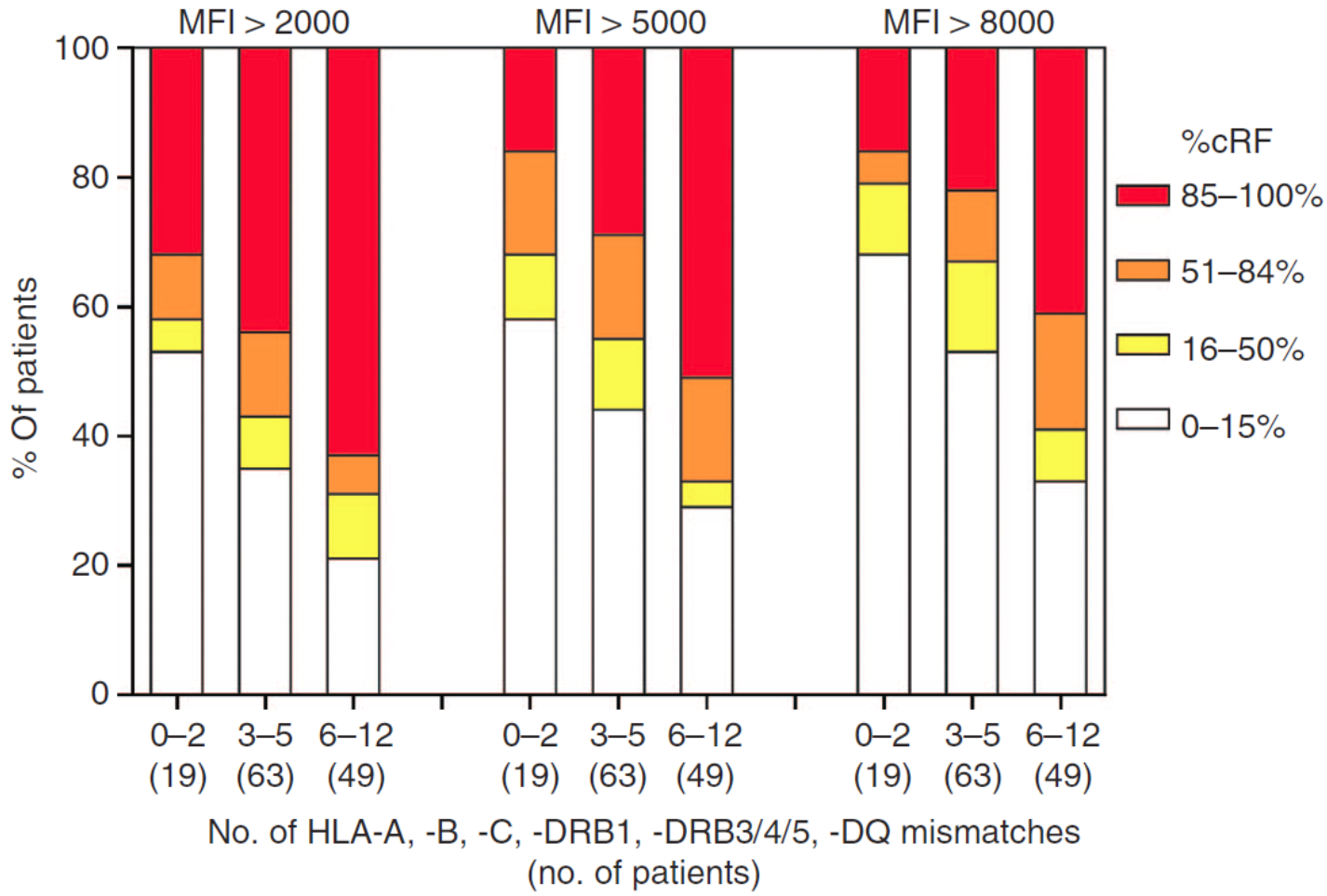
[Opelz et al, Transplant 2007]

HLA as a principal target of the immune response: CDC-XM negative, DSA-positive transplants and graft survival



[Lefaucheur et al, JASN 2010]

HLA as a principal target of the immune response: Consequences of HLA mismatch



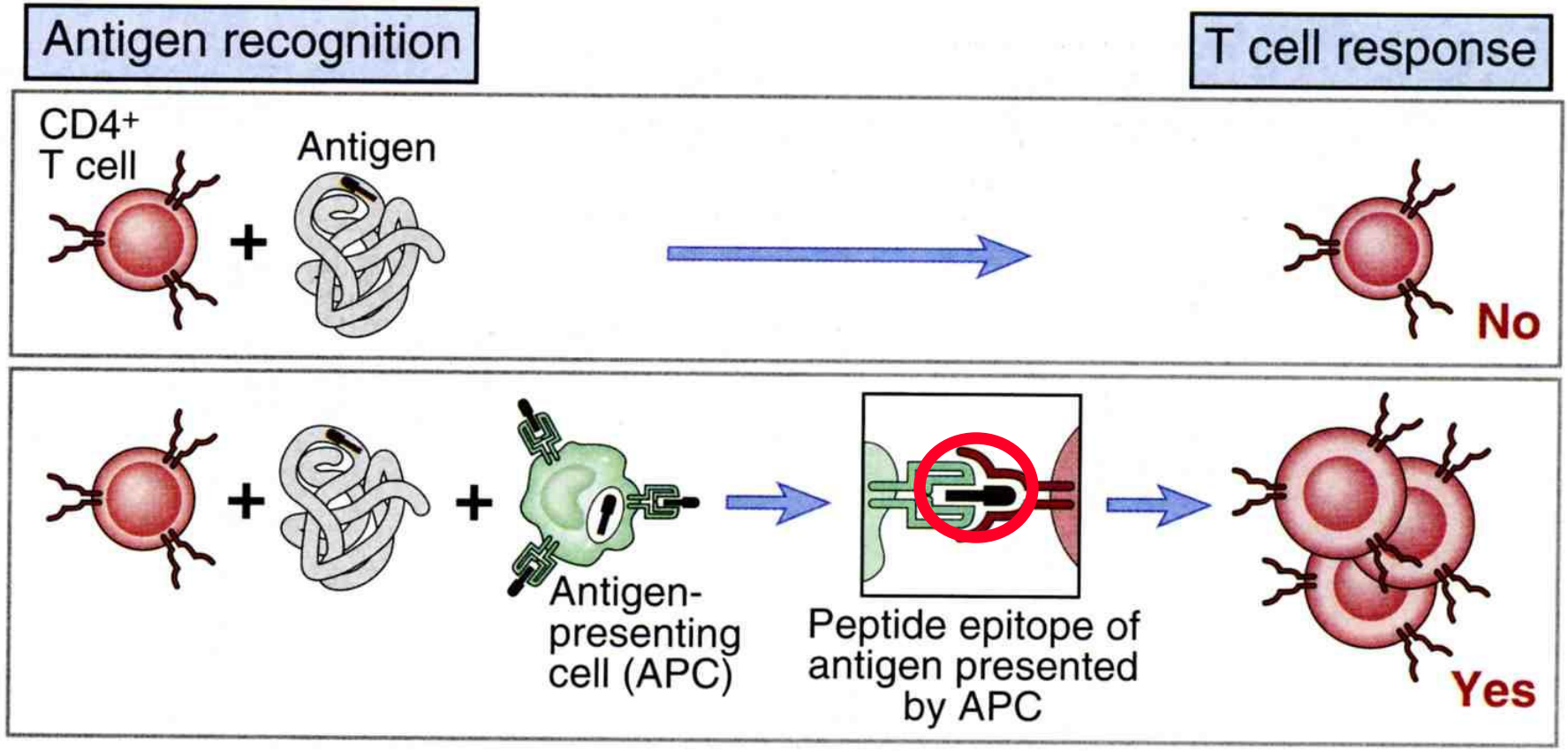
[Kosmoliaptsis et al, KI 2014]

HLA enables antigen presentation to the adaptive immune system: antigen recognition by T cell

- Whilst B cells (Ab) recognise Ag directly (as a soluble Ag or on other cells) **T cells can only recognize Ag if these are presented by other cells in the context of the MHC molecules**

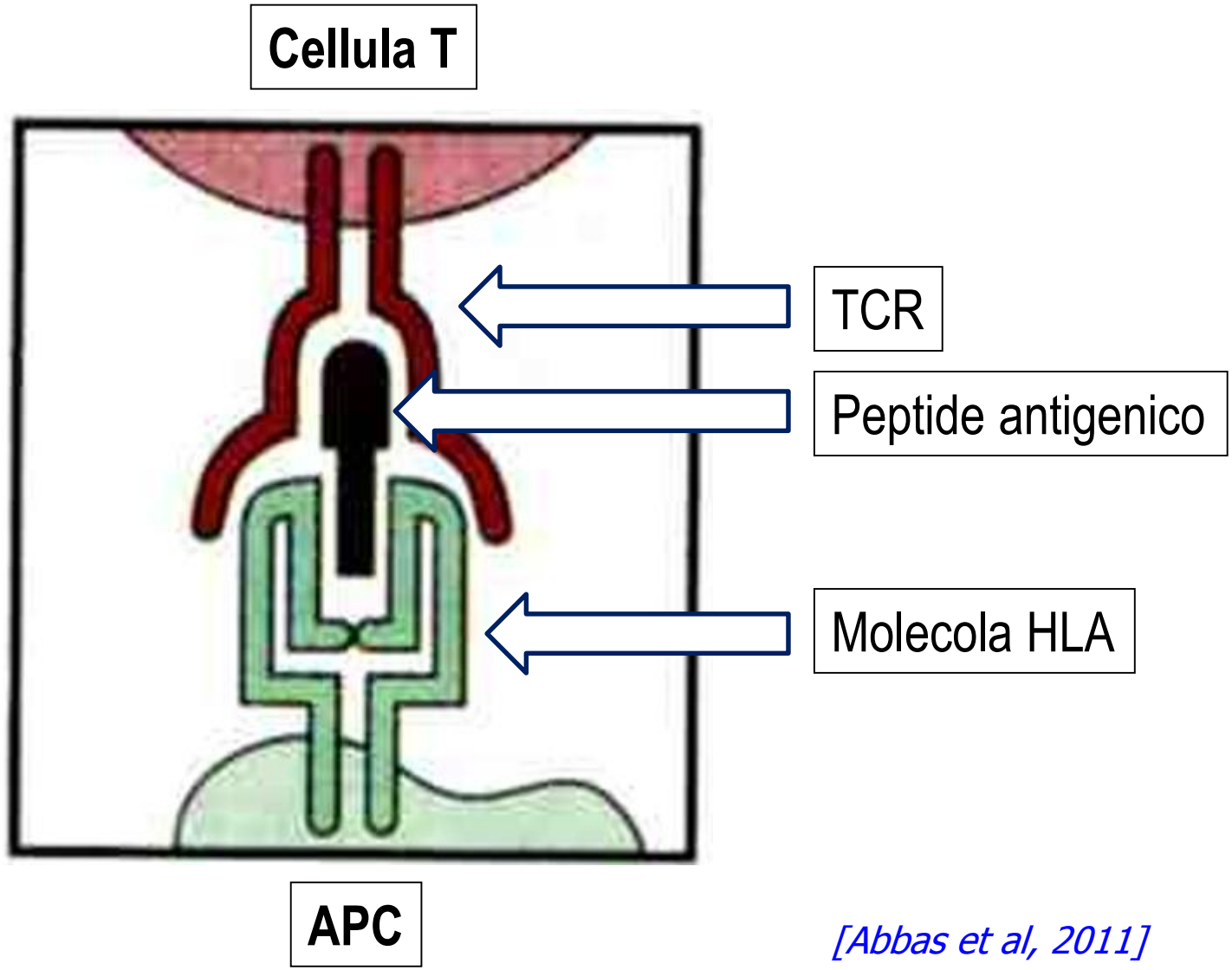
- T cell receptors recognise the **antigen** AND the **presenting MHC molecule**

HLA molecules enable antigen presentation to the T cells of the immune system



[Abbas et al, 2011]

HLA molecules enable antigen presentation to the T cells of the immune system



[Abbas et al, 2011]

The central role of alloantigen recognition by T-cells

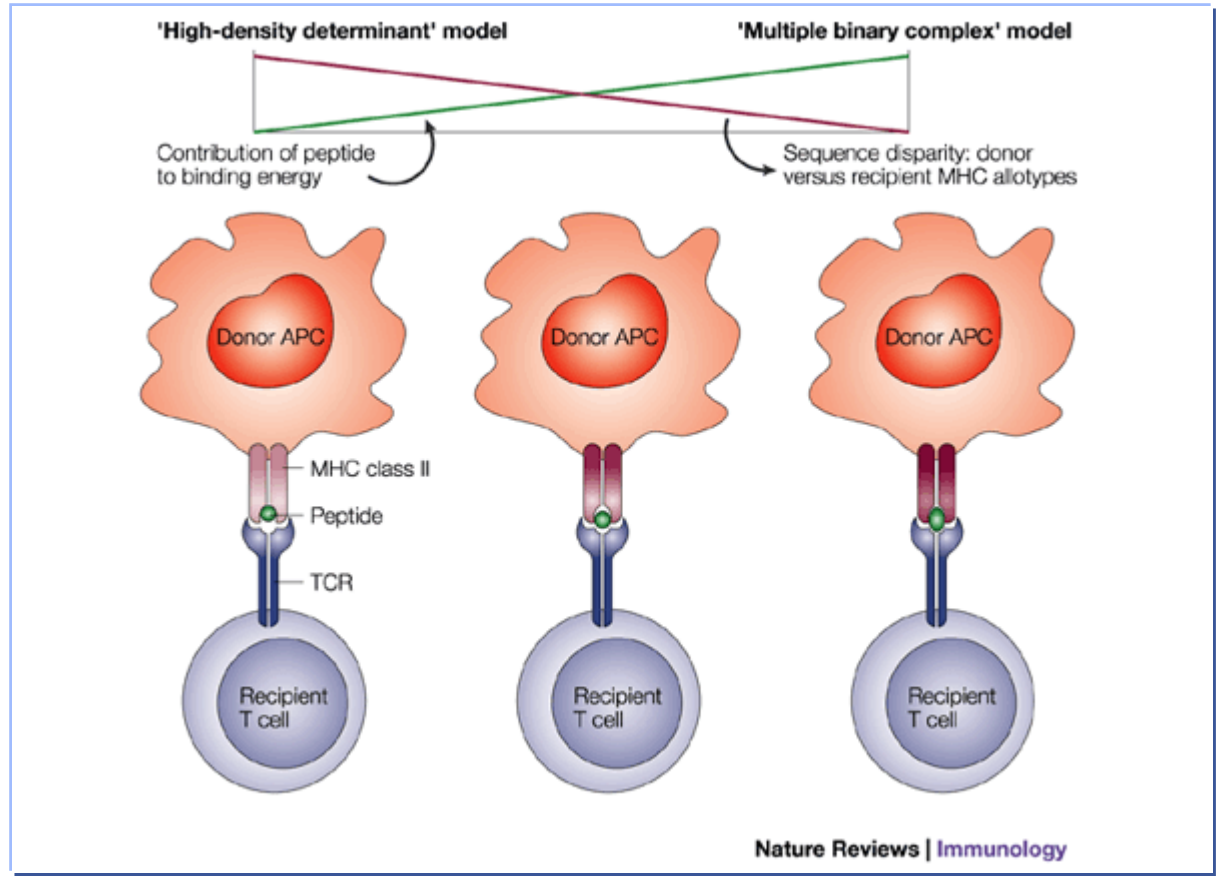
- Animals lacking T cells are unable to reject fully mismatched grafts
- Adoptive transfer of purified wild type T cells to these animals restores allograft rejection.
- In clinical transplantation, therapies that deplete peripheral leukocytes, including T cells, are effective in preventing and reversing acute rejection

Recognition of HLA-mismatched antigens by circulating alloreactive T cells is a crucial event that ultimately leads to rejection.

One of the reasons that transplantation induces such a strong immune response is the high precursor frequency of T cells able to respond to mismatched HLA molecules.

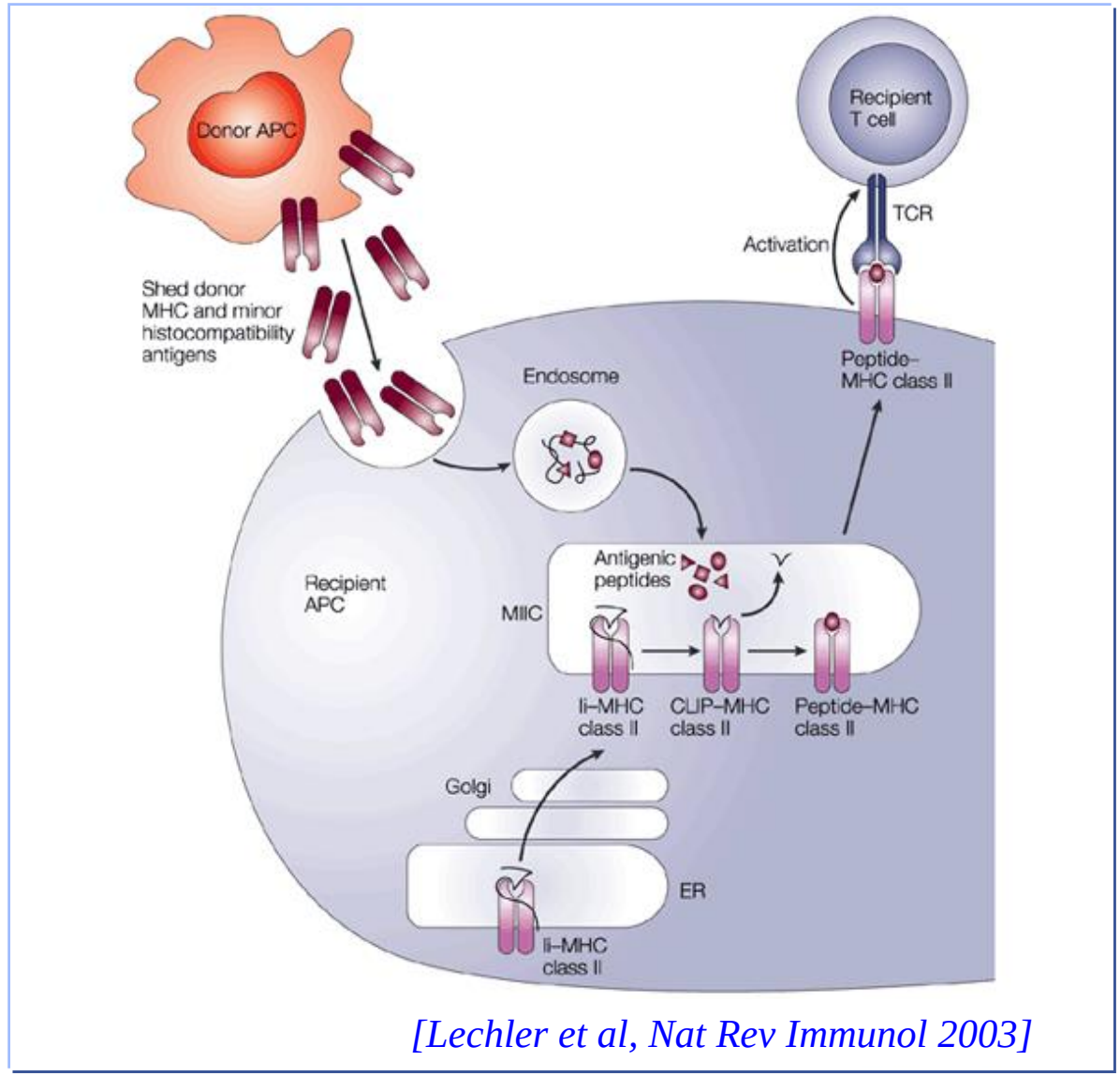
[Hara et al, J Immunol 2001; Wood et al, Transplant 2012]

MHC and direct allorecognition



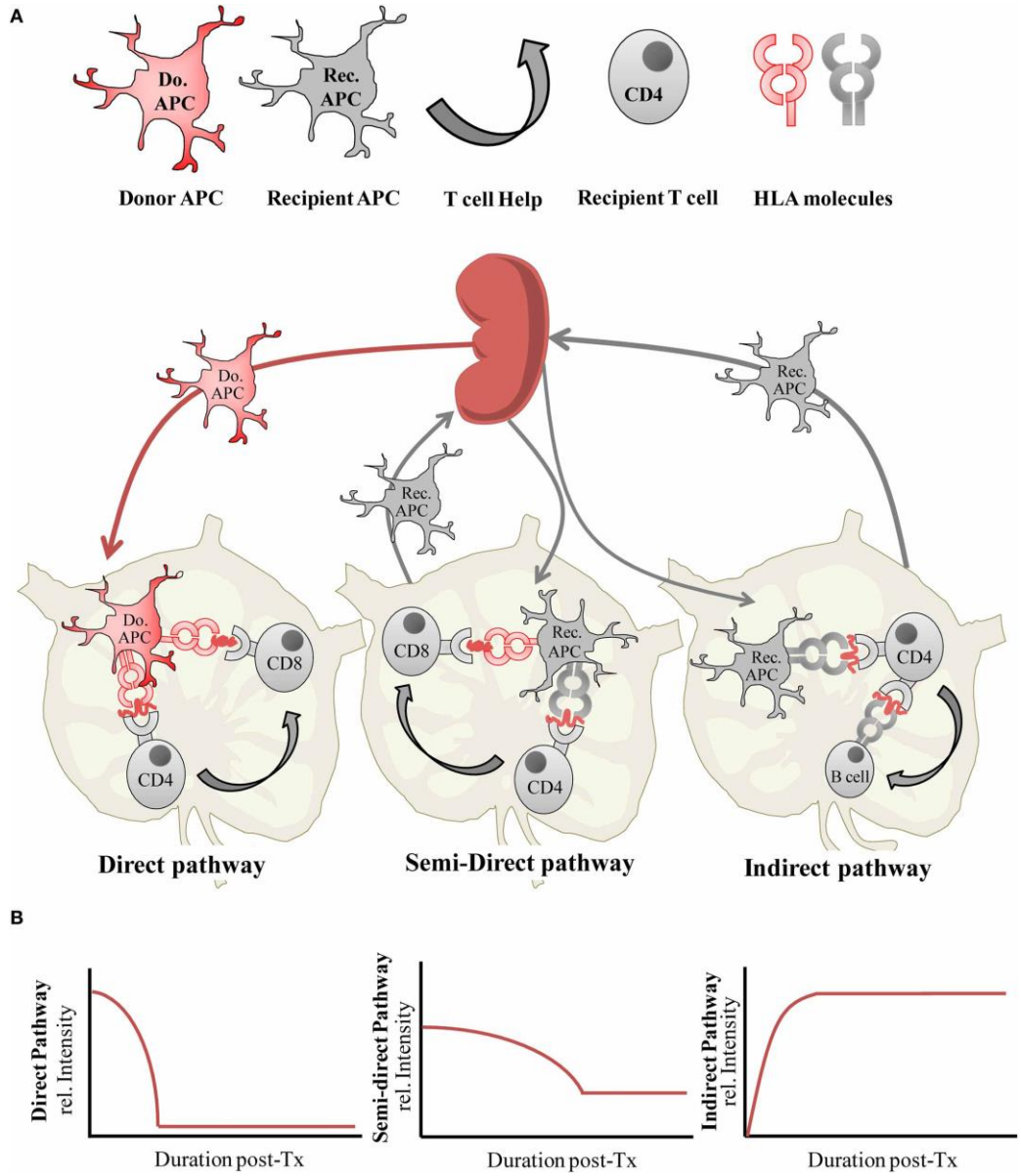
[Lechler et al, Nat Rev Immunol 2003]

MHC and indirect allorecognition



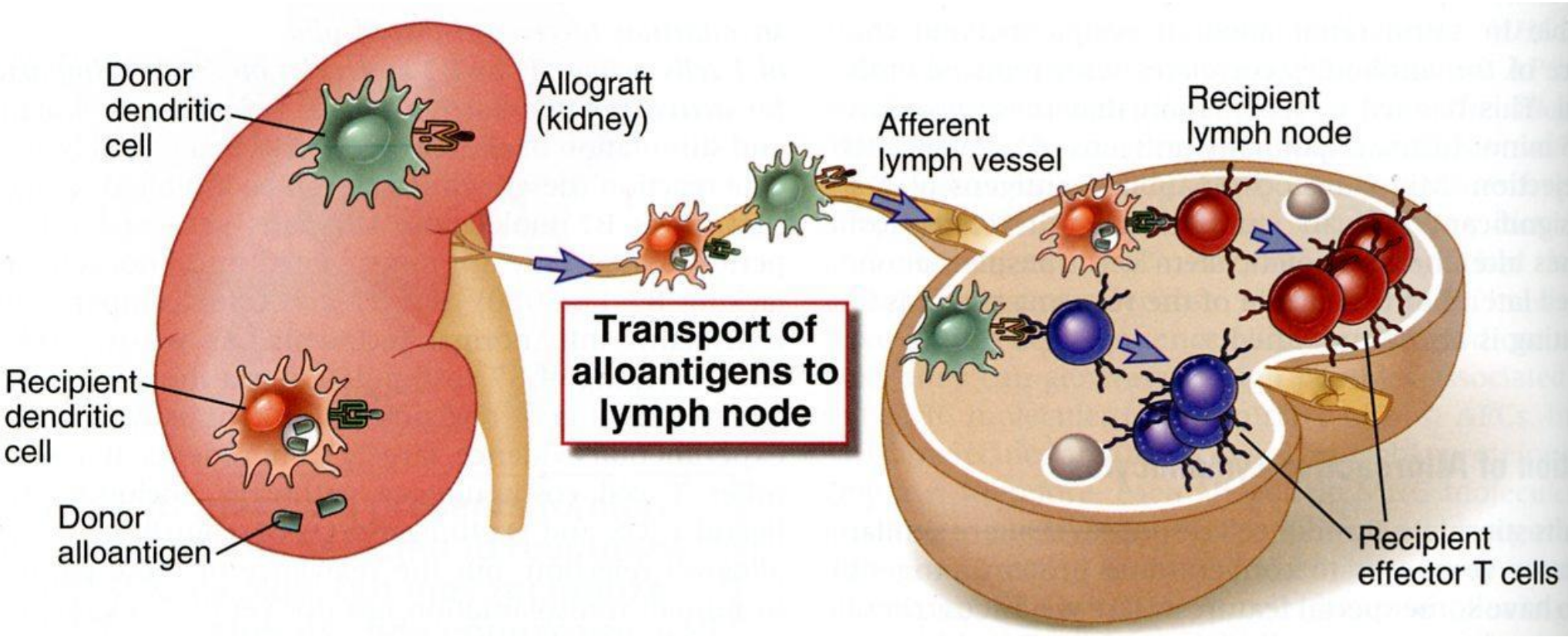
[Lechler et al, Nat Rev Immunol 2003]

Direct, indirect and semi-direct allorecognition



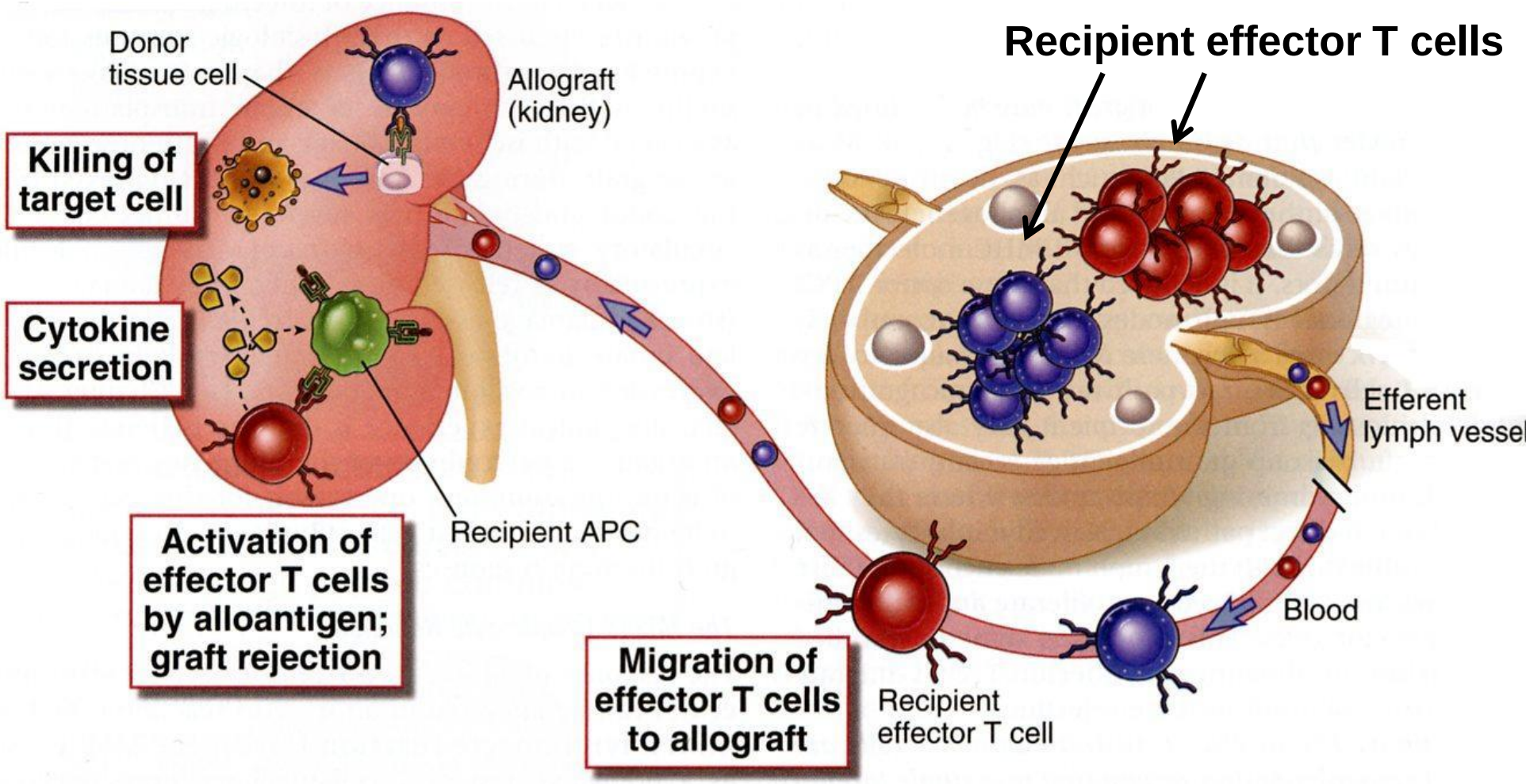
[Lechler et al, Frontiers in Immunol 2012]

Direct activation of alloreactive T cells



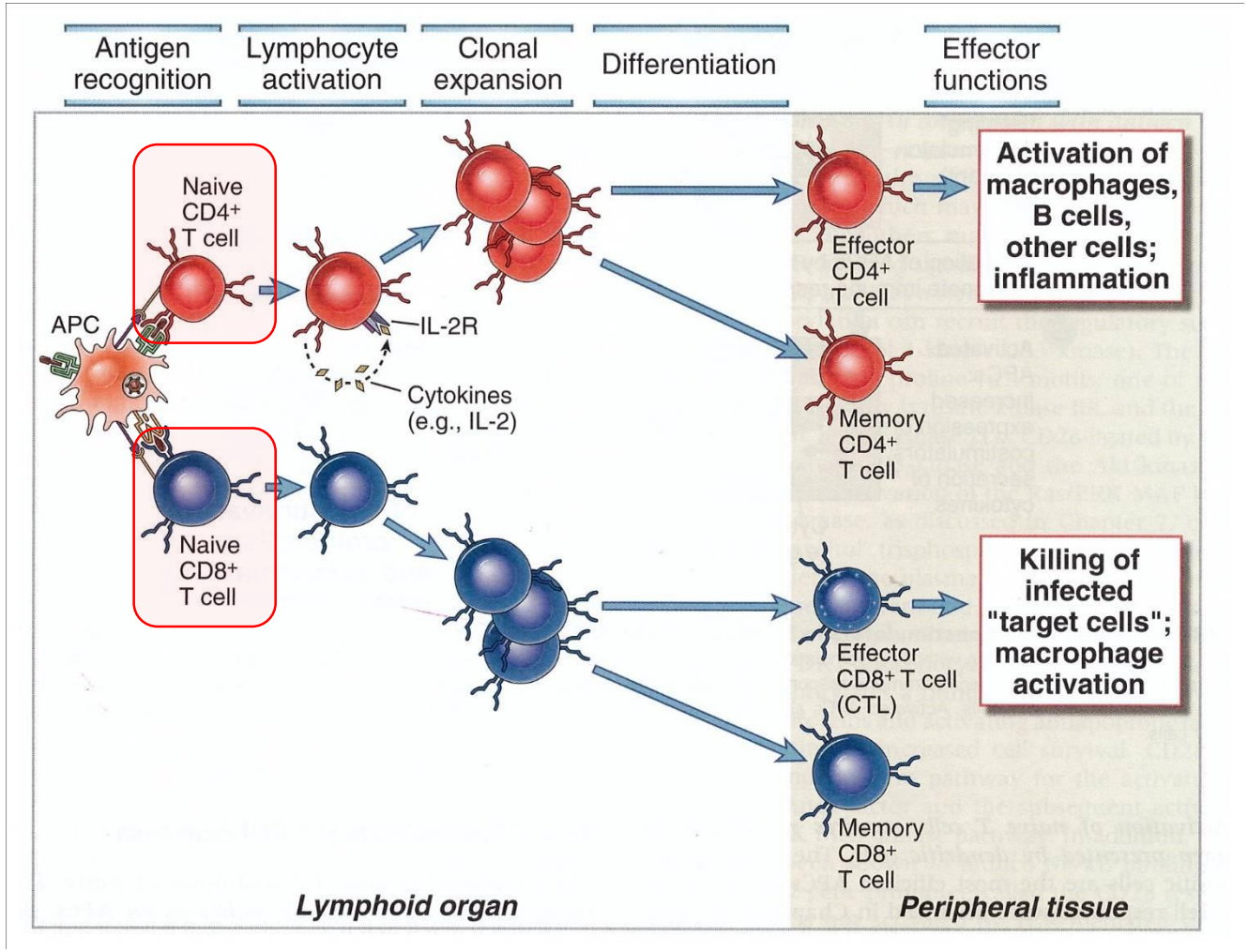
[Abbas et al, 2011]

Direct activation of alloreactive T cells (II)



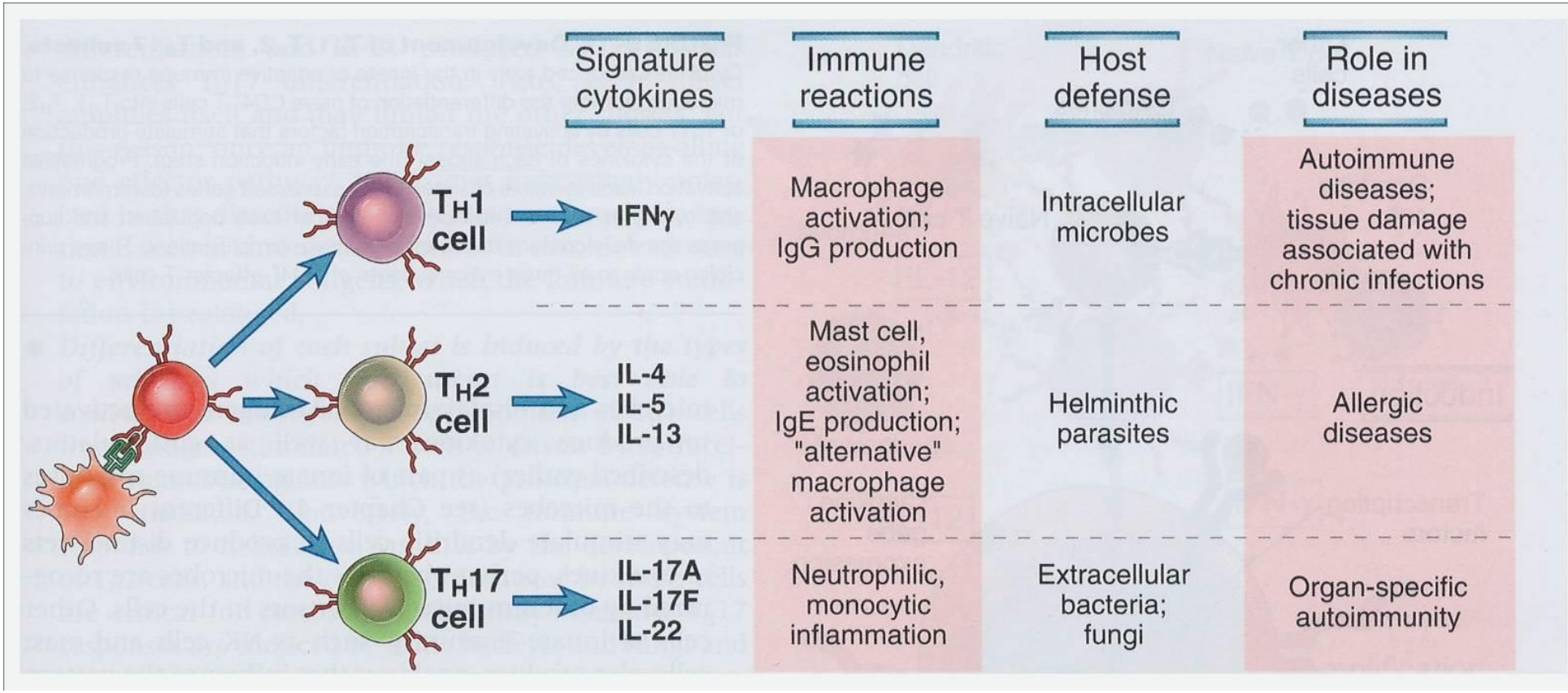
[Abbas et al, 2011]

Activation, expansion and differentiation of CD4+ helper T-cells and CD8+ cytotoxic T-cells



[Abbas et al, 2011]

Distinct subsets of CD4+ T-cells



[Abbas et al, 2011]

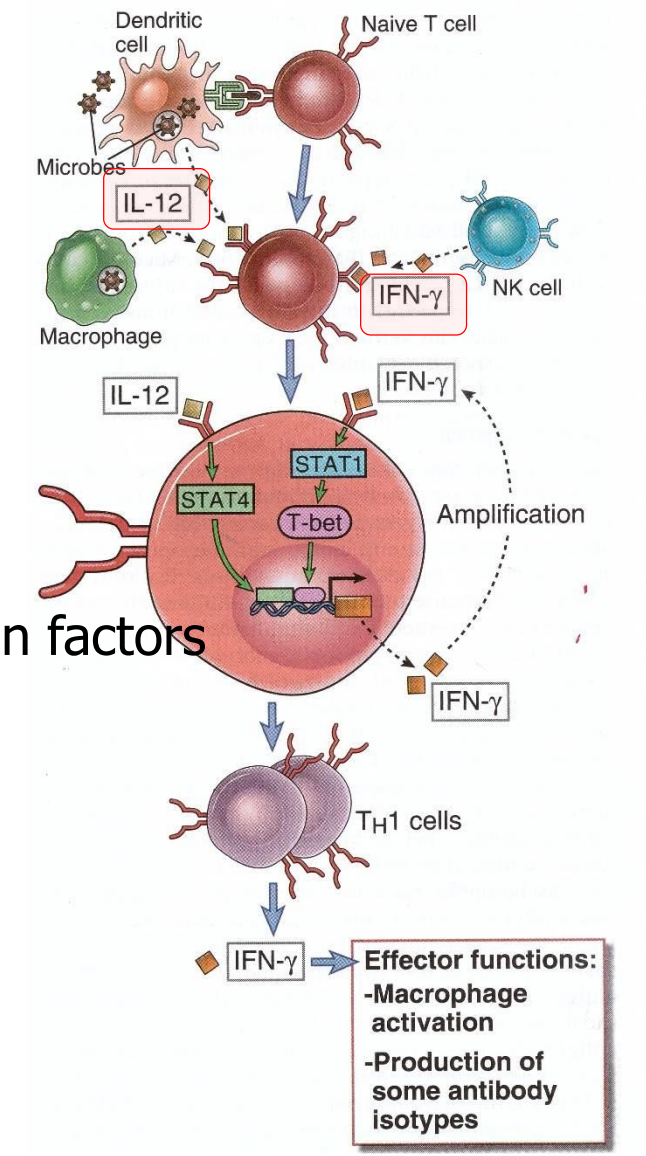
Factors influencing recipient T-cell differentiation Following transplantation

- the immune status of the recipient at the time of transplantation
- the degree of ischemia-reperfusion injury
- the degree of donor recipient mismatch
- the antigen load
- The immunosuppressive regimen used

[Wood et al, Transplantation 2012]

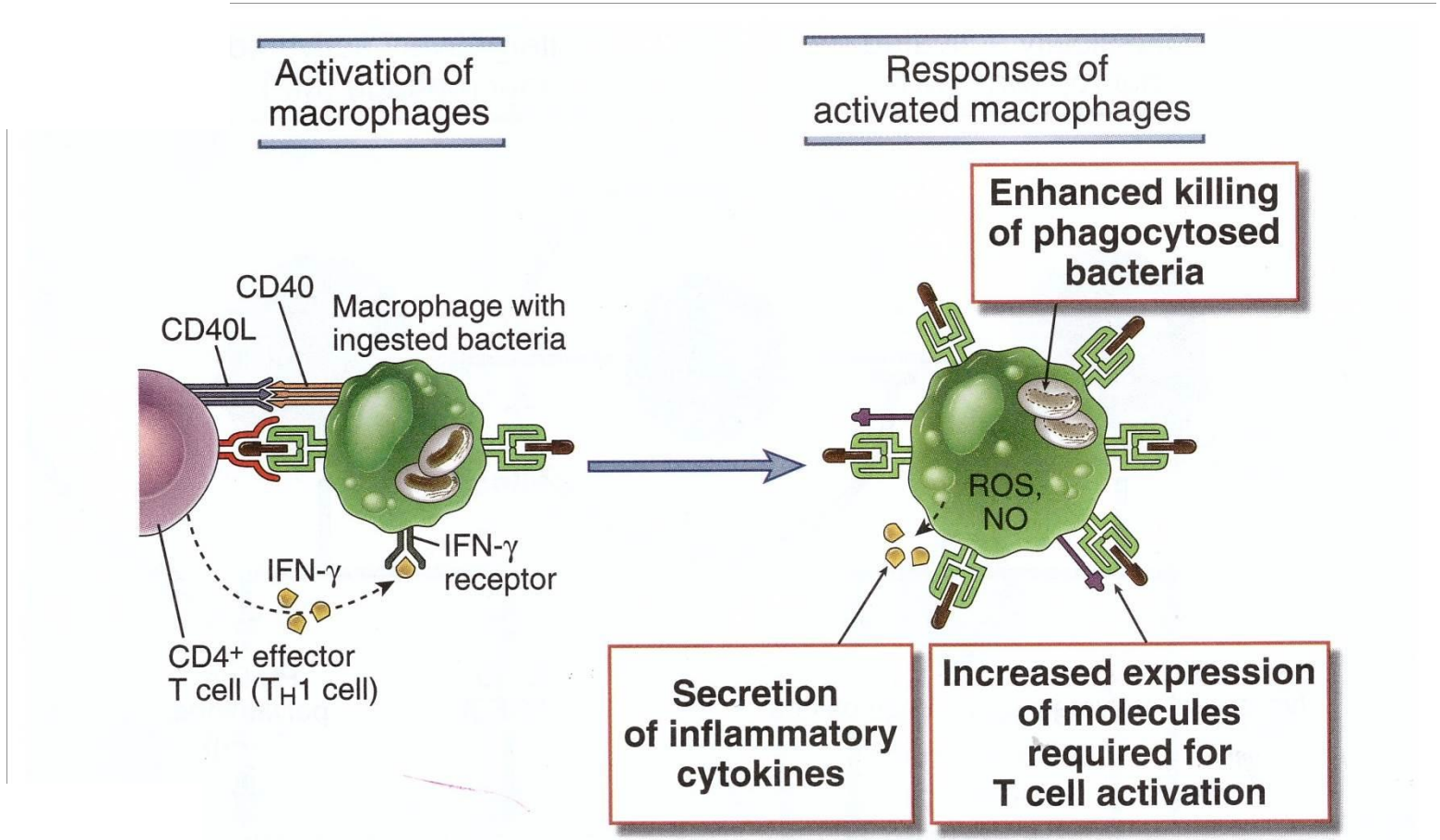
Th1 differentiation by IL-12 and IFN-γ

Transcription factors



[Abbas et al, 2011]

Macrophage differentiation by $T_H1$cells



[Abbas et al, 2011]

Types of Immunity

	INNATE (natural, native)	**ACQUIRED** (adaptive, specific)
Specificity	Against microbes + damaged host cells	Against any type of antigen
Diversity	Limited	Very large
Memory	No	Yes
Reactivity against self	No	No
Cellular and chemical barriers	Skin, mucosa	Lympocytes and antibodies
Blood proteins	Complement	Antibodies
Cells involved	MΦ, Neutrophils, NK	Lymphocytes

Recognition of molecular structures by the cells involved in the innate immunity

Specificity

Pathogen-associated molecular patterns (PAMPs)
[Structures shared by classes of microbes (LPS, Flagellin)]

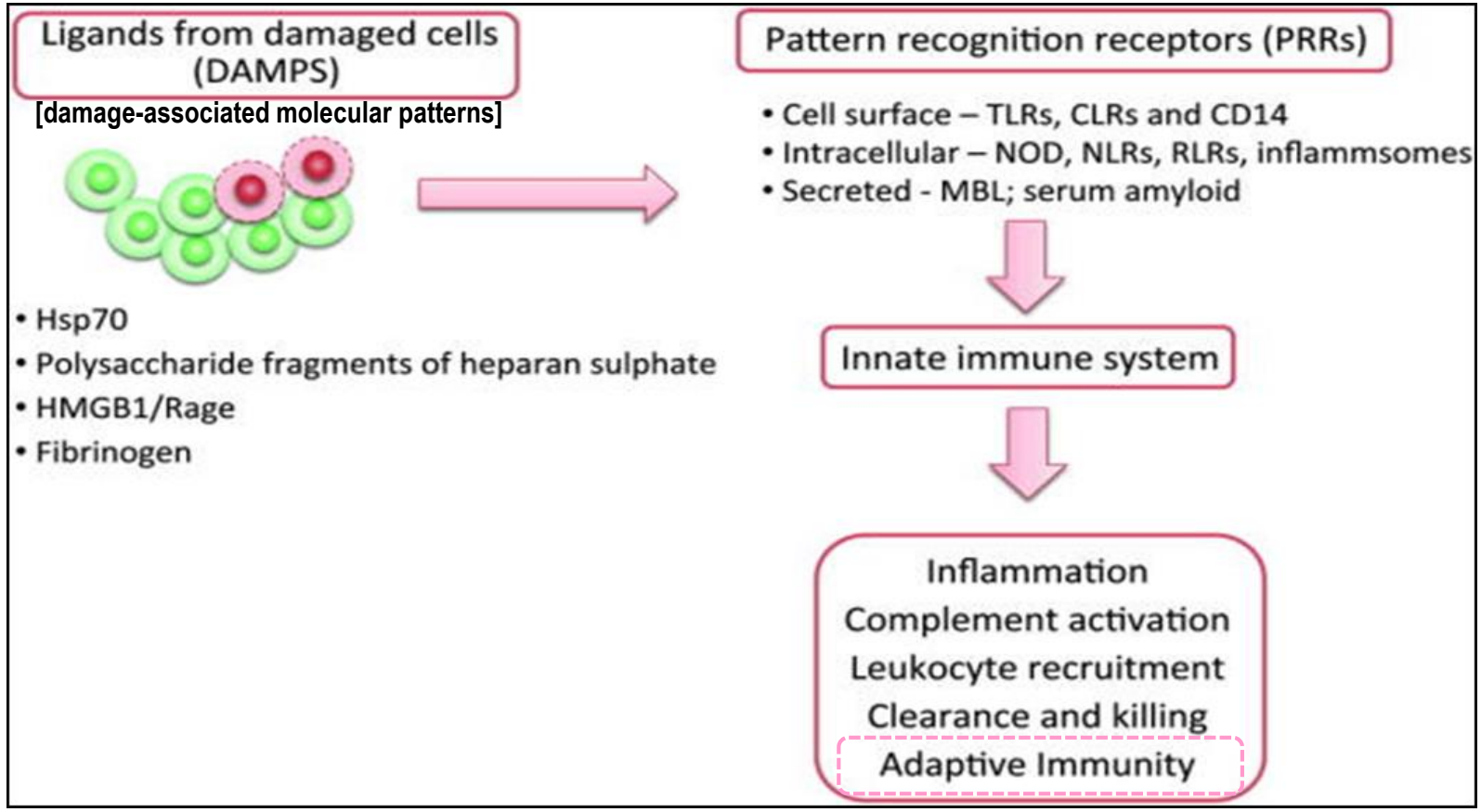
Damage-associated molecular patterns (DAMPs)
[Result of cell damage (HSP, urates…)]

Receptors

Pattern recognition receptors (PRRs)
[Encoded in germline with limited diversity (TLRs, mannose receptors…)]

[Wood et al, Transplant 2012]

The innate immunity sets the scene for rejection



Activation of the innate immune system in the early phase posttransplant is largely, a non-specific response to tissue damage

It occurs irrespective of whether there is a genetic difference between the donor and recipient

[Wood et al, Transplant 2012]

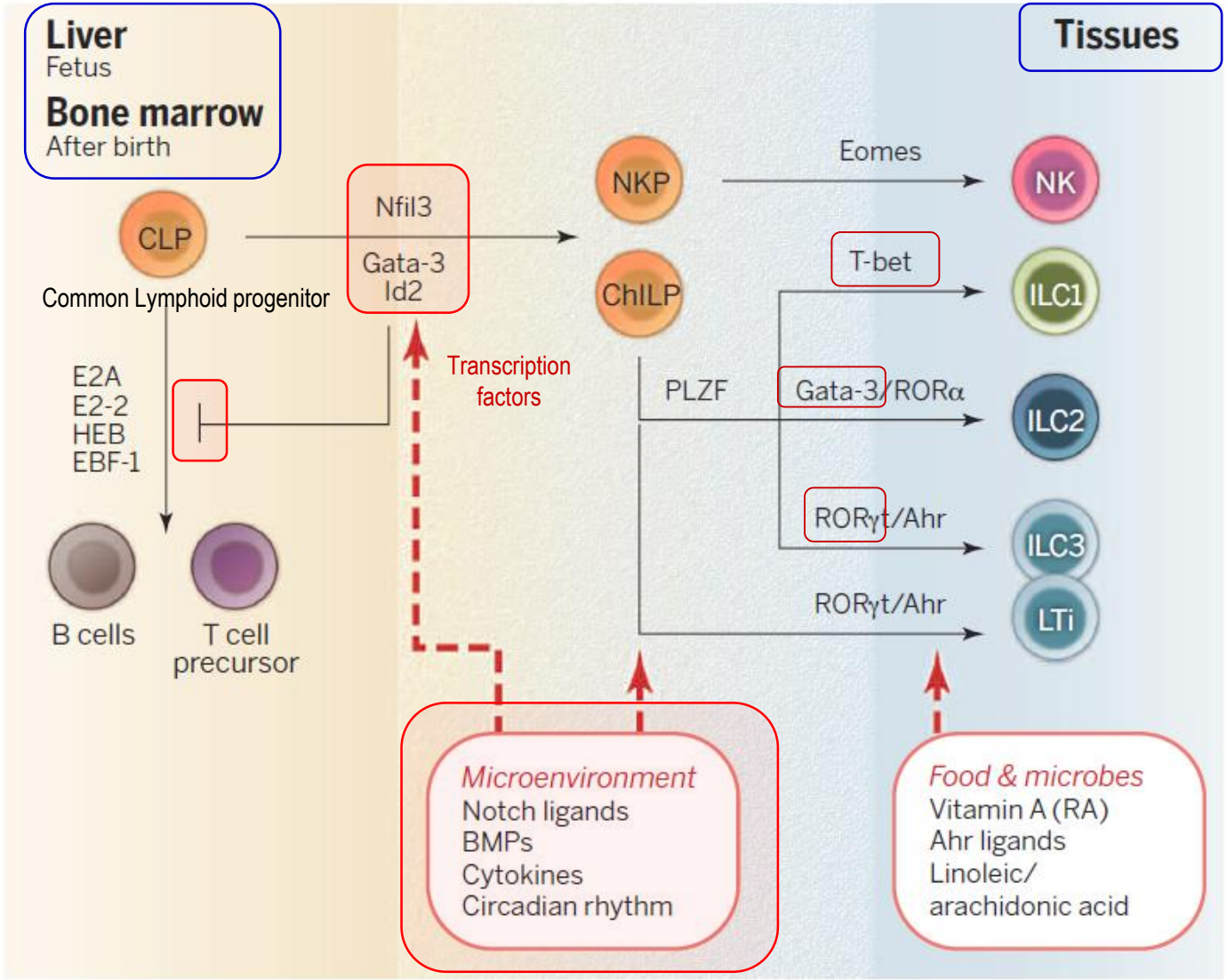
An important observation

INNATE LYMPHOID CELLS

Innate lymphoid cells: A new paradigm in immunology

[Eberl et al, Science 2015]

Development of innate lymphoid cells



[Eberl et al, Science 2015]

ILCs as *evolutionary precursors* to T cells: Similarities between ILC and T-cell differentiation

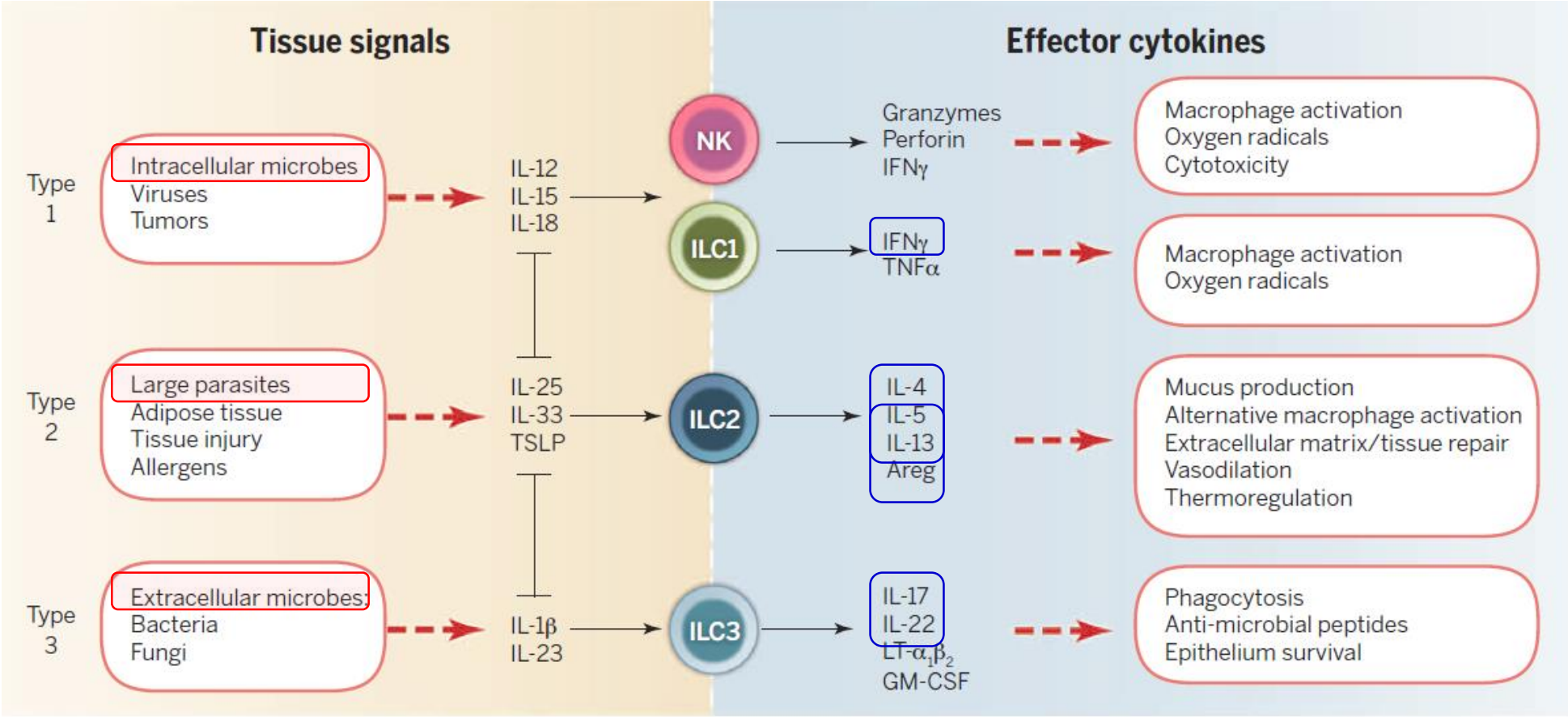
Transcription factors

TH1	T-bet	T-bet/STAT1/STAT4
TH2	Gata-3/RORα	Gata-3/STAT6
TH17	RORγt/Ahr	RORγt/STAT3

[Eberl et al, Science 2015]

ILCs translate signal cytokines into effector cytokines

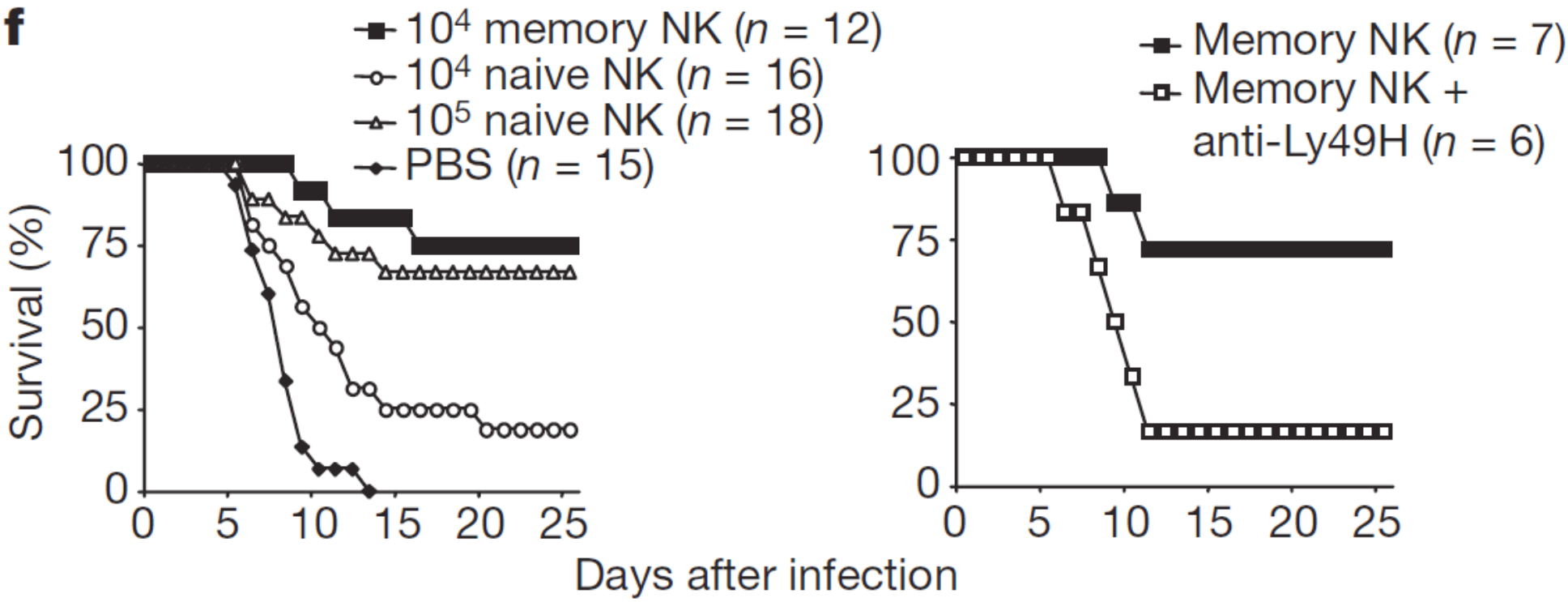
In the absence of adaptive antigen receptors (TCR), ILCs react to the microenvironment through cytokine receptors.



Effector cytokines activate local innate and adaptive effector functions

[Eberl et al, Science 2015]

Adaptive immune features of NK cells in a murine CMV model: immunological memory



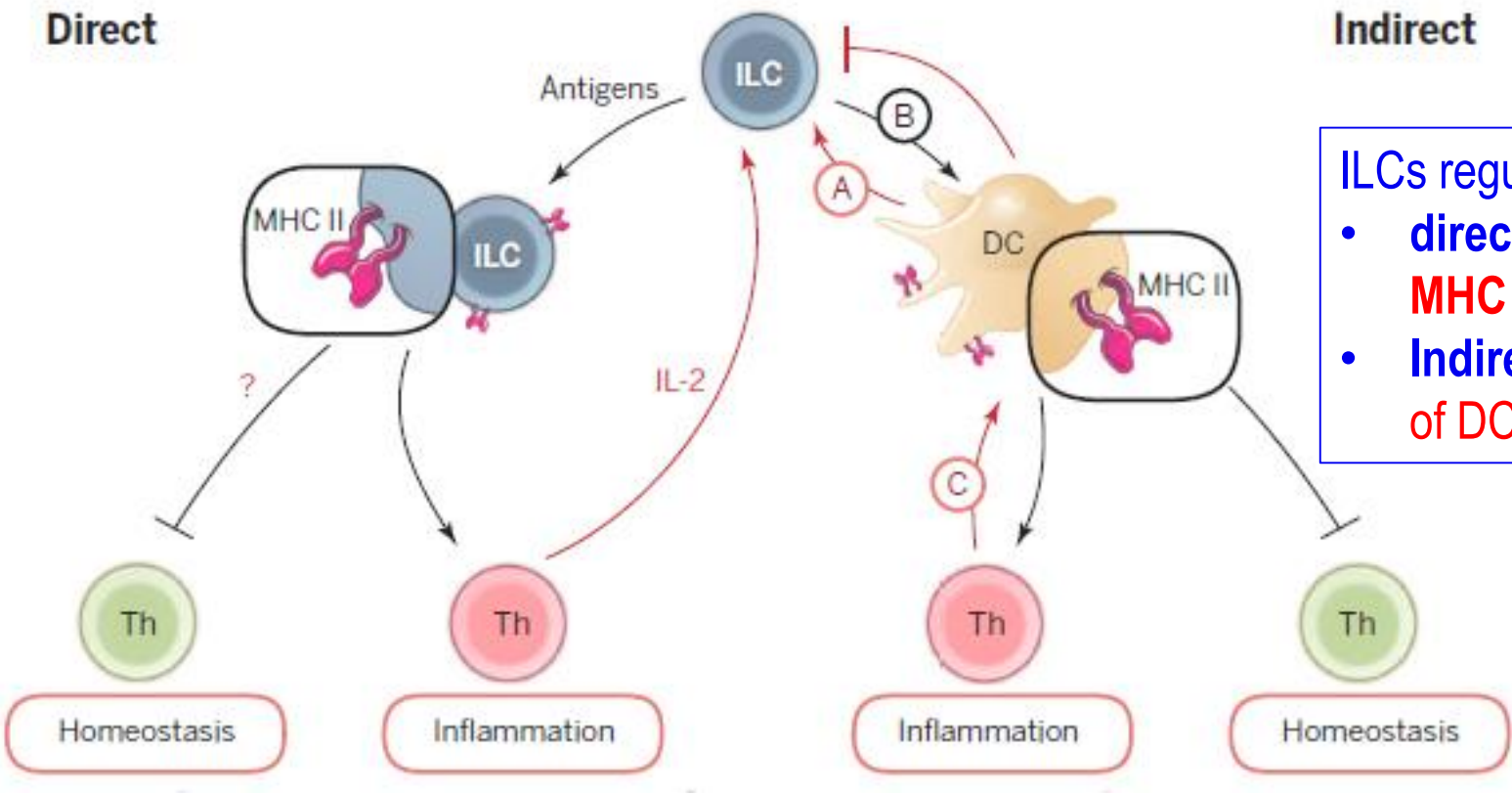
[Lanier et al, Nature 2009]

NK cells, ILCs and effector functions

- NK cells, ILC1s, ILC2s, and ILC3s mirror the cytokine production and effector functions of CD8+ T cells, TH1, TH2, and TH17 cells
- NK cells, ILCs do not undergo antigen-driven clonal selection and expansion and can act promptly like a population of memory T cells.
- As a consequence, within hours after infection or injury, the effector cytokines are produced mostly by ILCs.

[Eberl et al, Science 2015]

ILCs regulate the developing adaptive immune response

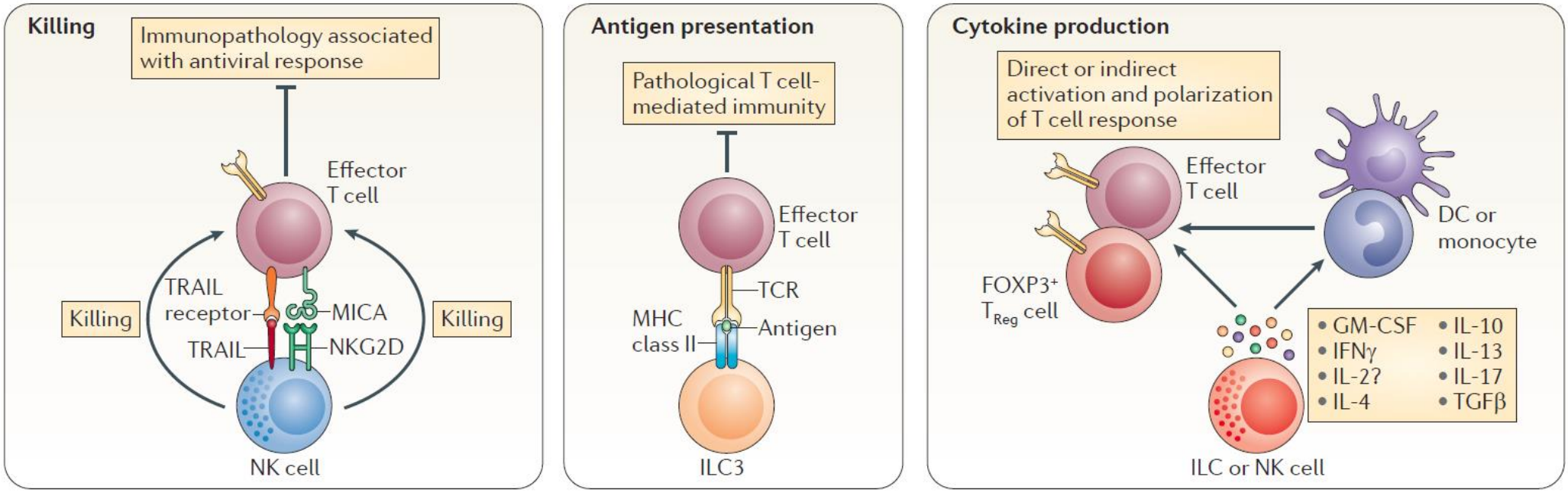


ILCs regulate the adaptive response:

- **directly** through **expression of MHC class II molecules**
- **Indirectly** through the regulation of DCs.

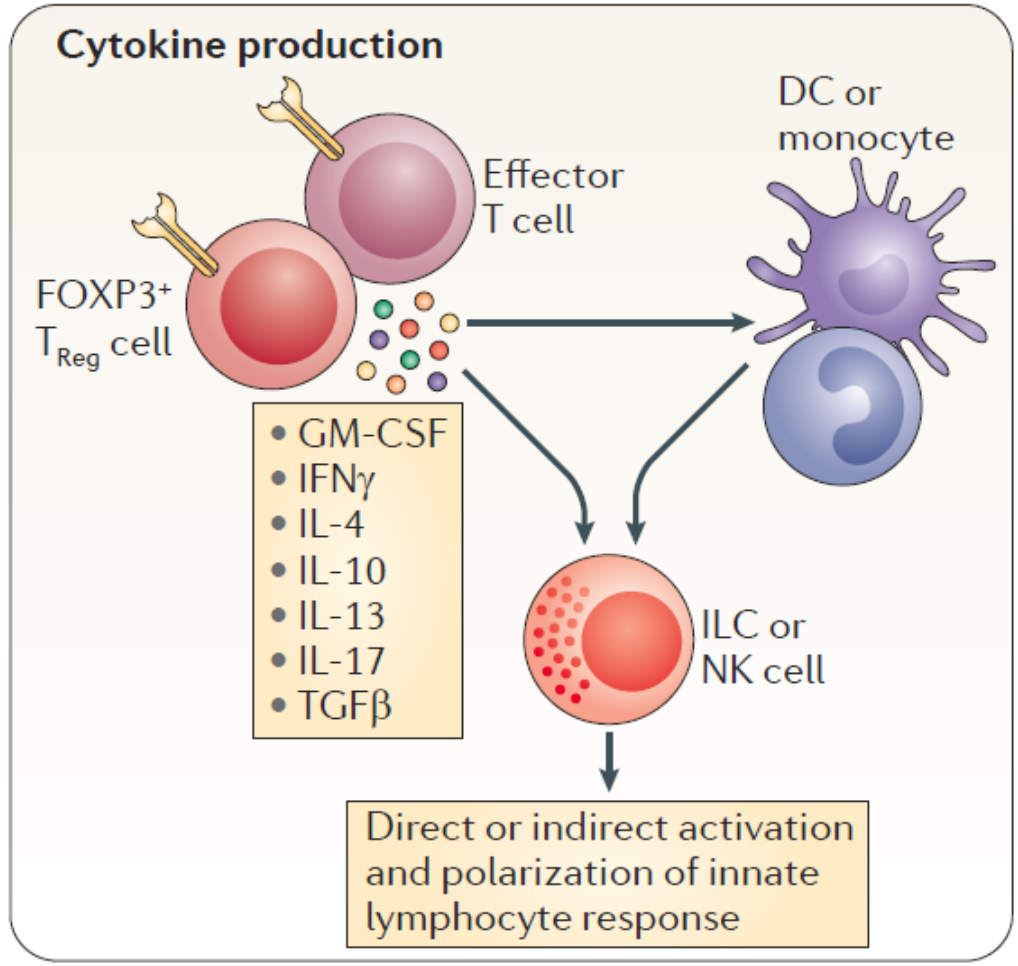
[Gasteiger et al, Nature Review Immunology 2014]

Innate regulation of adaptive immune responses



[Gasteiger et al, Nature Review Immunology 2014]

Adaptive regulation of innate immune responses



[Gasteiger et al, Nature review Immunology 2014]

Conclusioni

- La molecola HLA e l'immunità T cellulare rimangono centrali al processo di rigetto dell'organo trapiantato.
- In particolare il mismatch per l'HLA ed i DSA (al di sopra di un livello soglia di MFI) hanno un impatto negativo sull'esito del trapianto.
- In quest'ambito non va dimenticato il ruolo giocato dalla immunità naturale, *prima linea di difesa essenziale*.
- La linea di demarcazione tra immunità naturale e acquisita è infatti sempre più sottile
- Appare sempre più evidente che un buon controllo dell'immunità sia naturale che specifica sia indispensabile per il progresso della medicina del trapianto.

emanuele.cozzi@unipd.it