

# Apoptosis and immune system

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Apoptosis and homeostasis

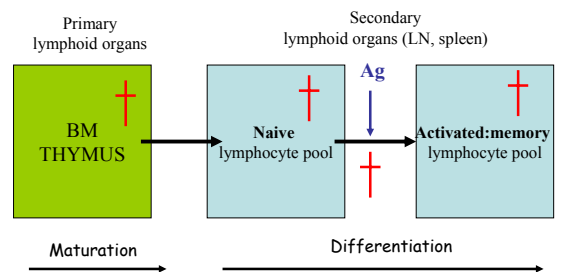
Apoptosis and effector functions

Apoptosis and Ag presentation

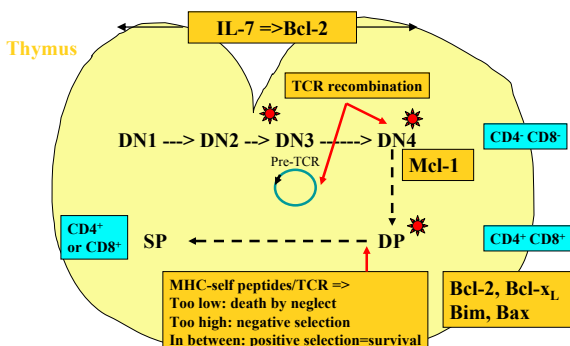
Apoptosis and pathogenesis

## Apoptosis and homeostasis

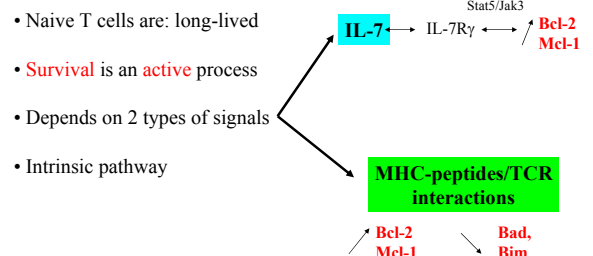
## Apoptosis: a key component of lymphocyte homeostasis



## Apoptosis and T cell development



## Apoptosis and naive T cell survival

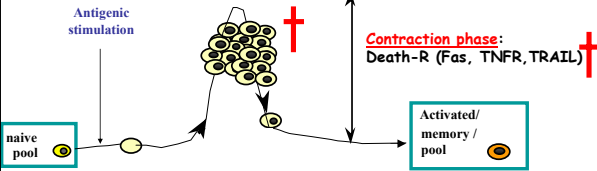


## Apoptosis and T cell immune response

**Activation phase:** IL-2 ?,  
TCR/costimulatory molecules  
Bcl-2, Bcl-x<sub>L</sub>

**Expansion phase:** perforin

**Contraction phase:**  
Death-R (Fas, TNFR, TRAIL)



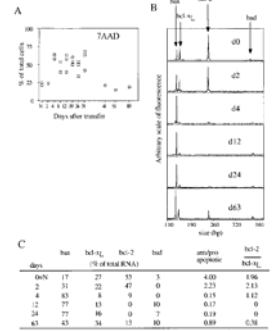
## Following the Development of a CD4 T Cell Response In Vivo: From Activation to Memory Formation

S. Garcia et al,  
Immunity, 1999, 11:163

In vivo CD4 T cell response  
against system antigen in  
mice at different times

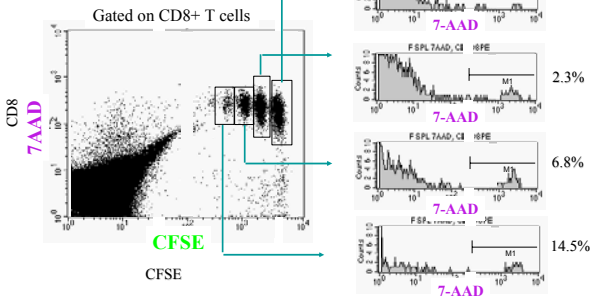
⇒

- Differential susceptibility to apoptosis:  $N = M < E$
- Correlated with levels of mRNA of anti and pro-apoptotic factors from Bcl-2 family.



## Main proliferating cells are apoptotic

CFSE/7AAD



## Apoptosis and memory T cell survival

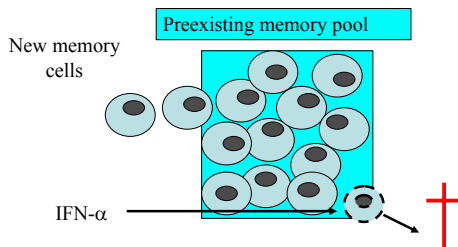
Naive T cells

Memory T cells

- Naive T cells are: long-lived
- Survival is an active process
- Depends on 2 types of signals
- Intrinsic pathway

- Memory T cells are long-lived
- Survival is an active process
- TCR-MHC? IL-7, IL-15 (CD8)
- Intrinsic pathway
- Attrition: replacement of « old » memory T cells by « new » ones. IFN-α dependent.

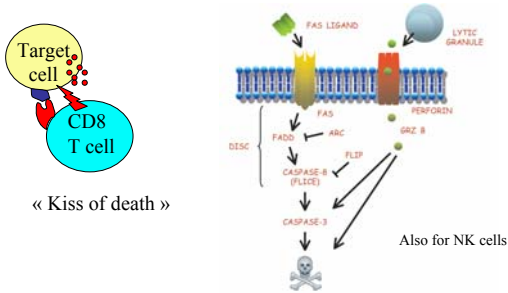
## Apoptosis and memory T cell attrition



Selin LK, Immunity, 1999, 11:733.

## Apoptosis and effector functions

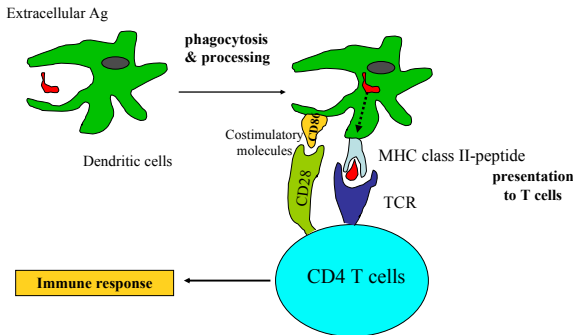
## Apoptosis and CTL effector function



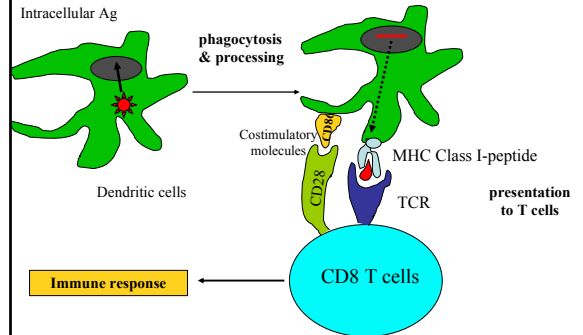
From: B. Faddel & S. Orrenius, *J Int Med*, 2005, 258:479

## Apoptosis and Ag presentation

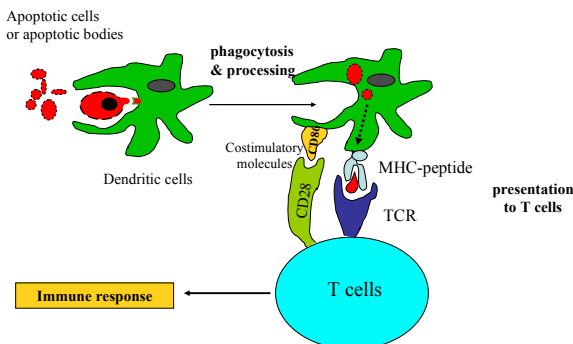
### Class II Ag presentation: extracellular Ag



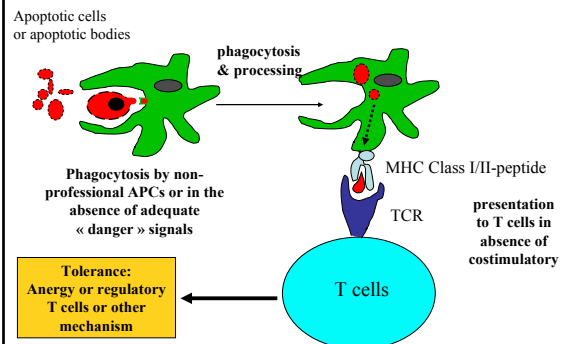
### Class I Ag presentation: intracellular Ag



### Apoptosis and Ag presentation: the cross-presentation



### Cross-presentation: immune response vs tolerance



## Apoptosis and immune pathogenesis

## Genetic defects for apoptosis in immune system and autoimmunity

Autoimmune lymphoproliferation syndromes (ALPs)	Gene mutated
Ia	Fas
Ib	Fas
Ic or Im	Fas
II	Caspase-10)
III	Molecularly undefined

• Defect in negative selection

• Defect in engulfment (absence of tolerance, chronic inflammation)

• Defect in the shutdown of immune responses (contraction phase)

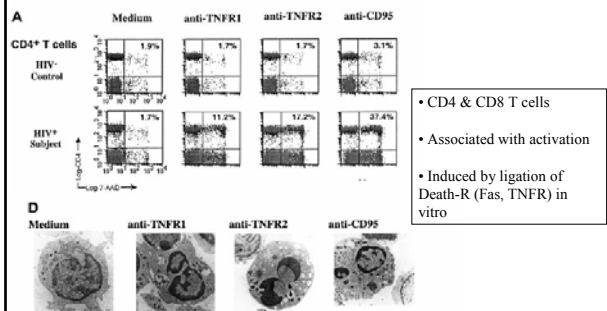
From: N. Bidère et al, Annu. Rev In Immunol, 2006, 24:321.

## Infectious diseases: the case of AIDS

- Chronic infection leading Acquired ImmunoDeficiency Syndrome.
- Due to retrovirus HIV
- Leads to progressive depletion of CD4 T cells
- Targets CD4/CCR5/CXCR4 => CD4<sup>+</sup> T cells, DC, MΦ
- Viral replication active throughout the infection in secondary lymphoid organs
- No direct cytopathogenic effect

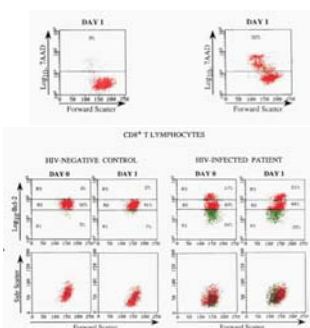
## Immunopathogenic mechanisms ?

## Increased susceptibility of HIV-infected patients lymphocytes to Death-R mediated apoptosis



L. Oliveira Pinto, S. Garcia et al, Blood, 2002, 99:1666.

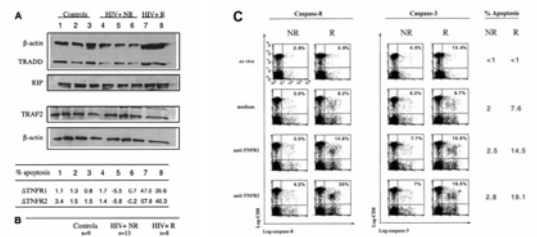
## Increase susceptibility of HIV-infected patients lymphocytes to apoptosis: role of Bcl-2



Susceptibility of CD8 T cells to die by apoptosis linked to a lower expression of Bcl-2.

Boudet et al, JI, 1996, 156:2282.

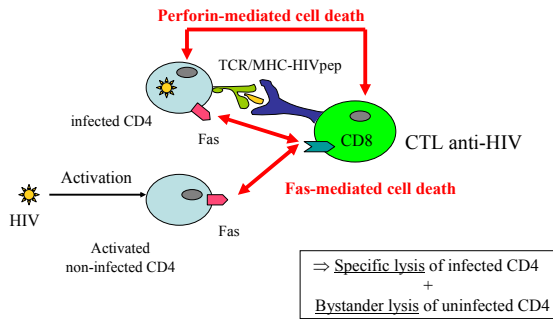
## Increased susceptibility of HIV-infected patients lymphocytes to apoptosis: role of caspases



• No difference in the expression of adaptor molecules between patients and controls.  
• Increased expression of active caspases-8 & 3.

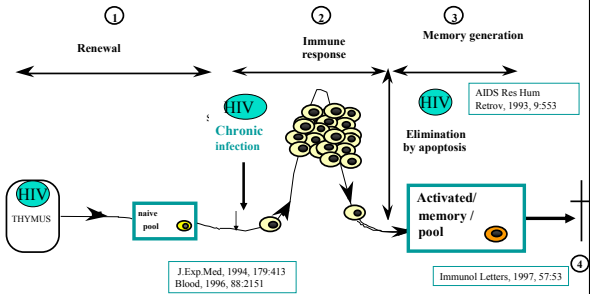
L. Oliveira Pinto, S. Garcia et al, JI, 2002, 99:1666.

## Deleterious potential effect of anti-viral CD8 T cells in CD4 T cell depletion



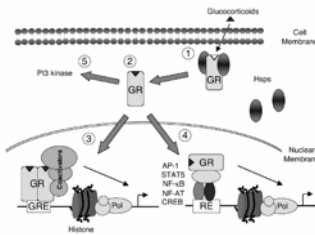
S. Garcia et al, Immunol Letters, 2002, 99:1666.

## Homeostasis of the T cell compartment during HIV infection: case of a chronic death due to chronic disease



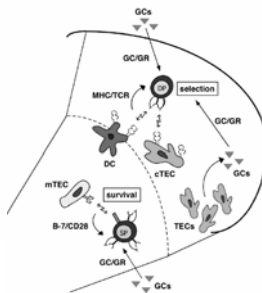
## Glucocorticoids: homeostatic regulator?

### Molecular mechanism



- Anti-inflammatory
- Immunosuppressive
- Apoptosis inducer

### Role in thymus



From: MJ Herold et al, Cell Mol Life Sci, 2006, 63:60.

## Conclusions

- Apoptosis is essential for the **development** and maintenance of **cellular homeostasis** of the immune system.
- During **development**, apoptosis ensures both the future **efficiency and self-tolerance** of lymphocyte responses.
- Maintenance of **cellular homeostasis** is crucial to ensure both the **diversity/quality and the safety** of an immune response.
- **Its control and mechanisms** depend on the **causing agent** of the death, on the **differential stage** of the cell and on **environmental conditions**.