Robert W. Franz Cancer Research Center
Earle A. Chiles Research Institute

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Immune regulation

Michael Gough PhD
Assistant Member, EACRI

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Disclosures

- No financial relationships to disclose.

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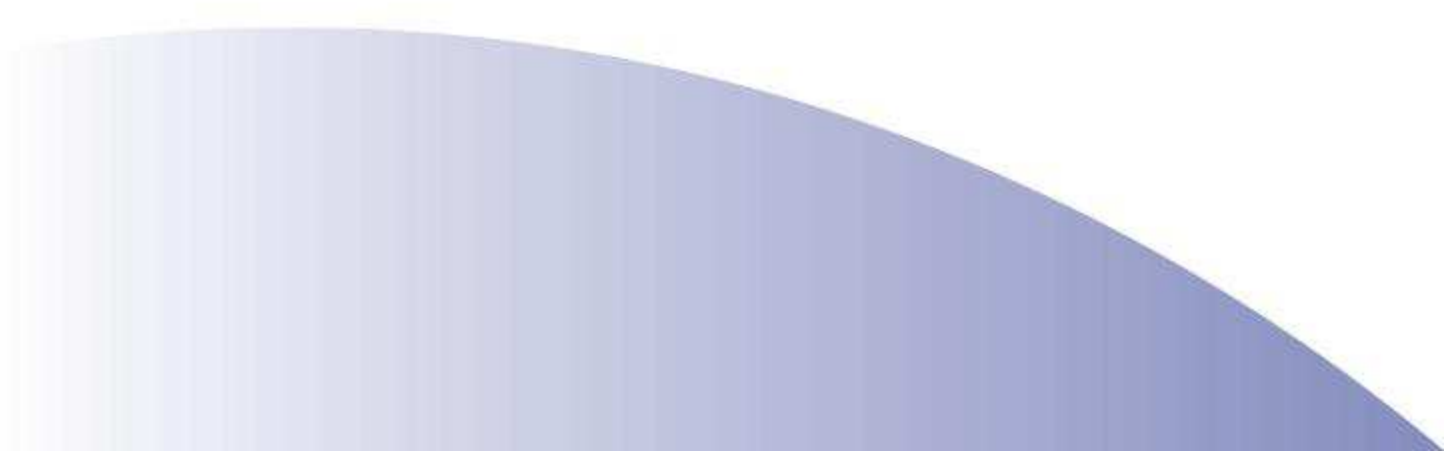
Critical issues in immune regulation

- The immune system requires multiple signals to initiate a new immune response.
- All immune responses are actively resolved, or turned off, to avoid immune pathology.
- Cancers are under a selection pressure to suppress immune responses



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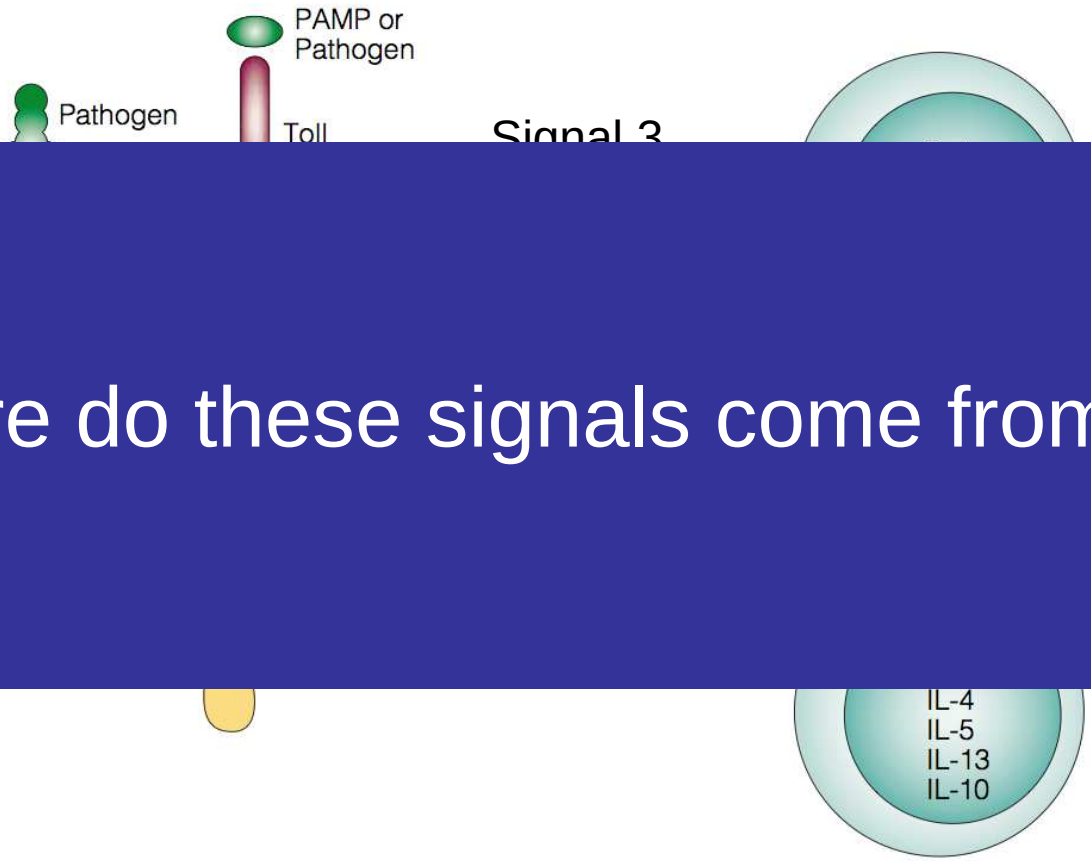
The combination of signals determines the nature of the response

THE IMMUNE SYSTEM REQUIRES MULTIPLE SIGNALS TO INITIATE A NEW IMMUNE RESPONSE.

T Cell Activation; a multi-signal process



Where do these signals come from?

Medzhitov R. *Nature Reviews Immunology* 2001

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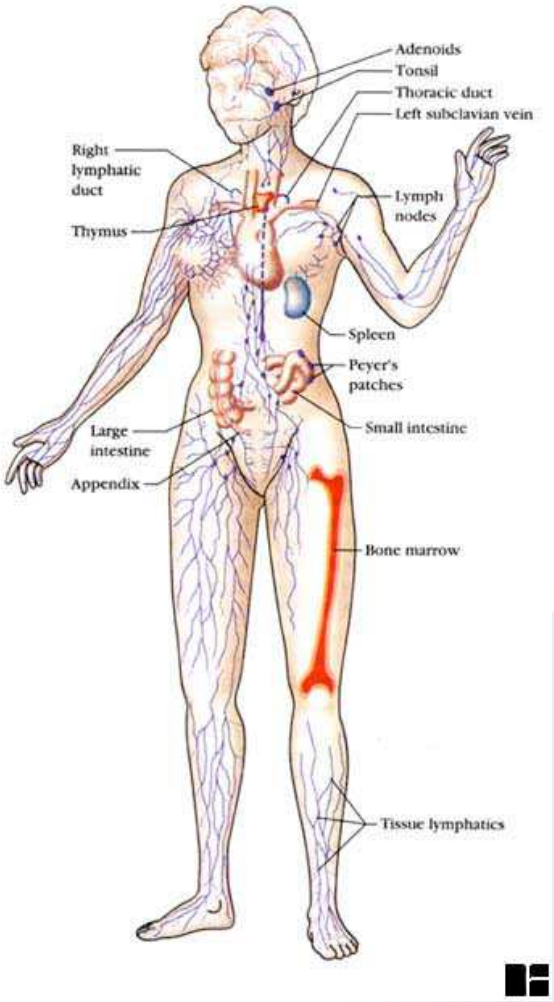
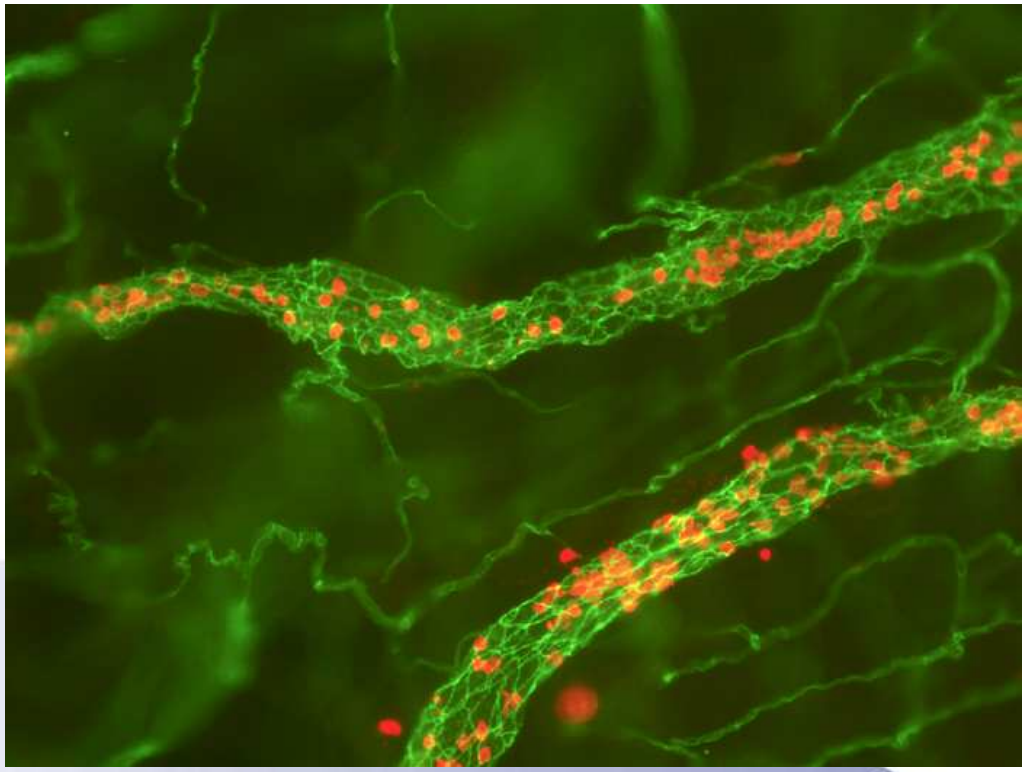
Where are the immune cells when you need them?





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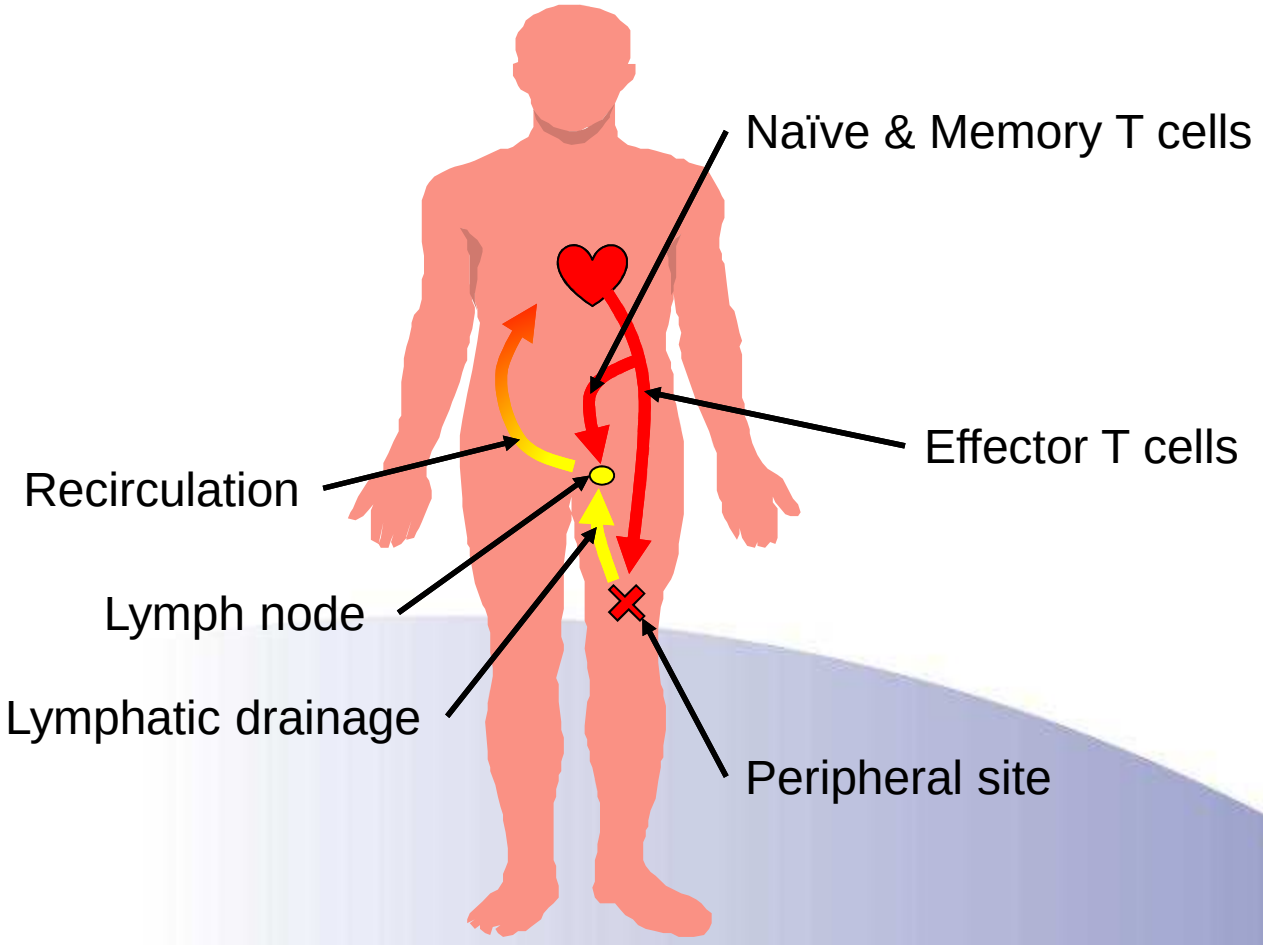
Immune recirculation



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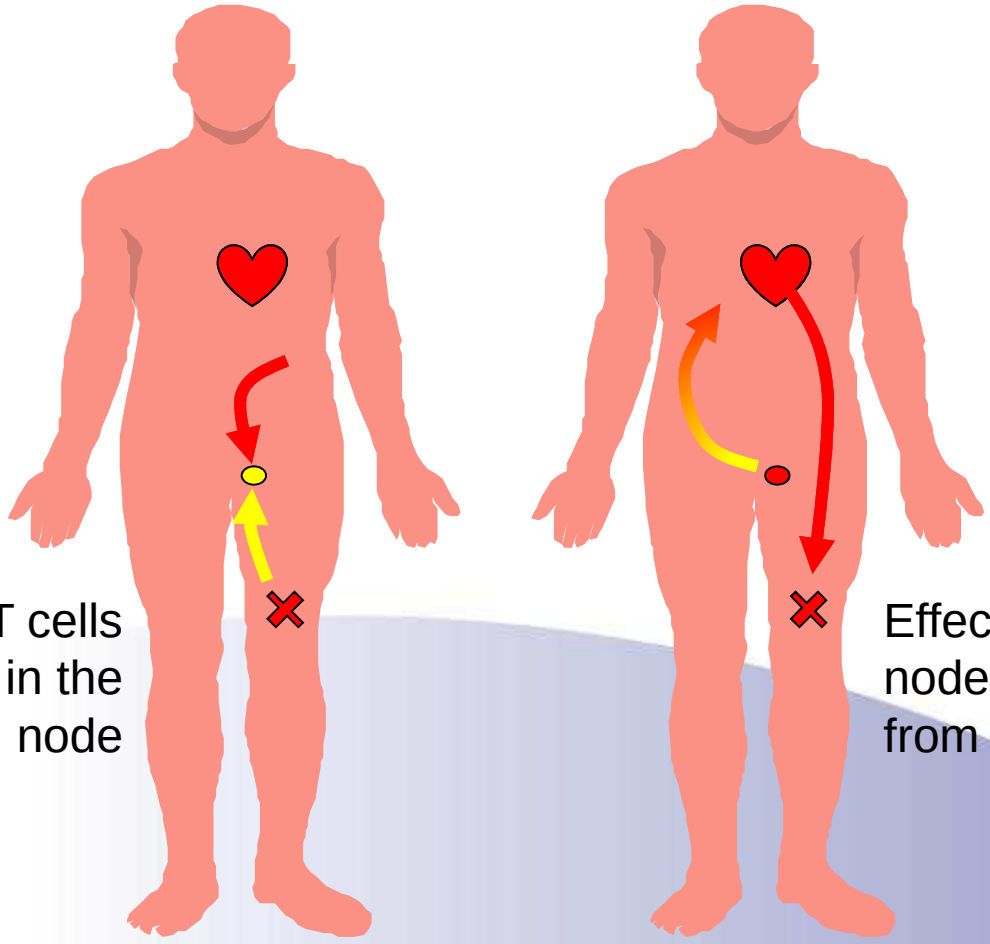
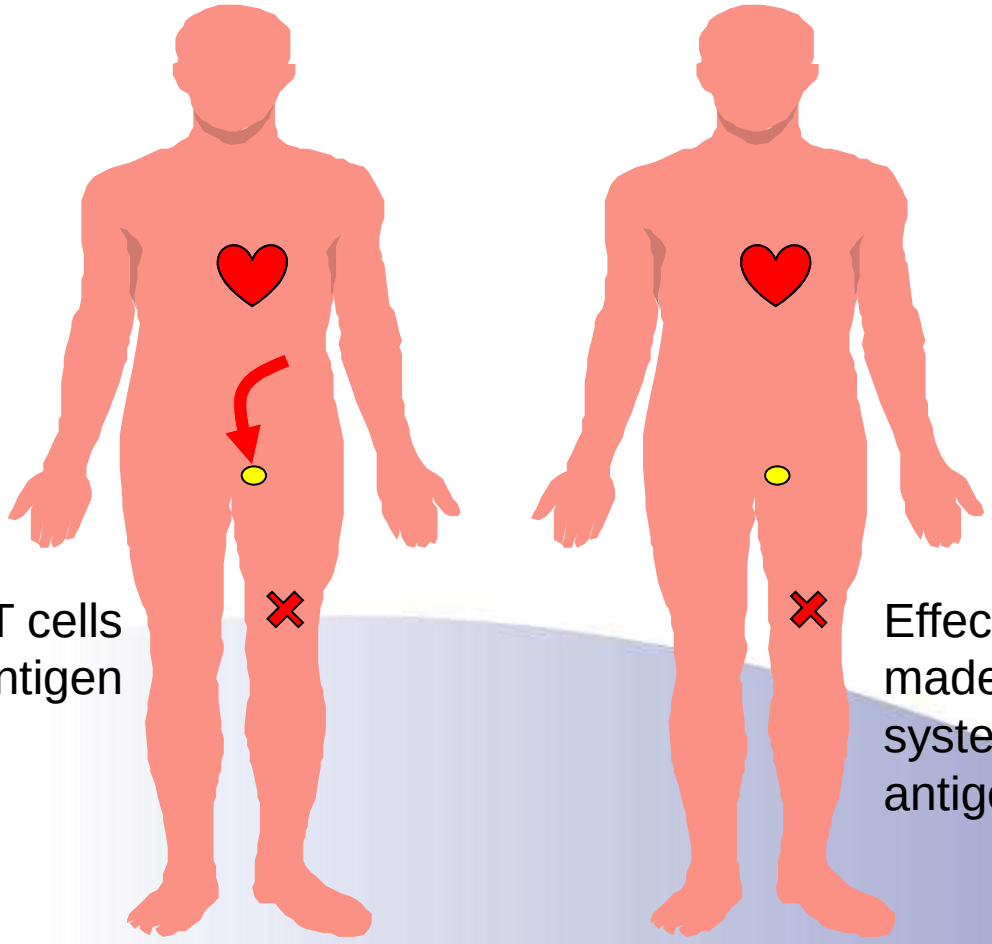
New adaptive responses start in LN



Naïve & Memory T cells meet antigen in the lymph node

Effector cells leave lymph node and enter tissues from the blood

What happens if antigen does not enter LN?



Naïve & Memory T cells do not see antigen

Effector cells are not made, the immune system is ignorant of the antigen

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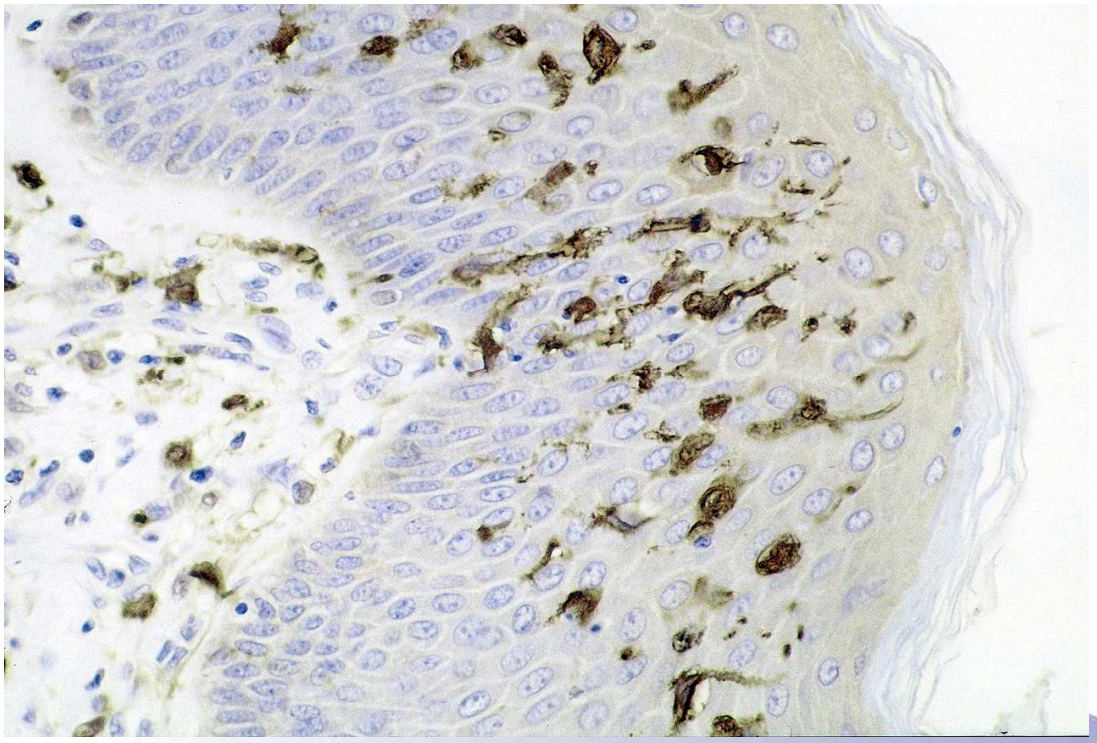
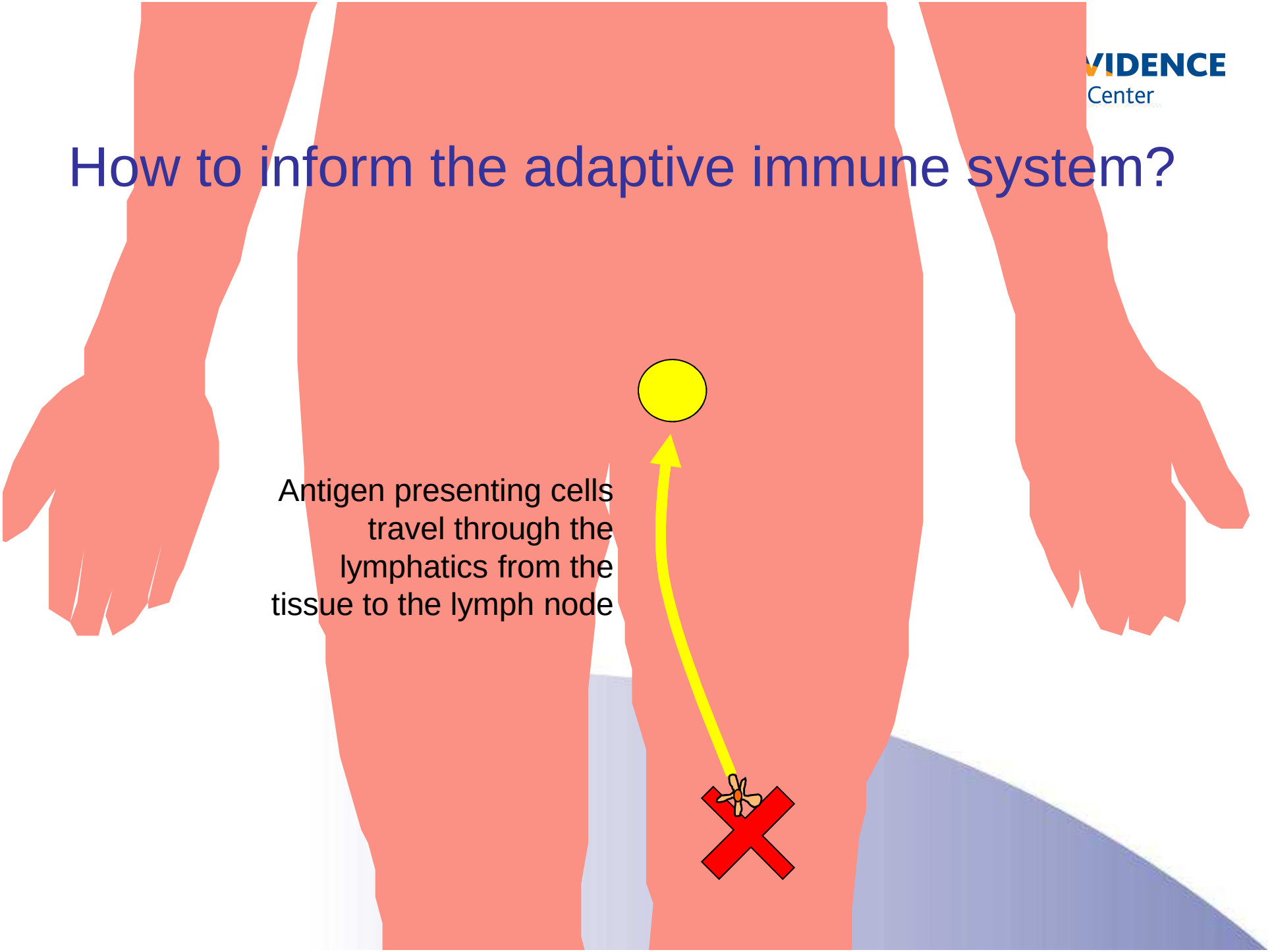
Dendritic cells as specialized reporters of infection



Wikipedia

How to inform the adaptive immune system?



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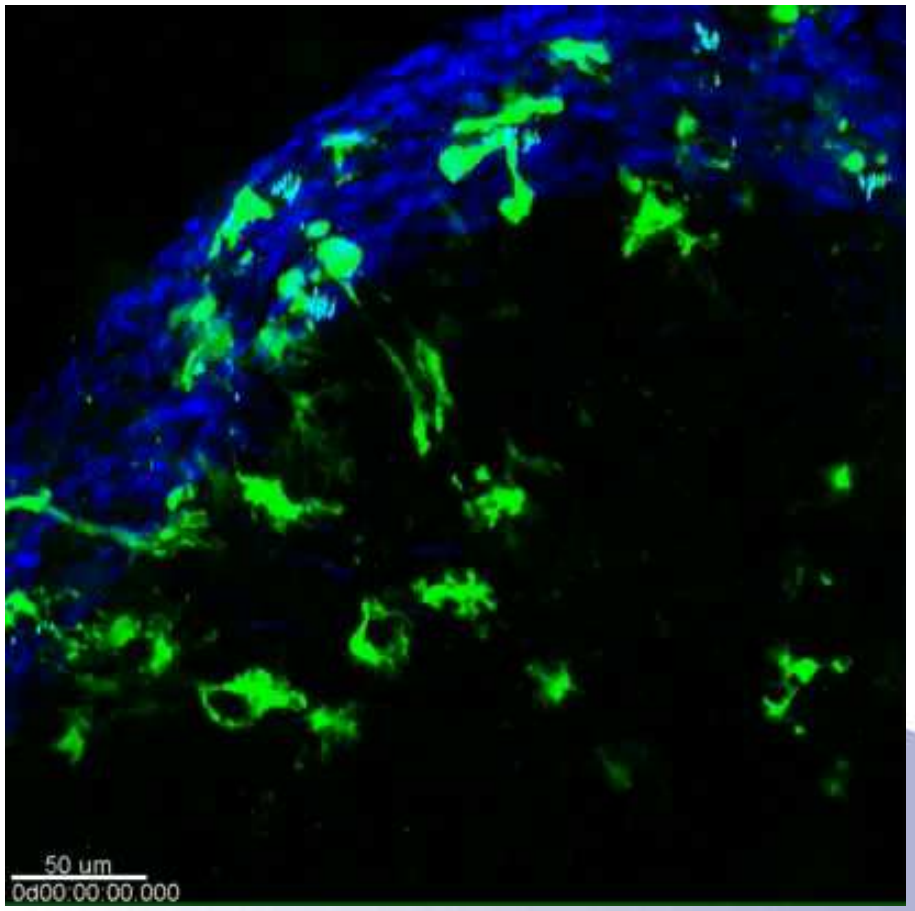
Informing the immune system of infection



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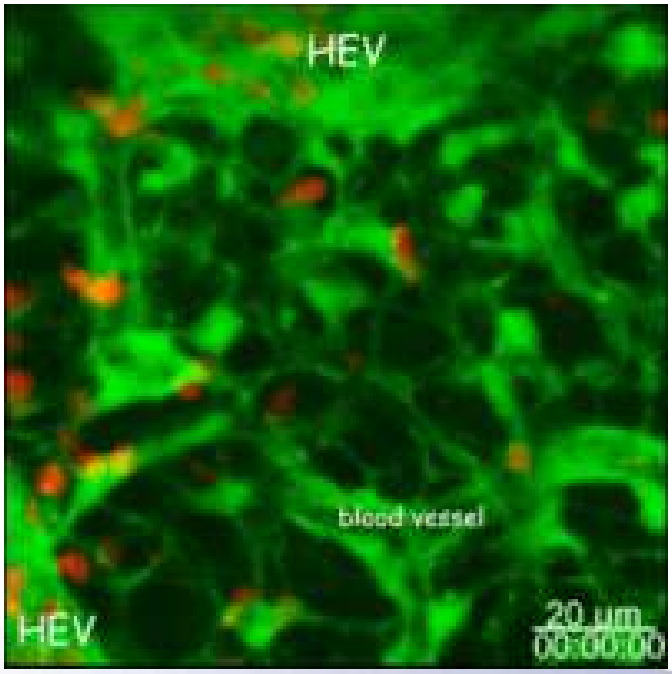
Lymphocytes patrolling the lymph node



Bajénoff, et al. 2006. Stromal Cell Networks Regulate Lymphocyte Entry, Migration, and Territoriality in Lymph Nodes. Immunity, Vol 25, 989-1001.

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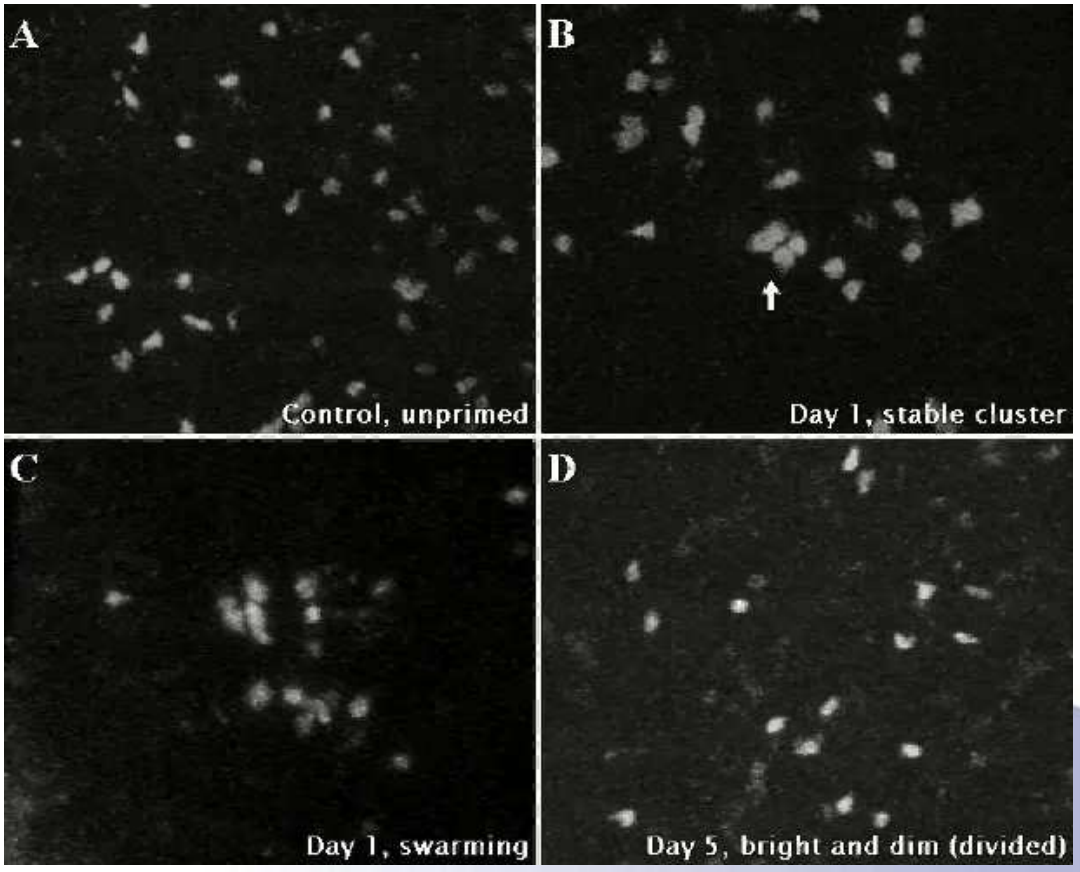
T cells in lymph node following infection



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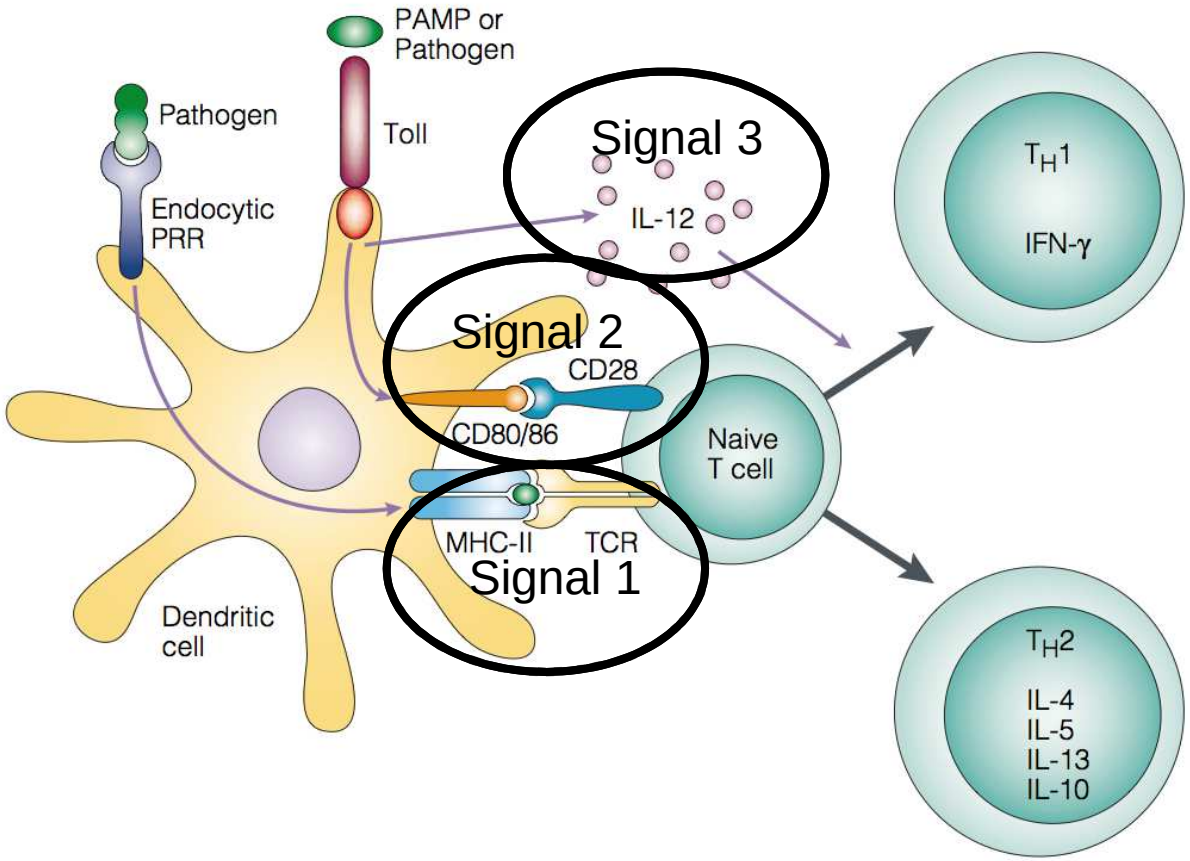
T Cell Activation; a multi-signal process



Medzhitov R. *Nature Reviews Immunology* 2001

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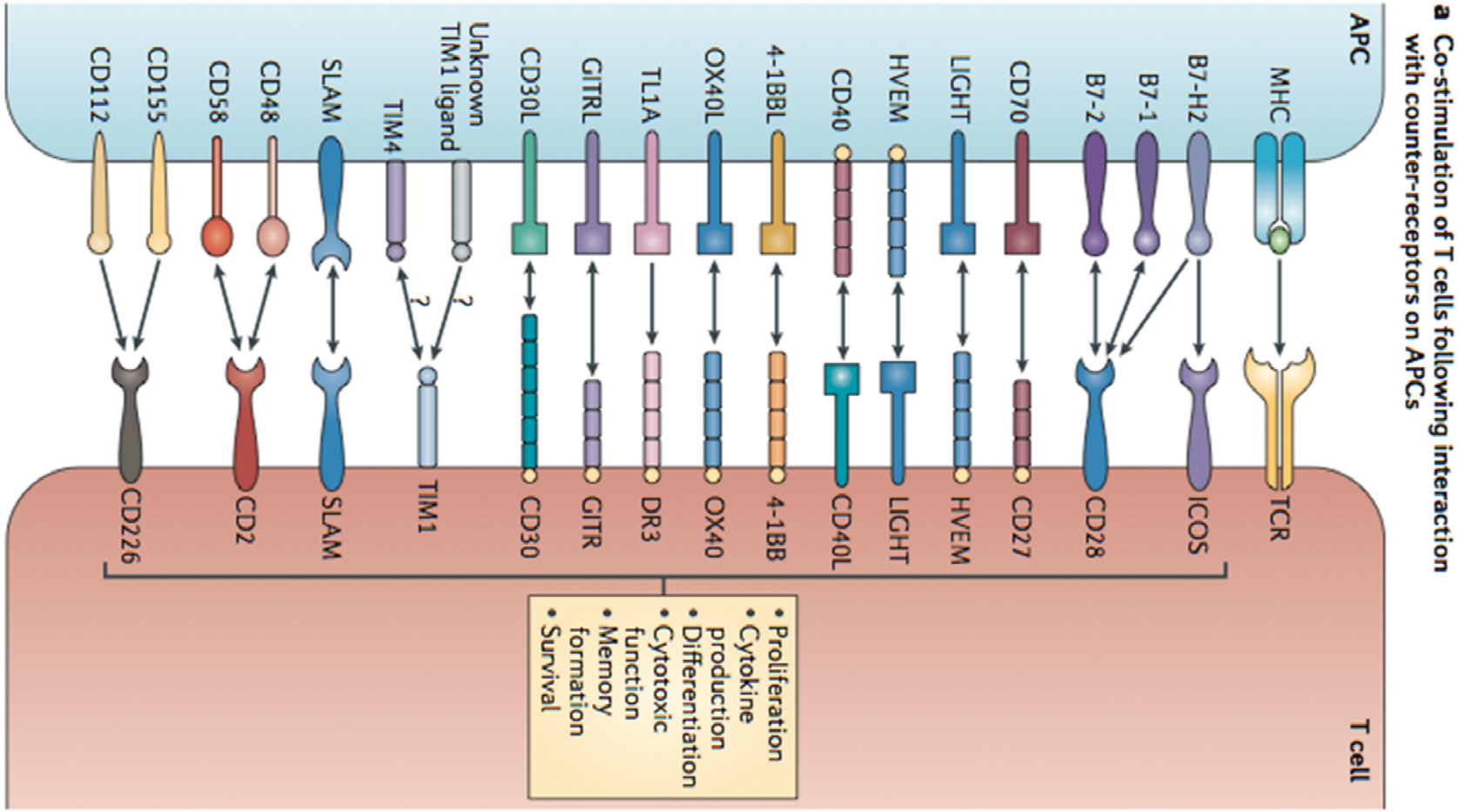
T Cell Co-stimulation Molecules



Chen & Flies. *Nature Reviews Immunology* 2013

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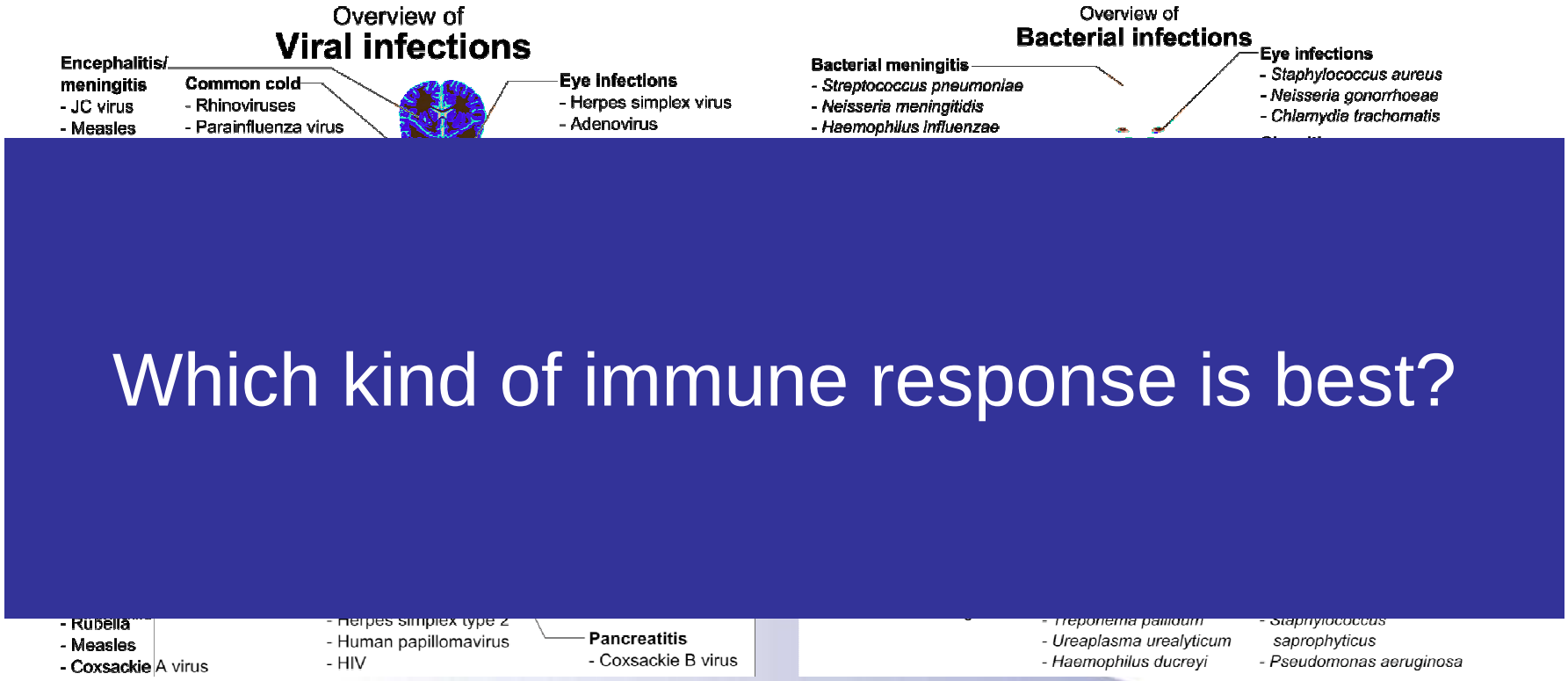
How to find the right response to an infection?



Which kind of immune response is best?

Häggström, Mikael. "Medical gallery of Mikael Häggström 2014". Wikiversity Journal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 20018762.

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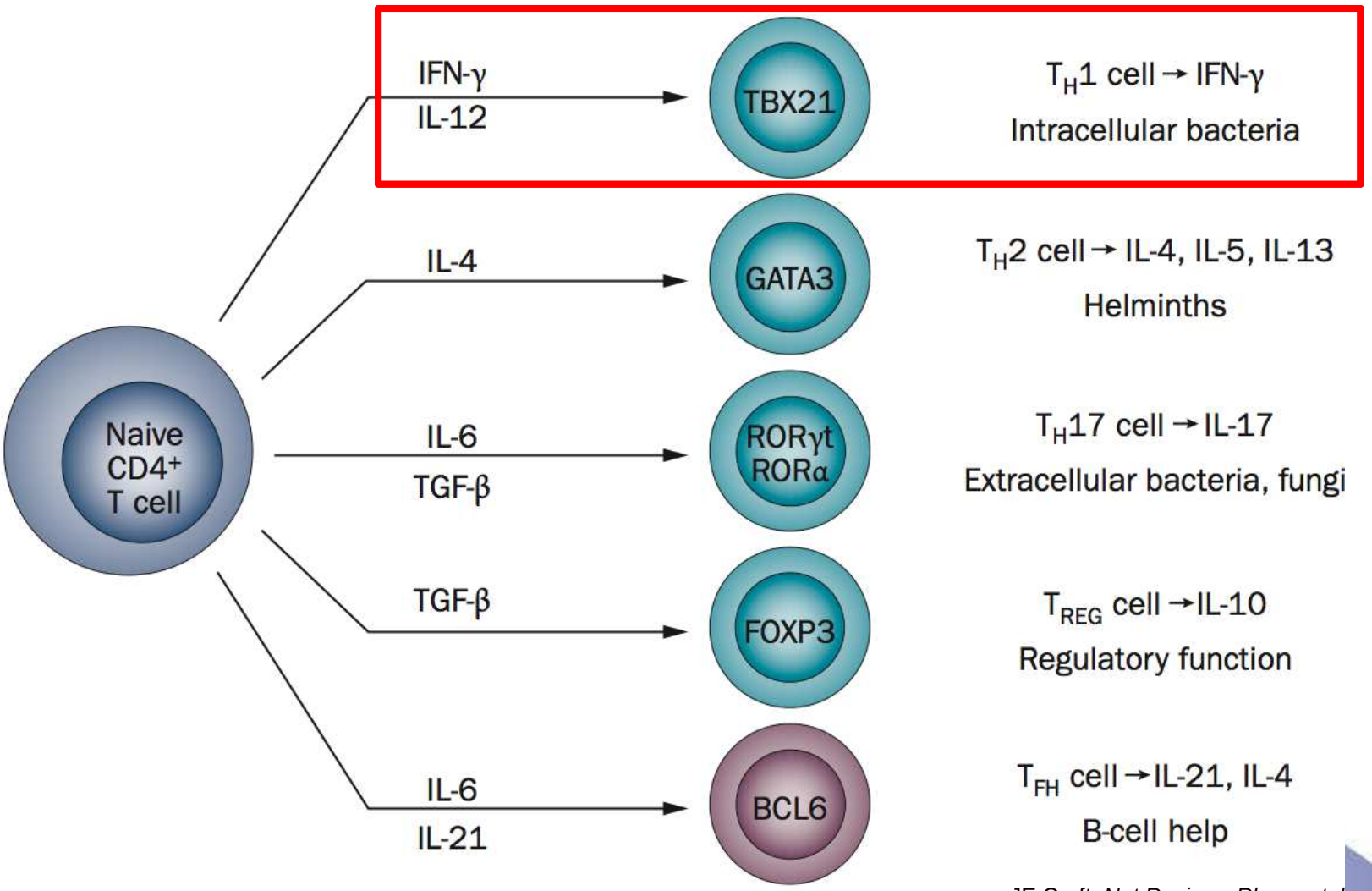
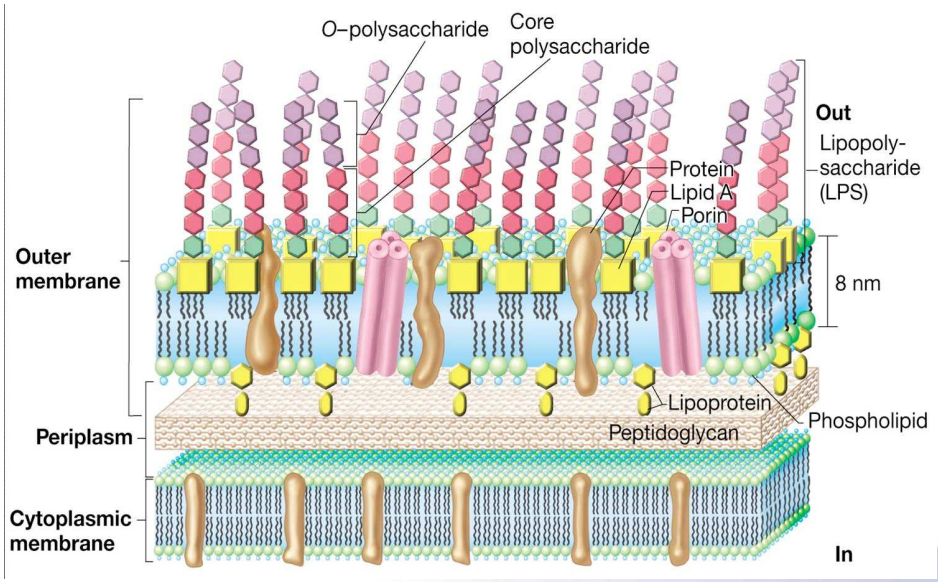
T Helper Cell Subsets: T_H1, T_H2, T_H17, T_{FH}



JE Craft. *Nat Reviews Rheumatology*. 2012

Innate short-cuts to identify infections



Brock/Madigan 10th ed.

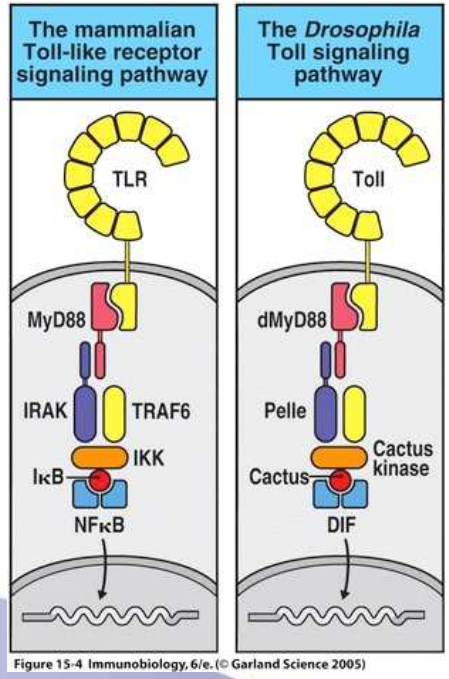


Figure 15-4 Immunobiology, 6/e. (© Garland Science 2005)

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Adaptive immunity only evolved recently

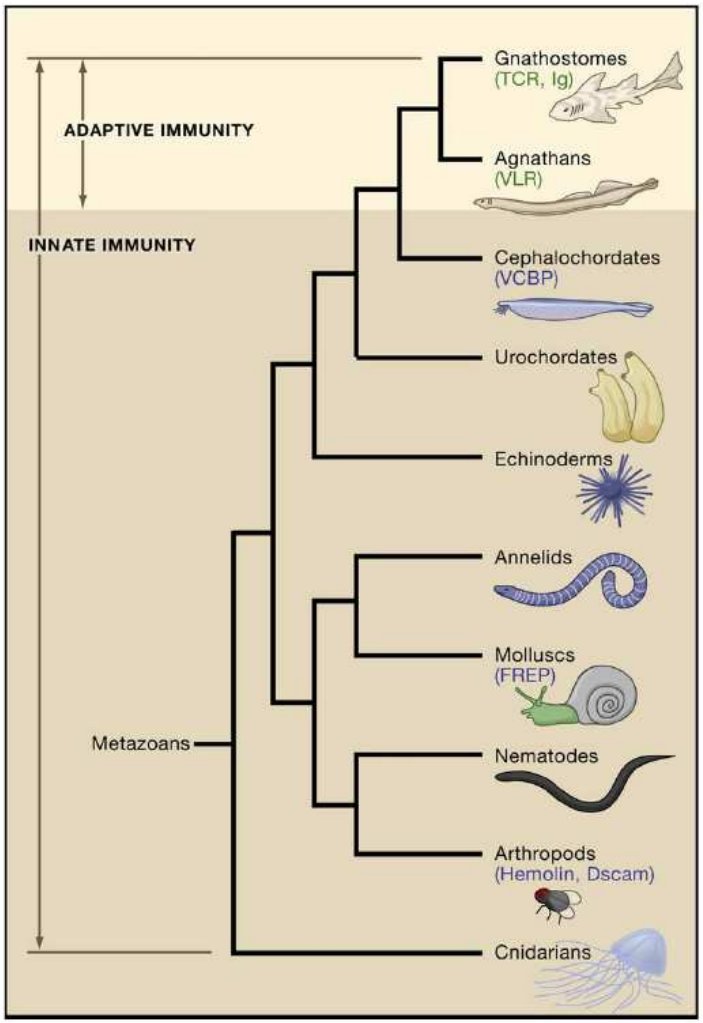

Figure 1. Phylogenetic Tree Indicating Theoretical Evolutionary Relationships of Metazoans and the Emergence of Adaptive Immunity in Conjunction with Innate Immunity

Families of immune molecules, other than Toll-like receptors, discussed in this review are indicated in blue: V type Ig domains and a chitin binding domain containing proteins (VCBP), fibrinogen-related proteins (FREPs), hemolin, and Down's syndrome cell adhesion molecule (Dscam). The recombinatorial-based immune receptors are indicated in green: T cell receptors (TCR), immunoglobulins (Ig), and variable lymphocyte receptors (VLR).

The Evolution of Adaptive Immune Systems

Max D. Cooper[1,2,*] and Matthew N. Alder[1,2]

Cell *124*, 815–822, February 24, 2006 ©2006 Elsevier Inc.

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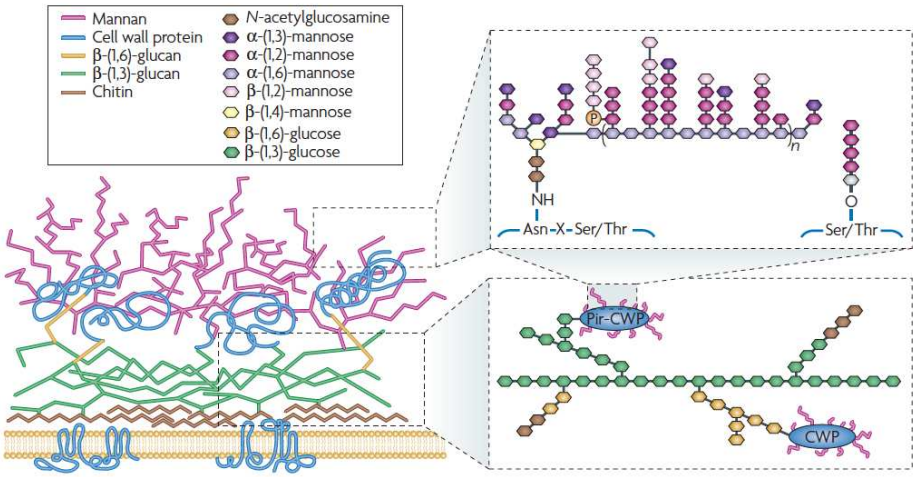
The major cells in innate immunity to *Candida*



An integrated model of the recognition of *Candida albicans* by the innate immune system

Mihai G. Netea, Gordon D. Brown[1], Bart Jan Kullberg* and Neil A. R. Gow[§]*

NATURE REVIEWS | MICROBIOLOGY
VOLUME 6 | JANUARY 2008 | 67

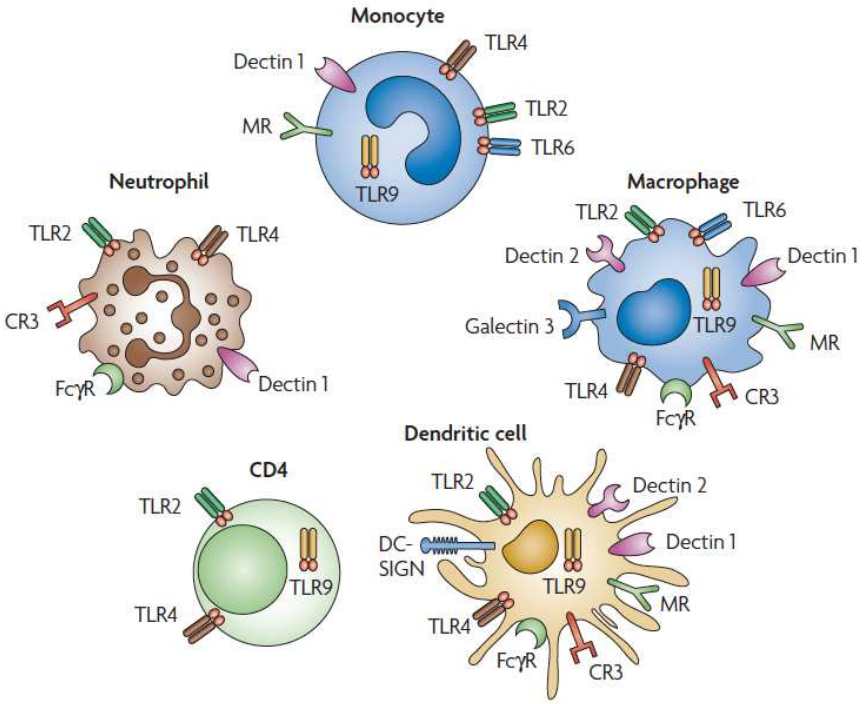


Figure 2 | **Cell populations and pattern-recognition receptors involved in *Candida albicans* recognition.** The main populations involved in the recognition of *C. albicans* during the innate immune response are the monocytes, neutrophils and macrophages. Dendritic cells are crucial for processing of, and antigen presentation to, T cells, and thus to activation of specific immunity. The differential expression of pattern-recognition receptors by these cell types is shown. CR3, complement receptor 3; FcγR, Fcγ receptor; MR, mannose receptor; TLR, Toll-like receptors.

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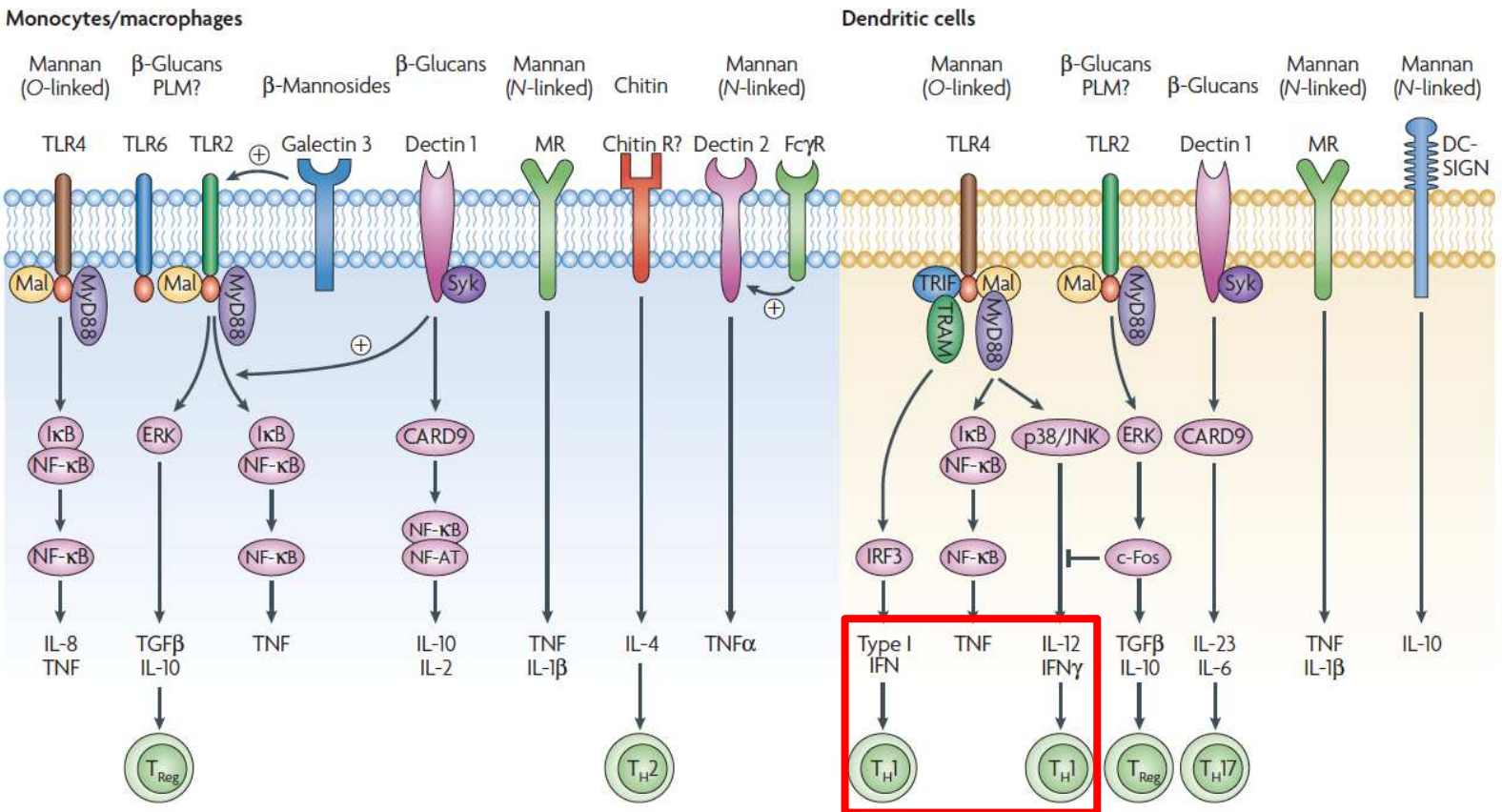
Innate signals have different consequences



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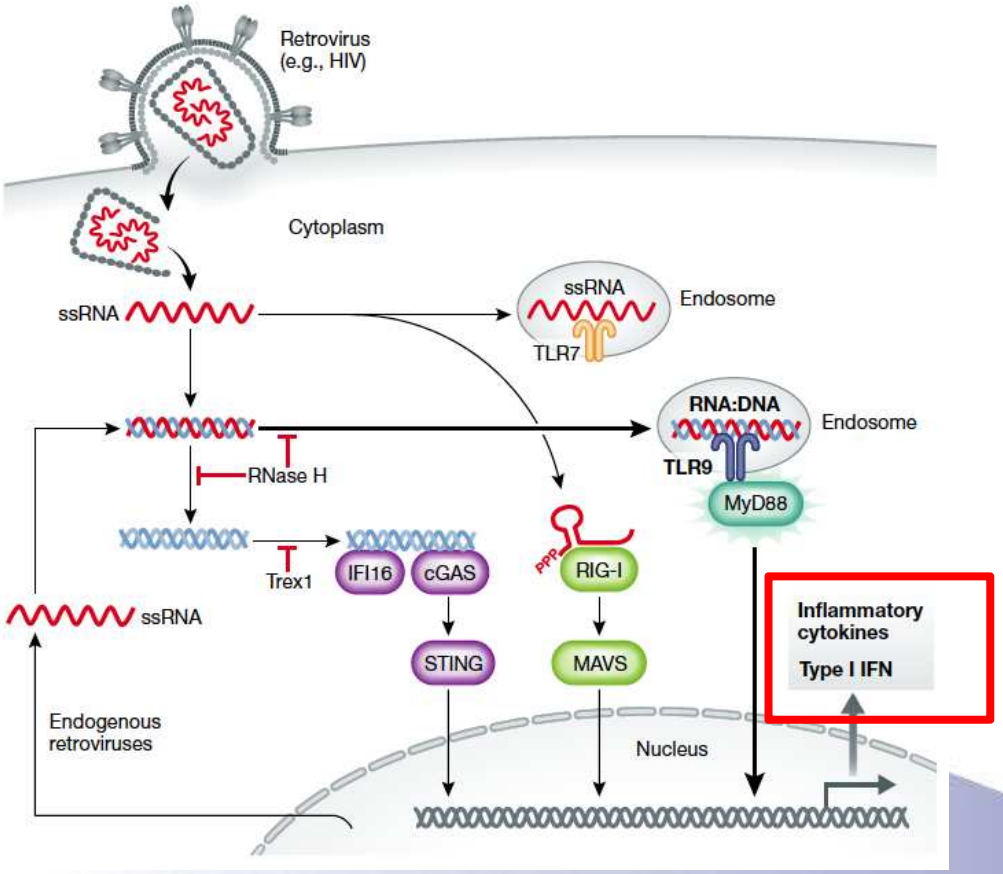
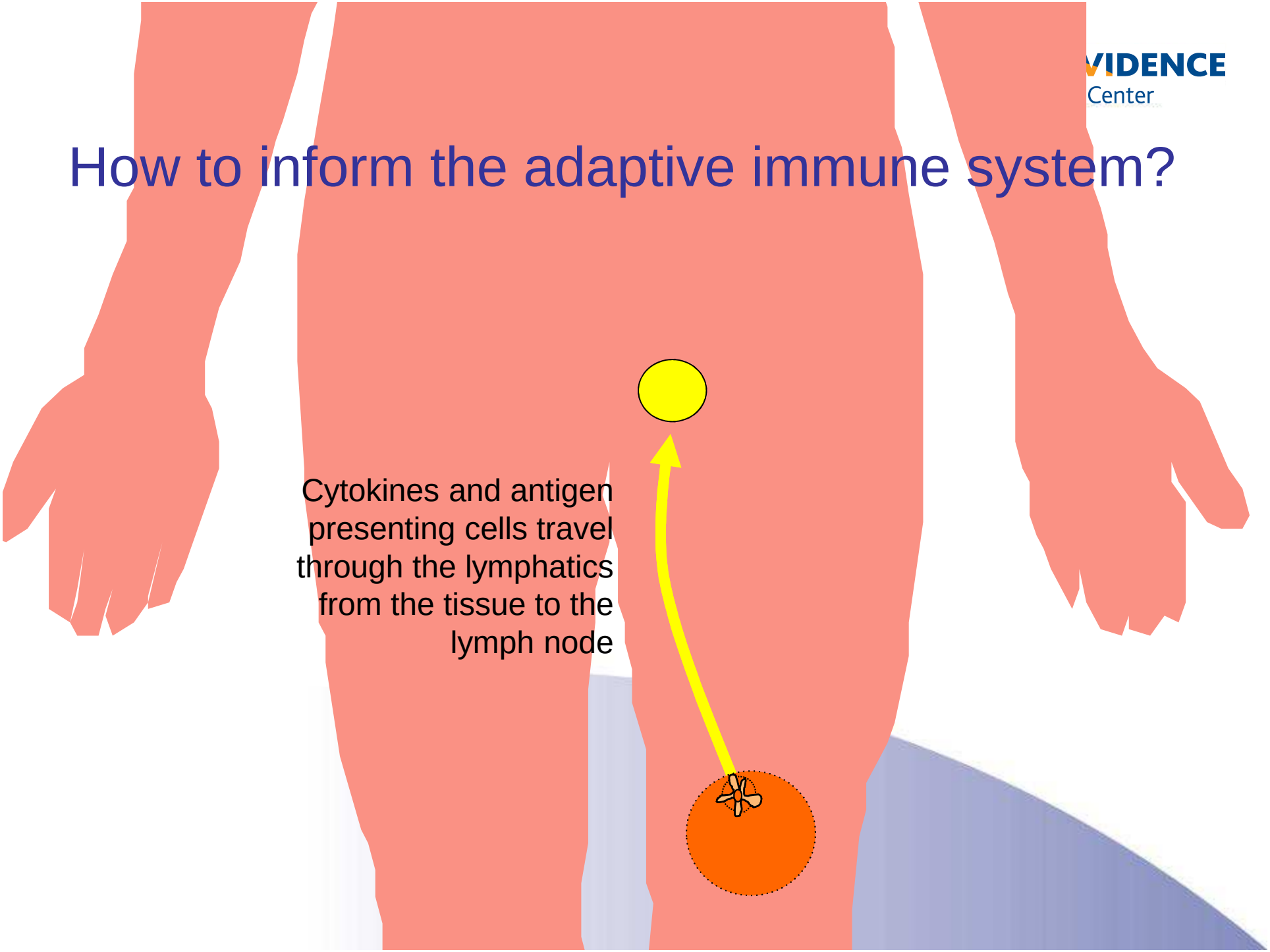
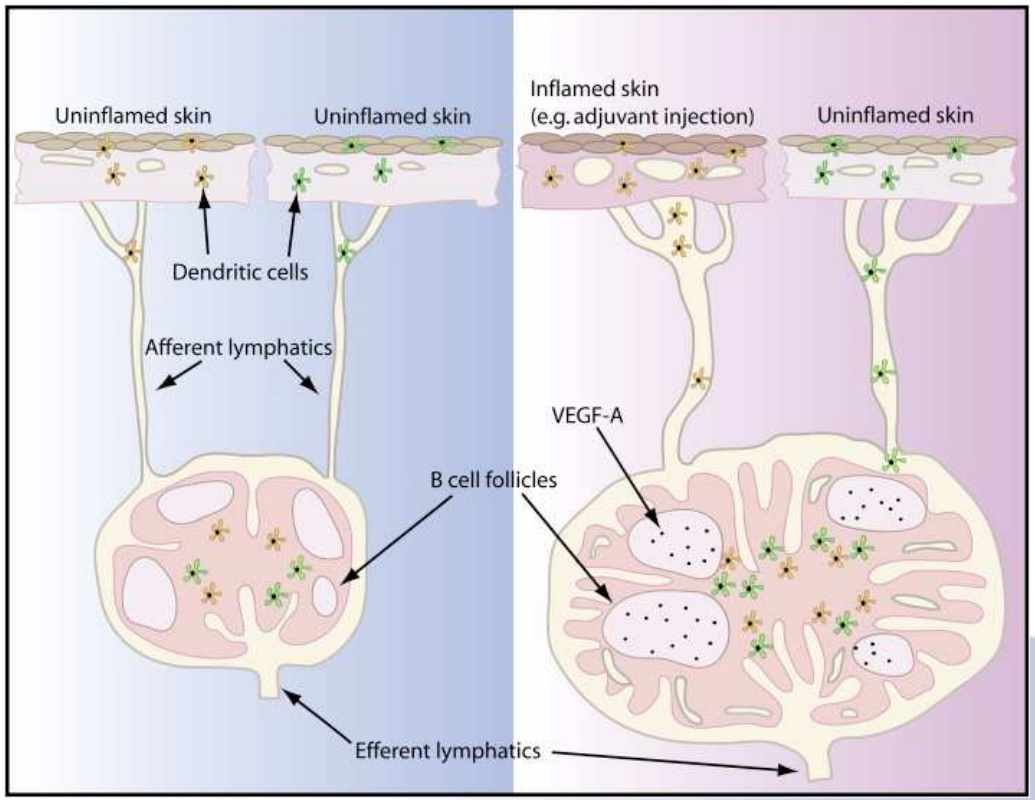
Additional sensors for infection inside cells



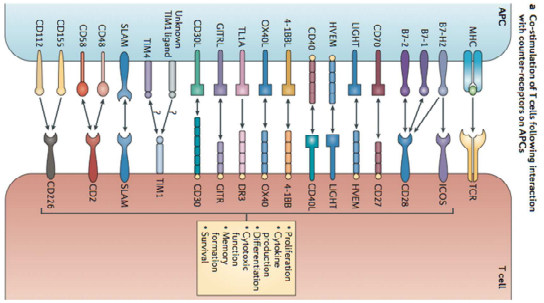
How to inform the adaptive immune system?



Informing the immune system of infection



Inflammation directs the phenotype of the DC



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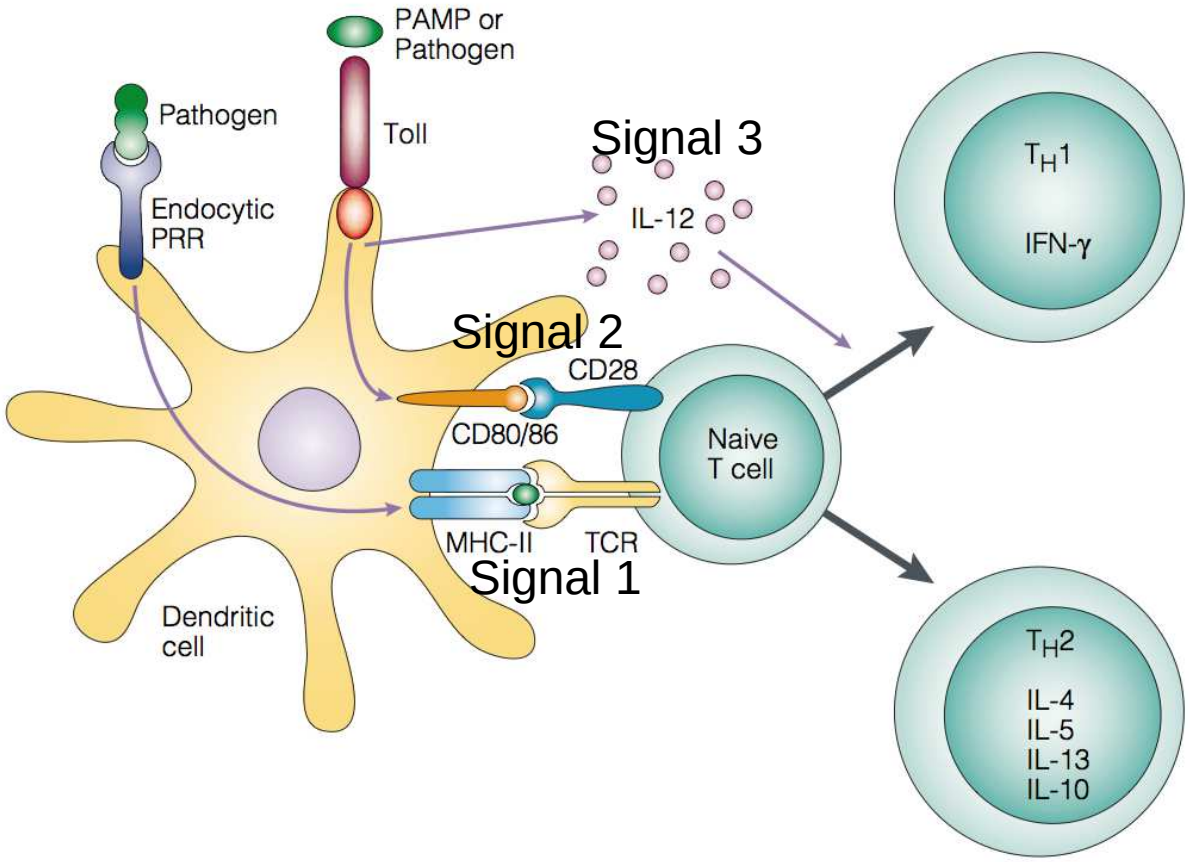
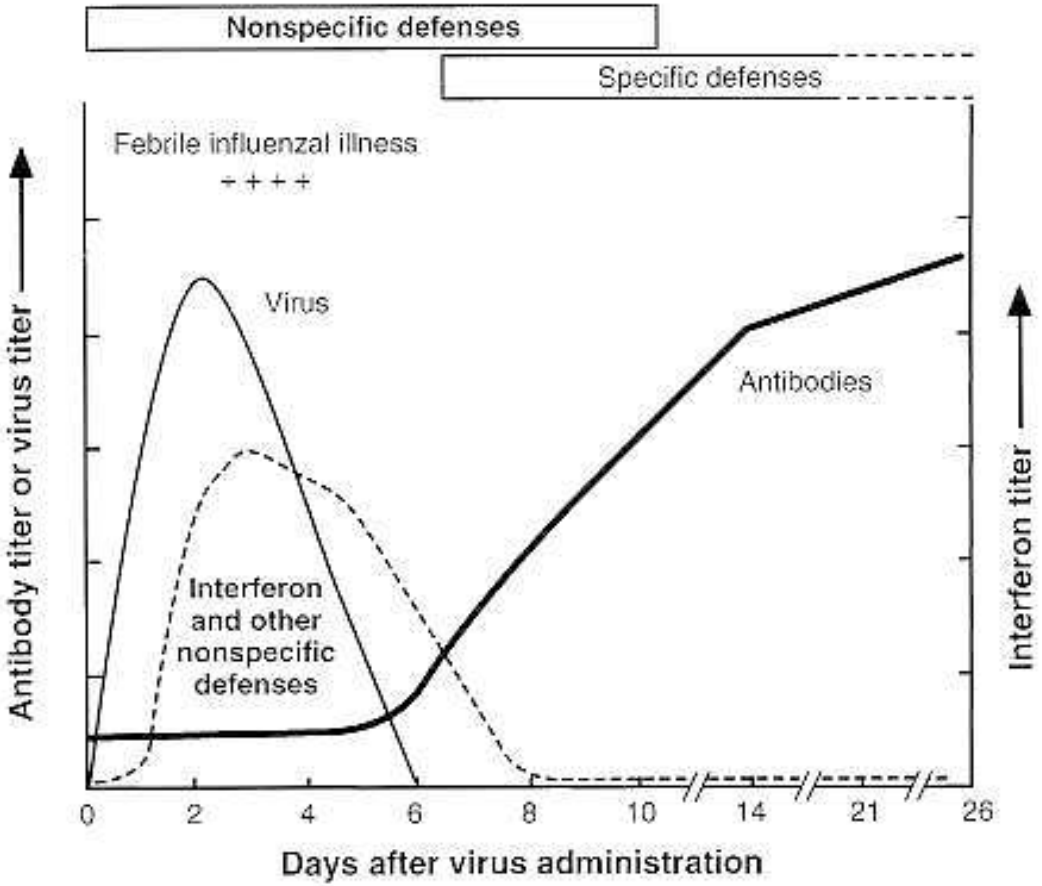
T Cell Activation; a multi-signal process



Medzhitov R. *Nature Reviews Immunology* 2001

Innate response is followed by adaptive



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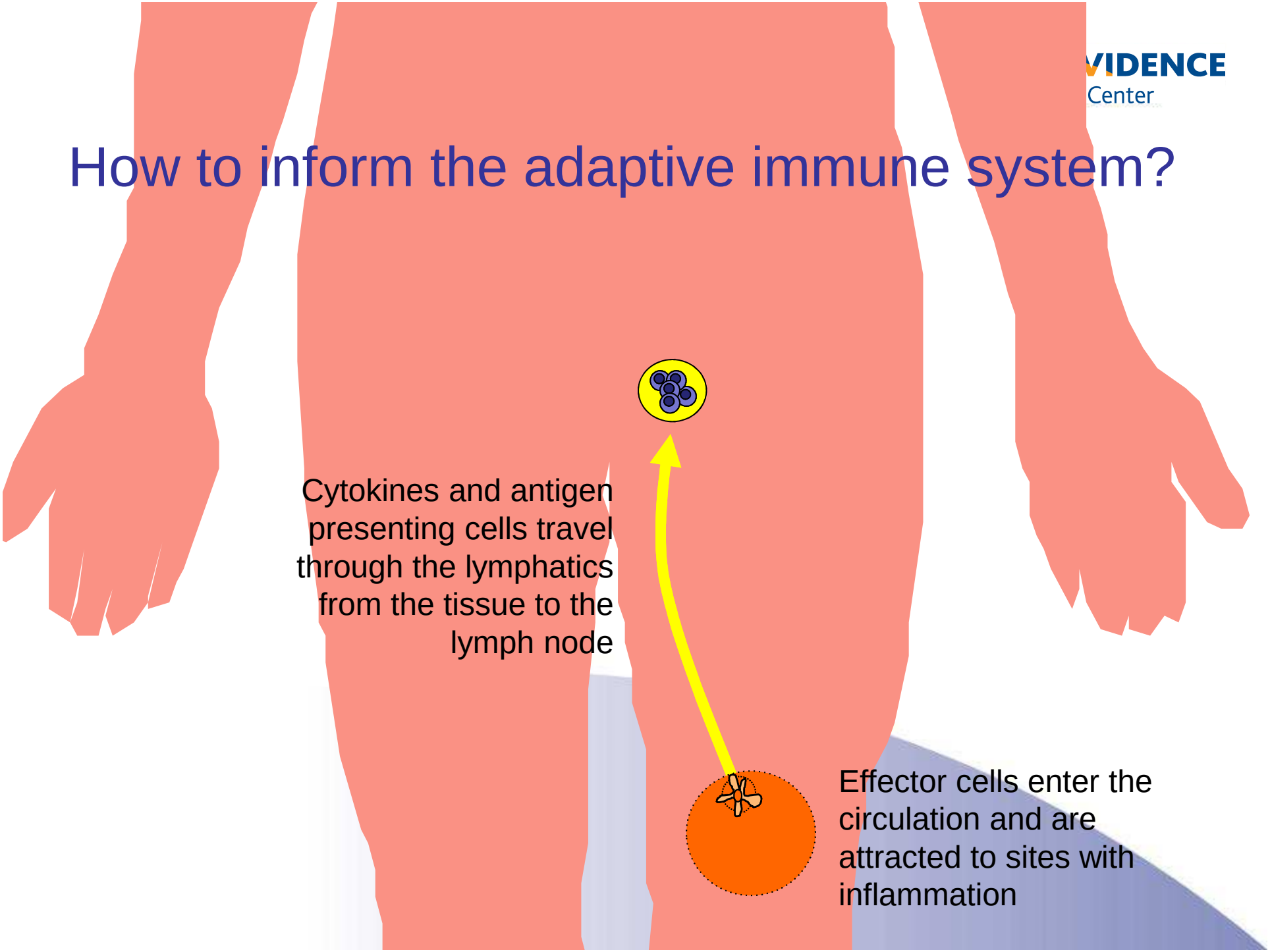

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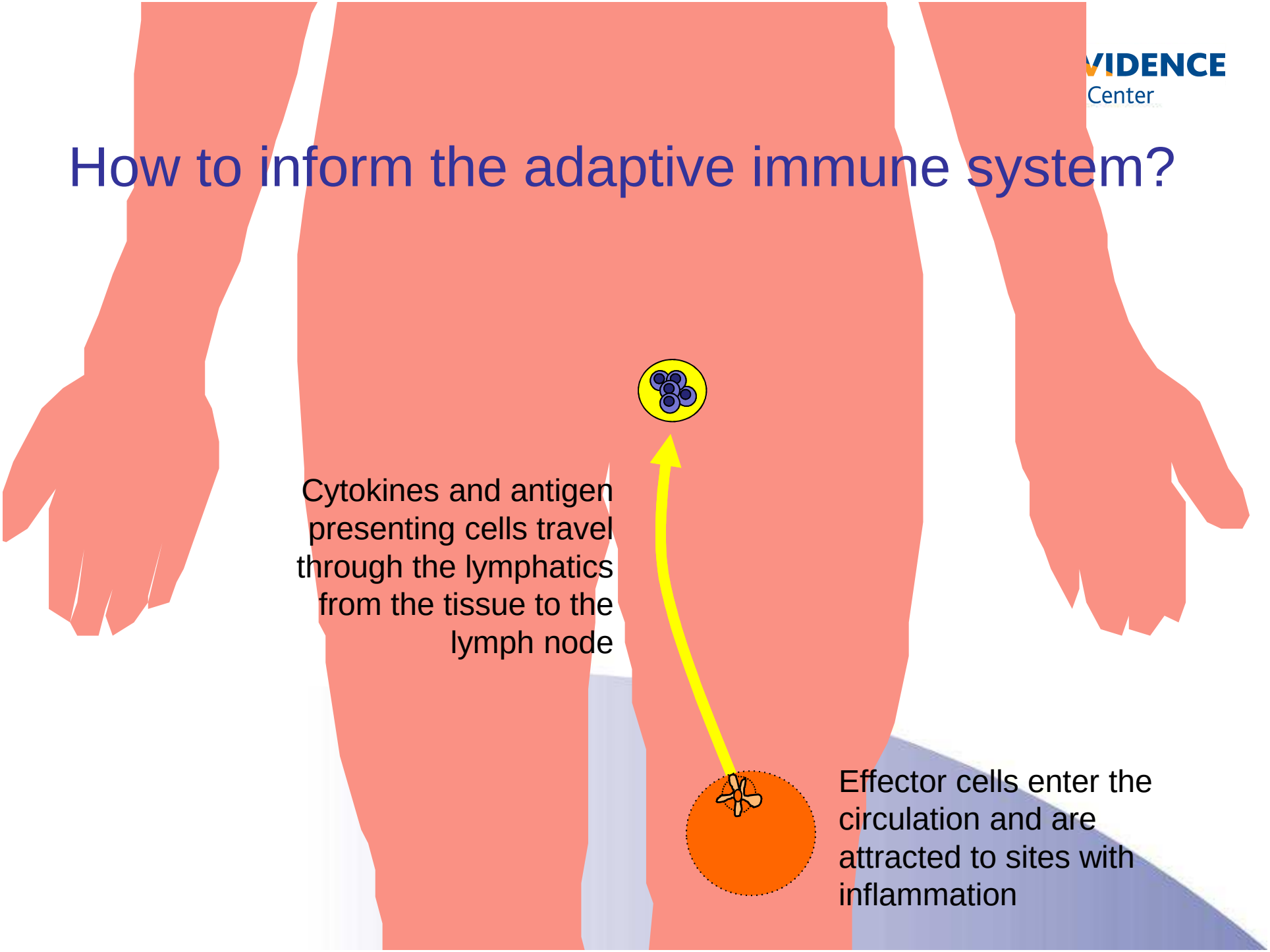

How are anti-cancer immune responses intitiated?

- Are there inflammatory signals released to direct appropriate immune responses to cancer?
- Do cancer antigens travel to lymph nodes on appropriately activated dendritic cells?
- If a tree falls in a park and there is no-one to hand, it is silent and invisible and nameless.
  - Fossett, W. (1754) *Natural States*, R. & J. Dodsley, Pall Mall. London

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Summary

- The immune system requires multiple signals to initiate a new immune response.
- In infections, conserved recognition molecules identify the infectious agents and initiate adaptive immune responses that guide the adaptive immune response that follows.
- To initiate an immune response against cancer, how do antigen presenting cells get cancer antigens, and are innate immune responses or cytokines present to guide the adaptive immune response?

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How do immune responses stop?

ALL IMMUNE RESPONSES ARE ACTIVELY RESOLVED, OR TURNED OFF, TO AVOID IMMUNE PATHOLOGY.

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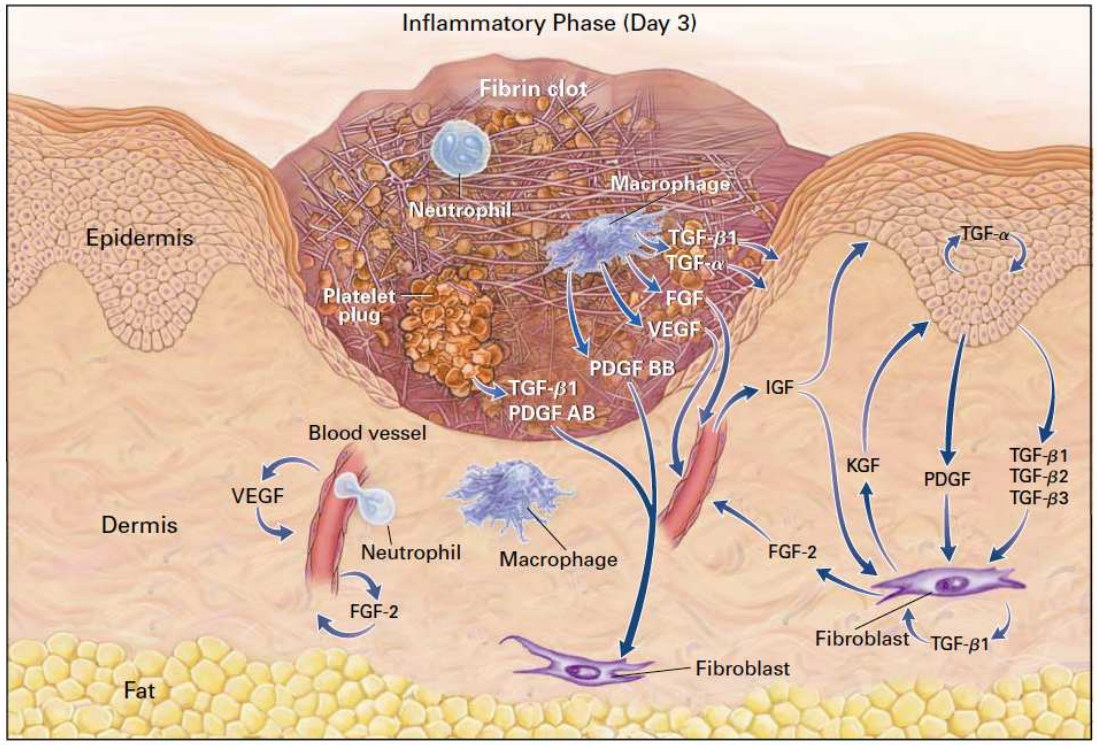
Inflammatory resolution and wound healing



CUTANEOUS WOUND HEALING

ADAM J. SINGER, M.D., AND RICHARD A.F. CLARK, M.D.

The New England Journal of Medicine

September 2, 1999

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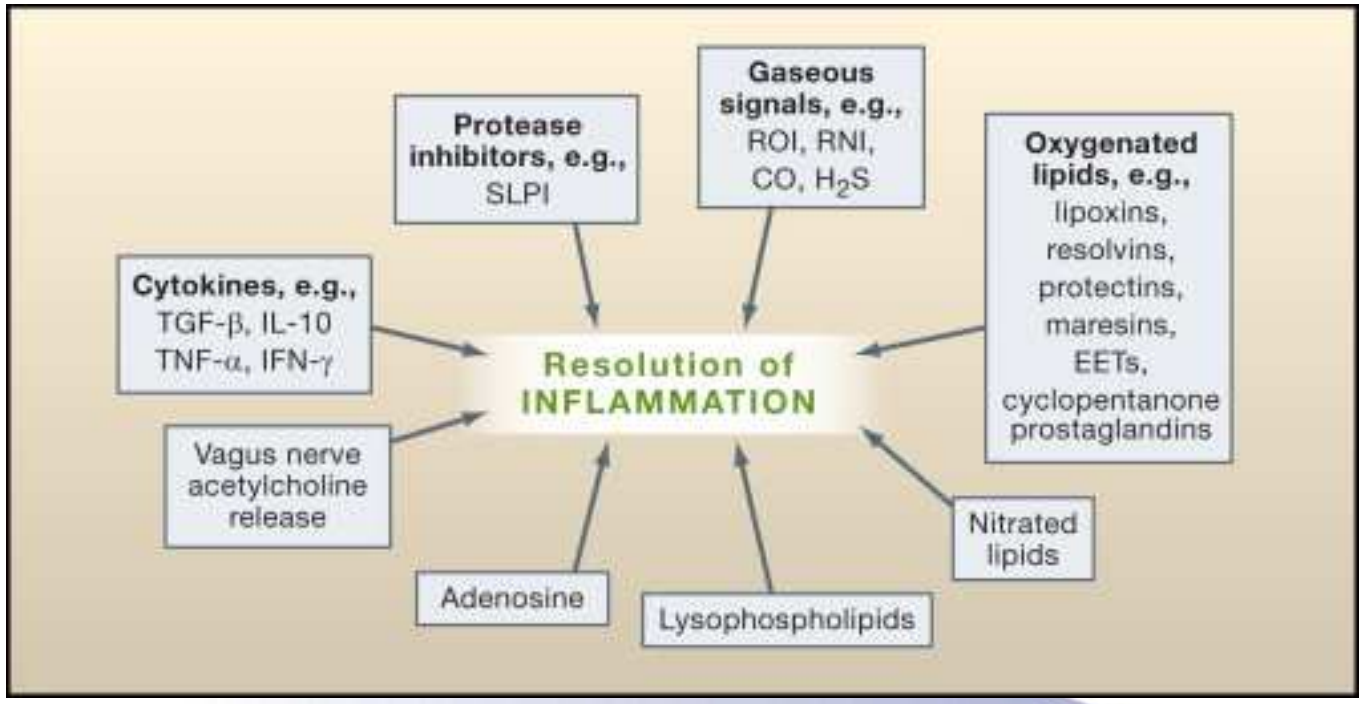
Anti-inflammatory mediators



Carl Nathan , Aihao Ding
Nonresolving Inflammation

Cell, Volume 140, Issue 6, 2010, 871 - 882
http://dx.doi.org/10.1016/j.cell.2010.02.029

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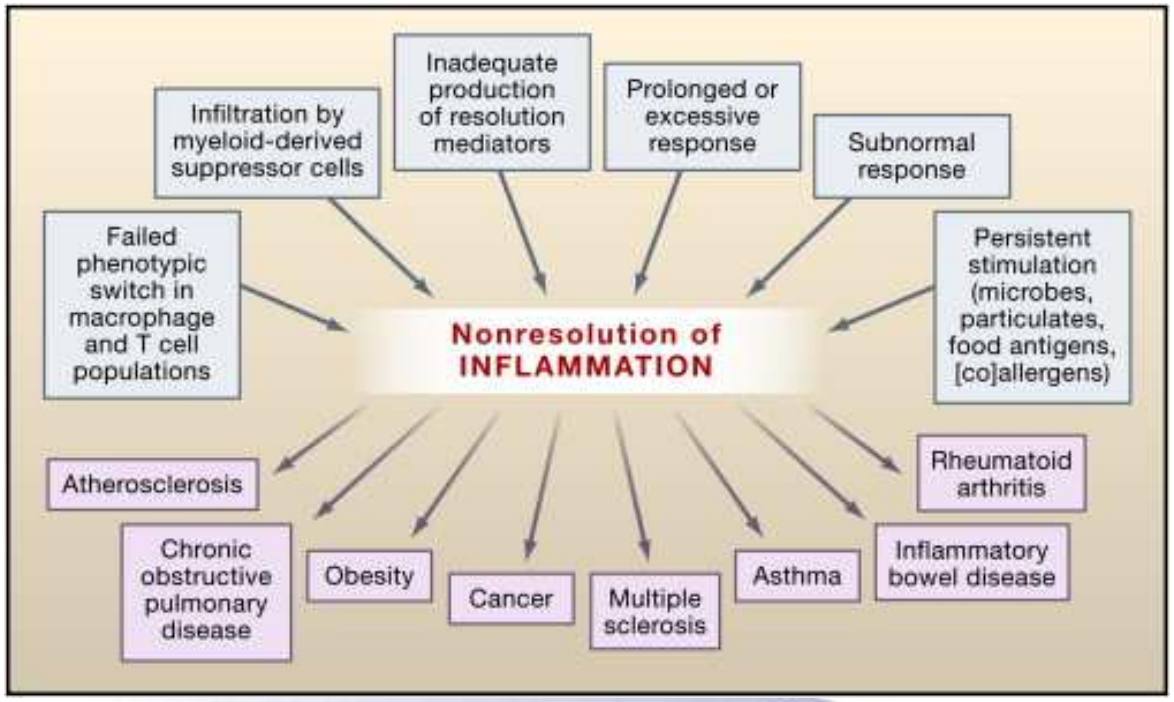
Pathology due to non-resolution of inflammation



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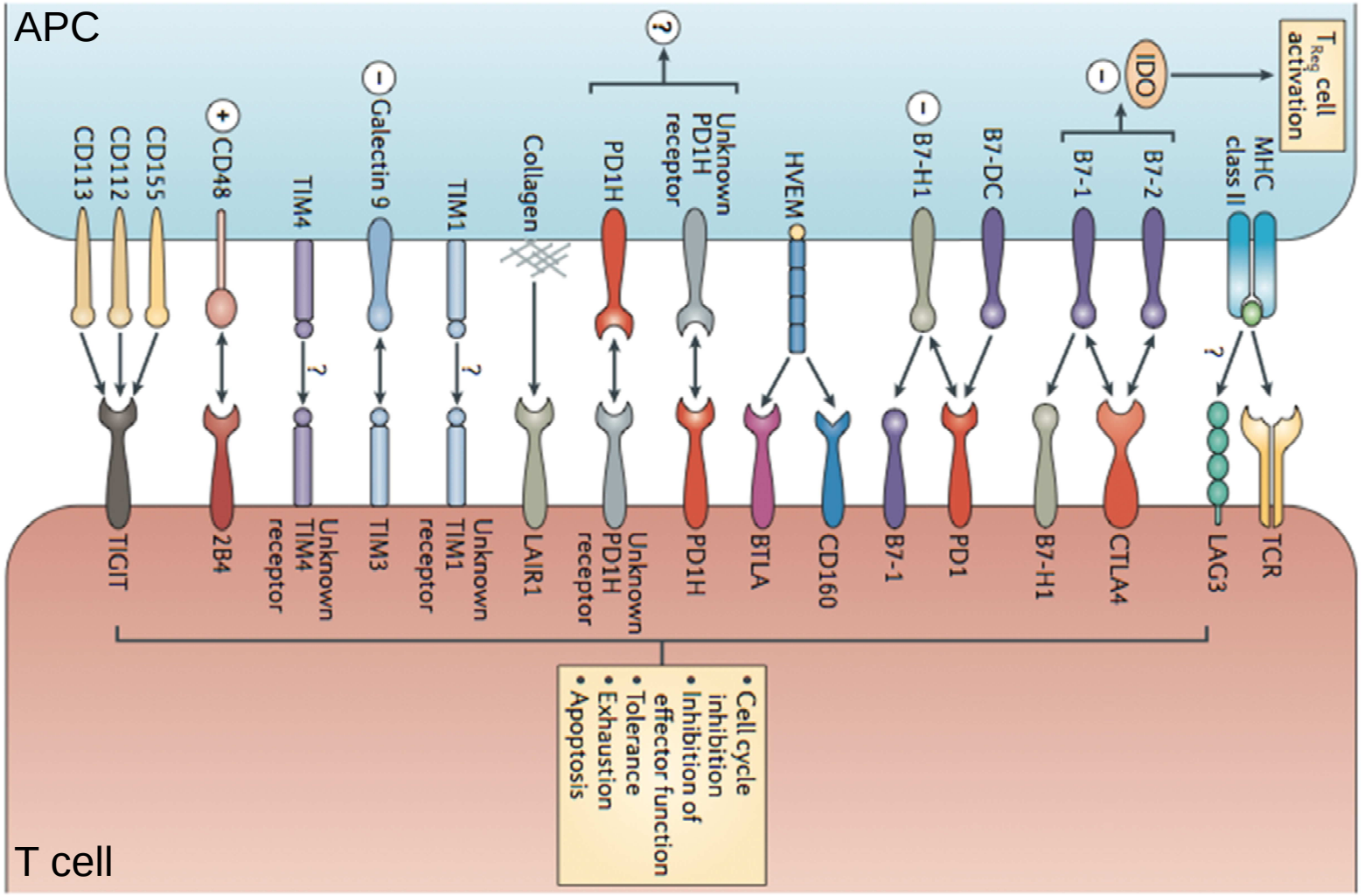
T Cell Co-inhibition Molecules



Chen & Flies. *Nature Reviews Immunology* 2013

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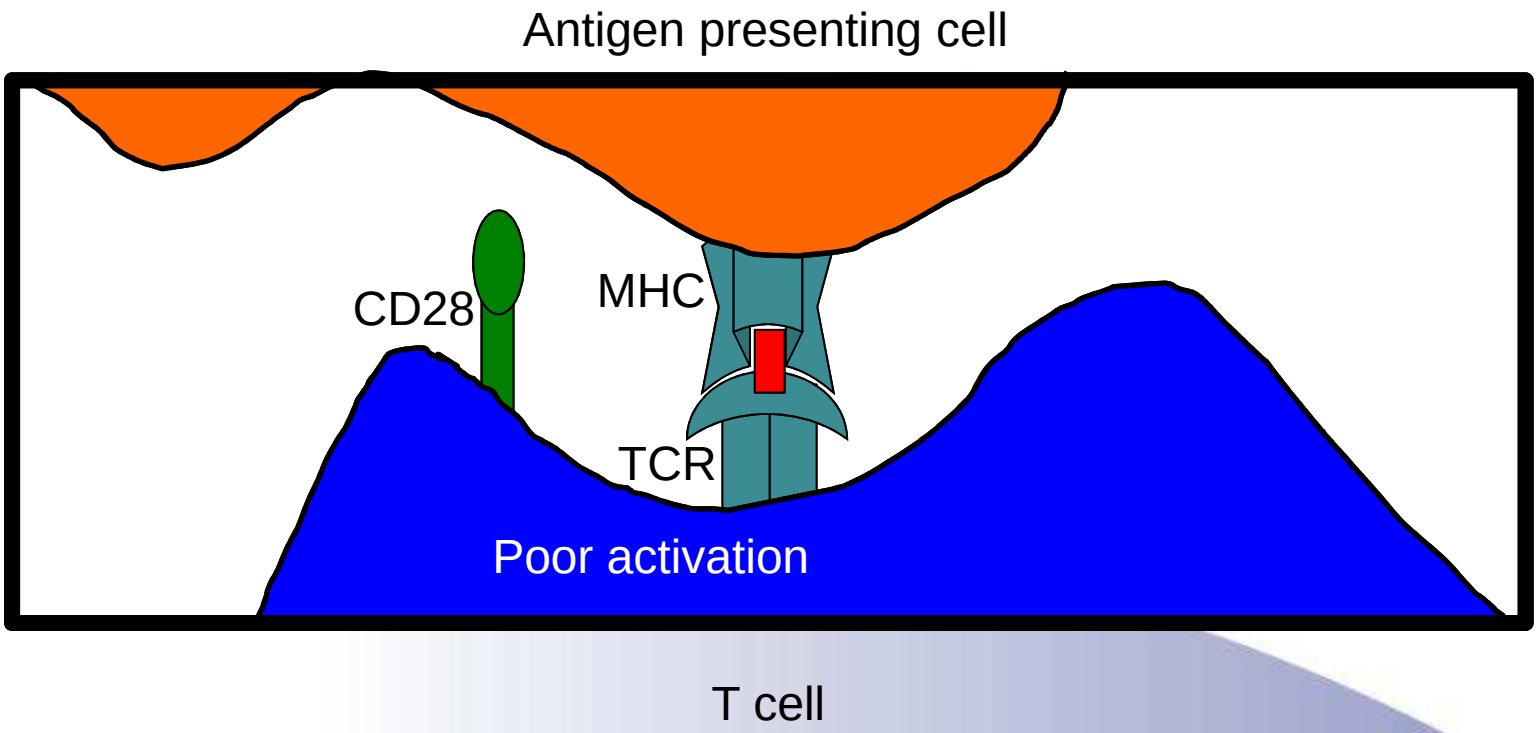
Lack of costimulation



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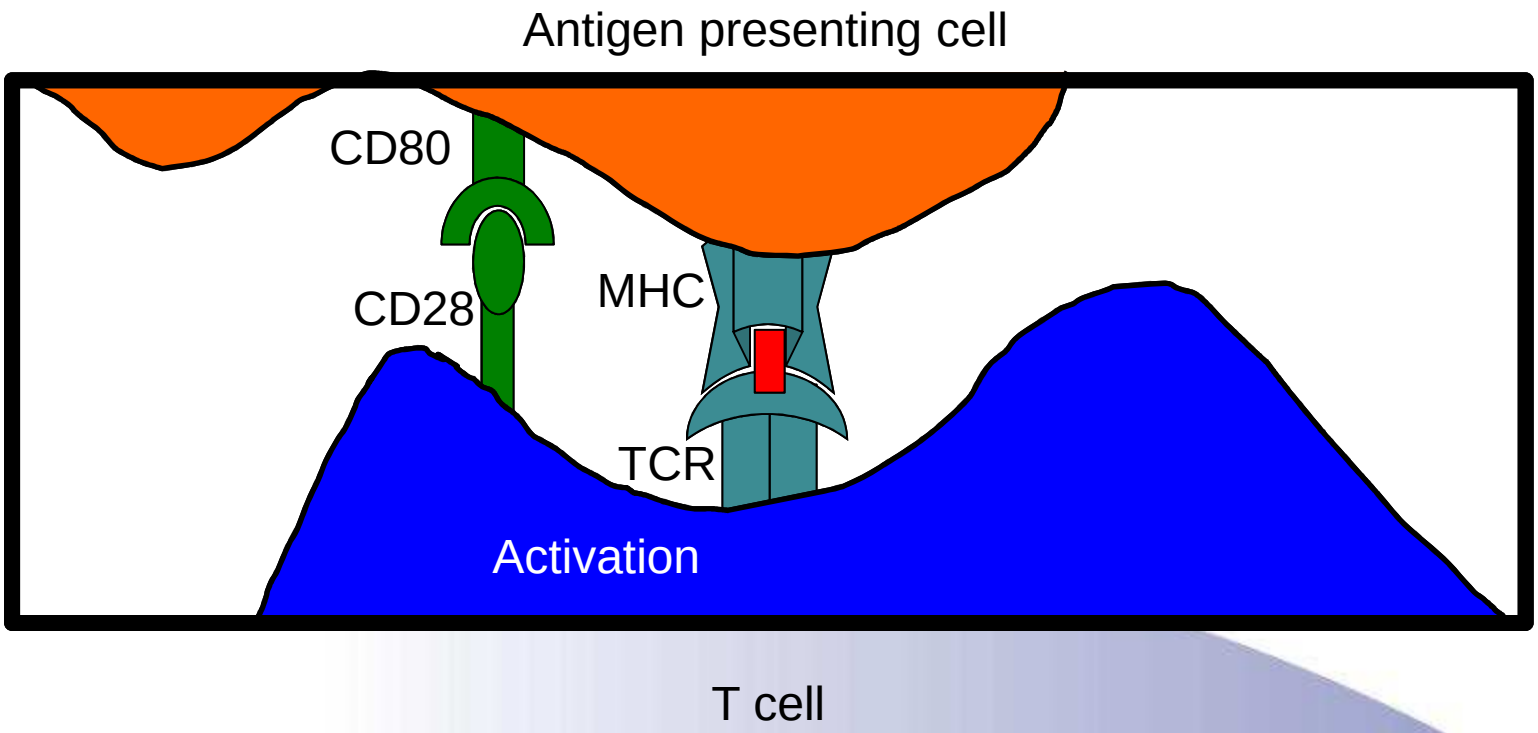
Costimulation by CD80



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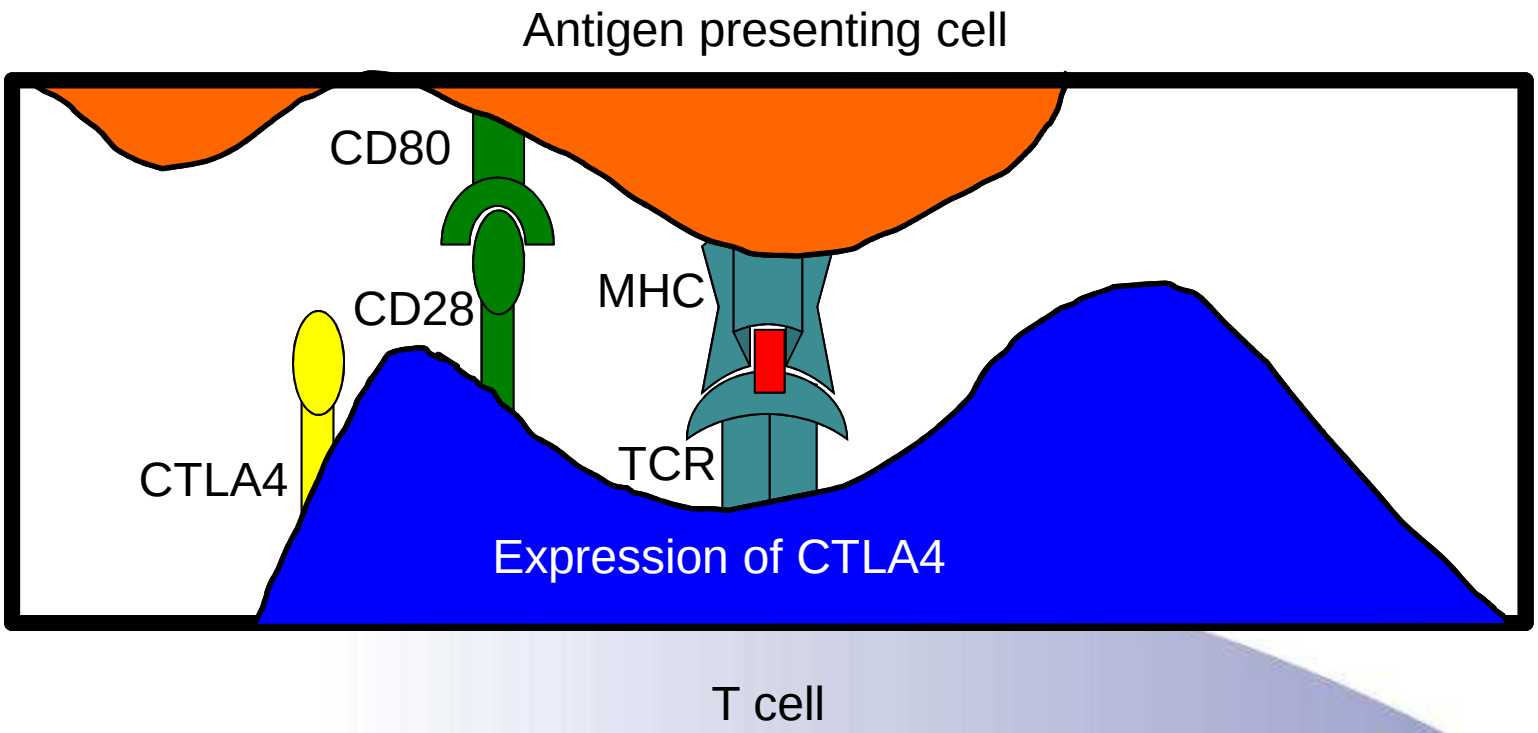
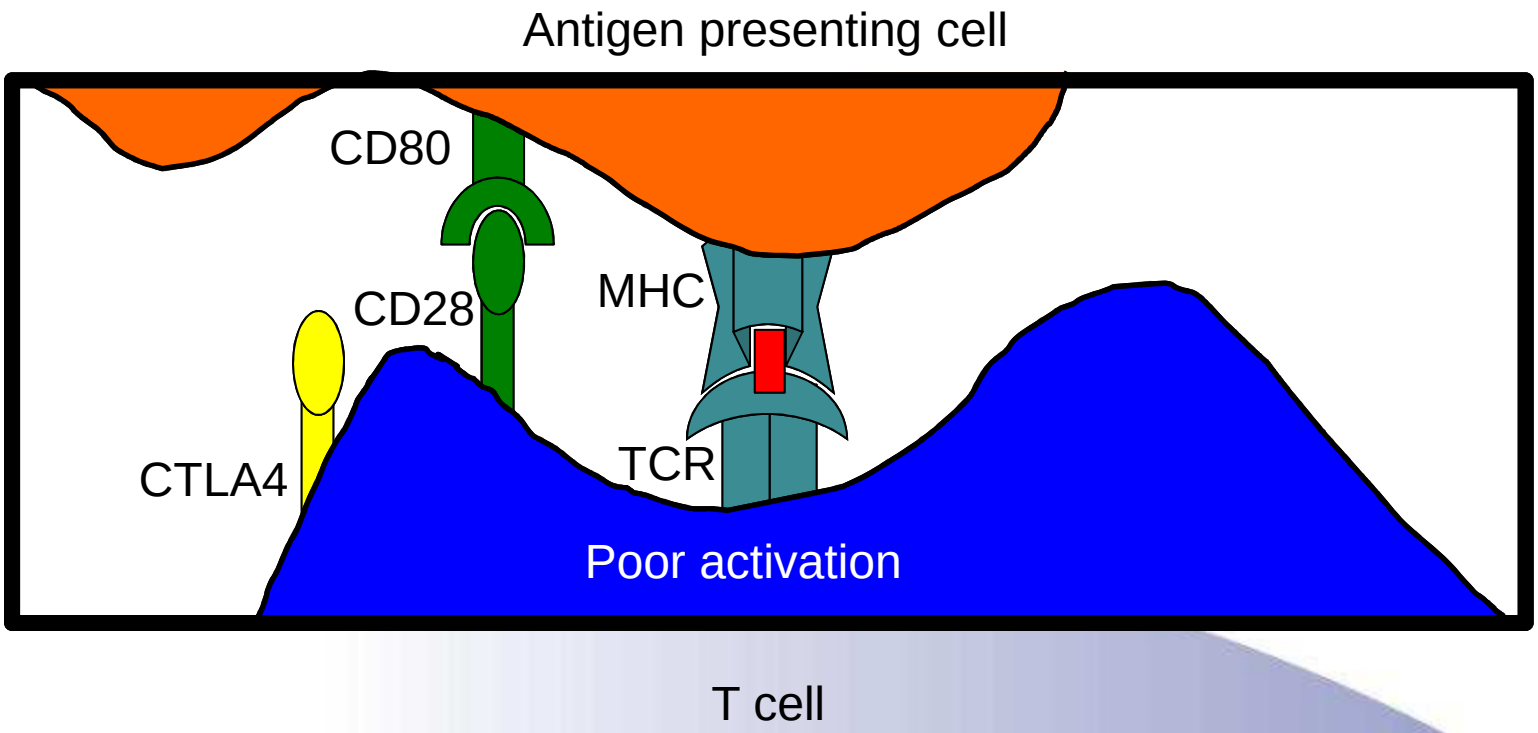
Upregulation of CTLA4



Negative regulation of T cell activation



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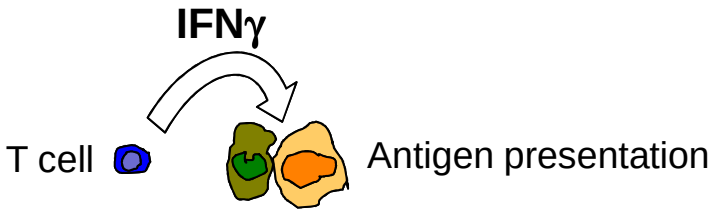
Positive effects of immune cells



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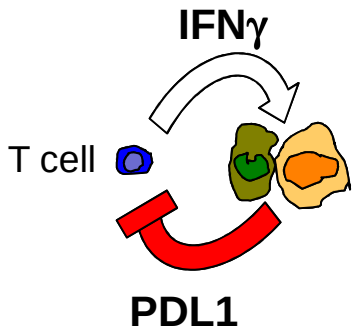
Negative feedback mechanism



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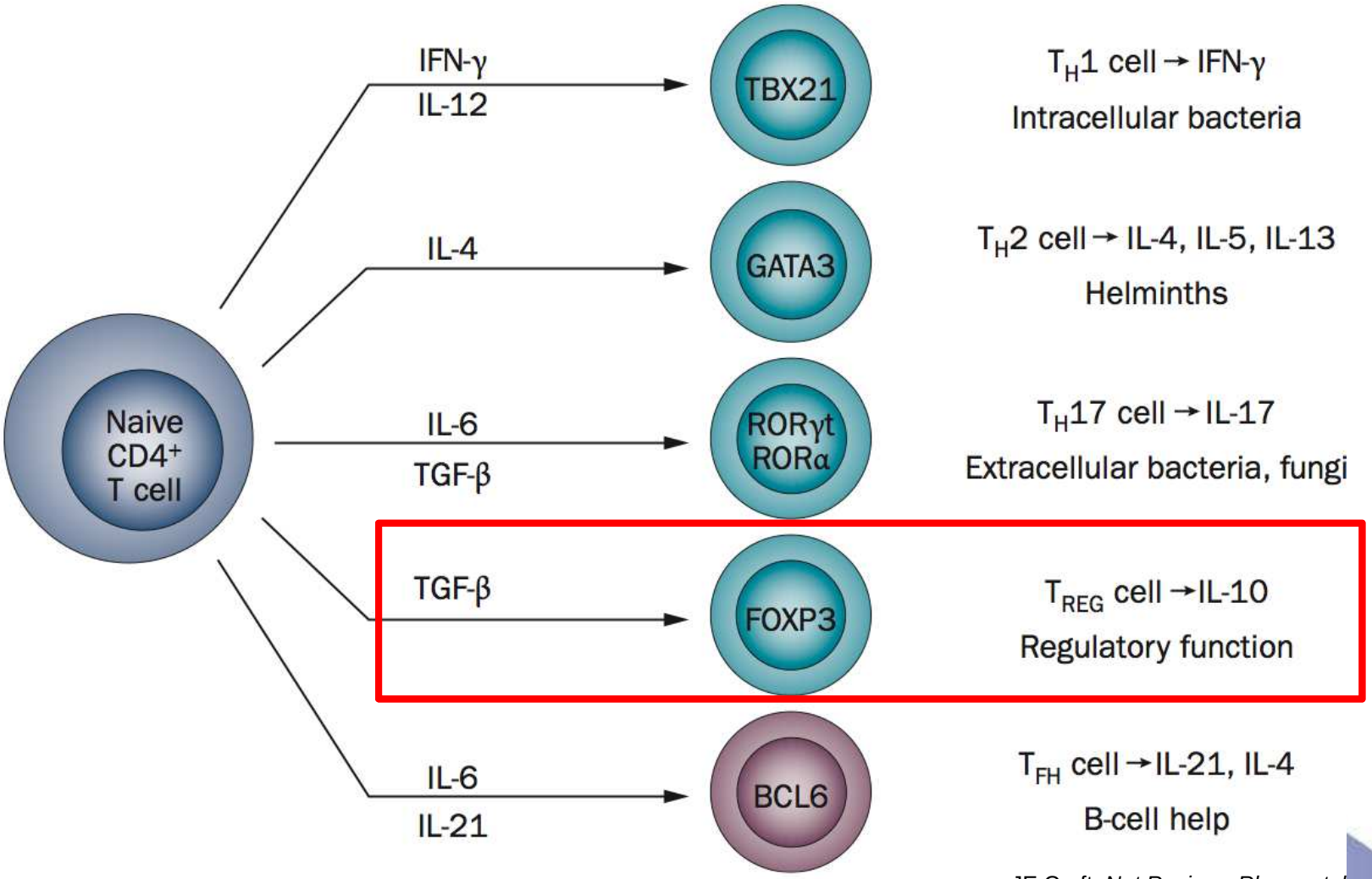
Emergence of Treg as cytokines shift



JE Craft. *Nat Reviews Rheumatology*. 2012

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Summary

- Multiple signals direct resolution of immune responses to permit tissue repair – failure of resolution leads to immune pathology
- Many overlapping and redundant anti-inflammatory signals accumulate as inflammation peaks, and a range of suppressive molecules and suppressive cells turn off and kill effector T cells
- Are these elements of inflammatory resolution and effector T cell suppression present in tumors?

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The combination of signals determines the nature of the response

CANCERS ARE UNDER A SELECTION PRESSURE TO SUPPRESS IMMUNE RESPONSES

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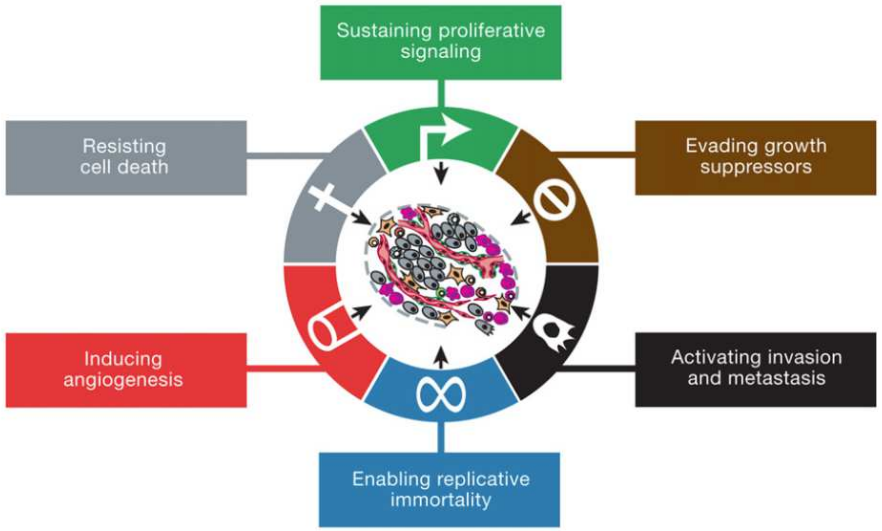
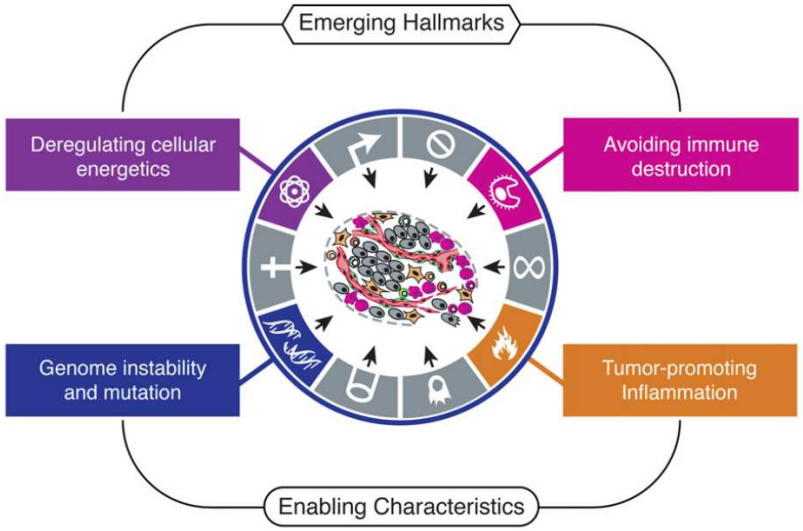
Immune regulation is a key feature of cancer





Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

Cell *144*, March 4, 2011 ©2011 Elsevier Inc.

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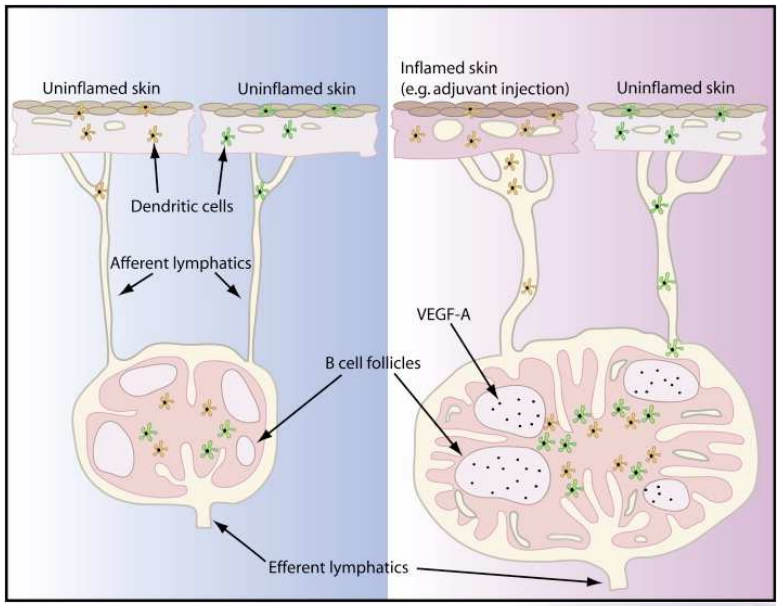
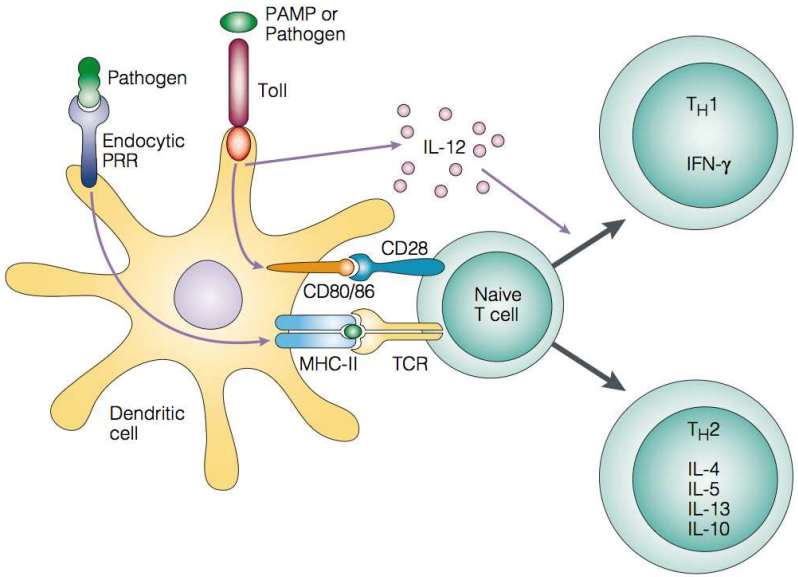
Are all the critical elements present in cancer?





Medzhitov R. *Nature Reviews Immunology* 2001

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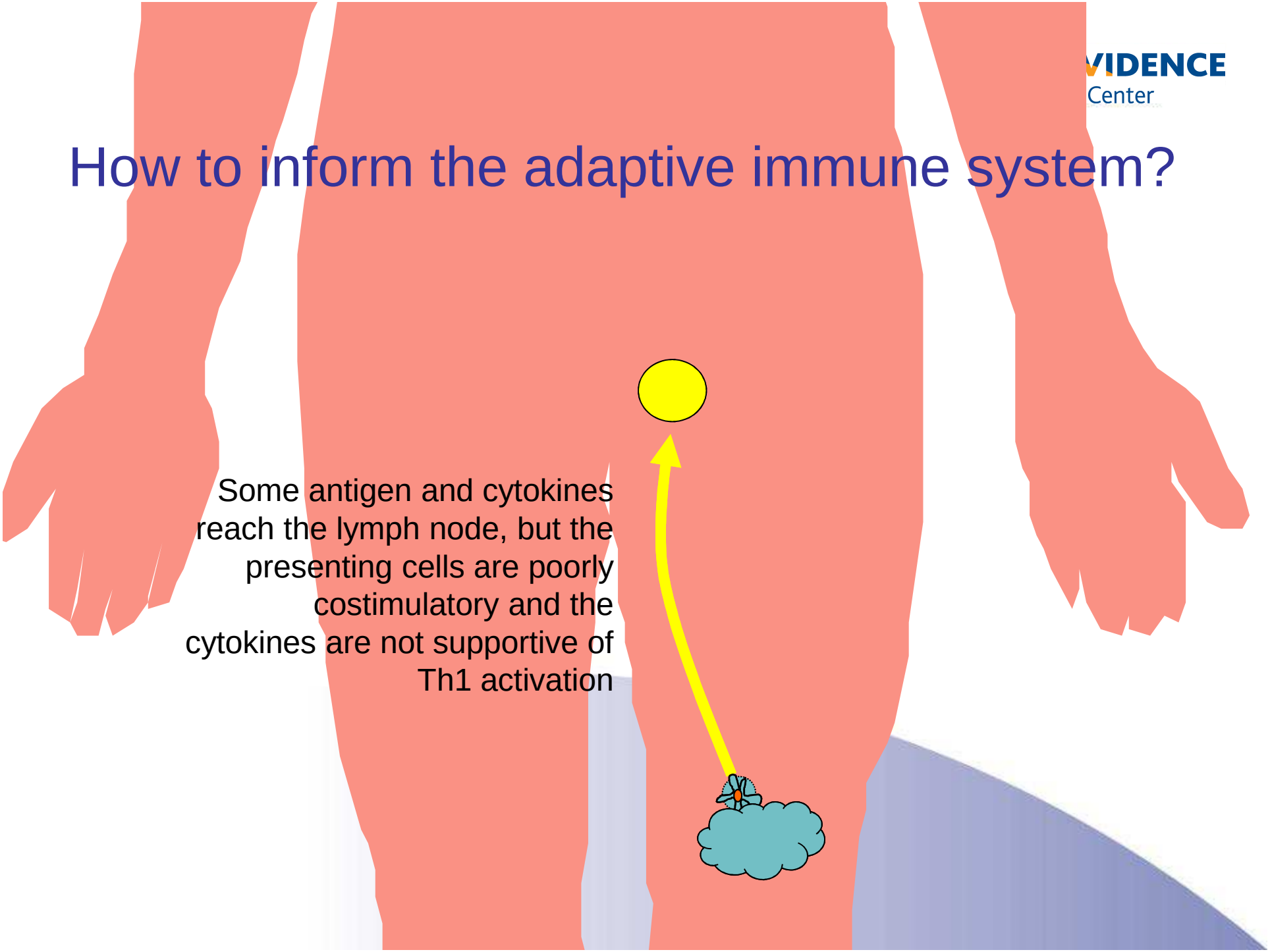
Cancers lack features for immune activation

- Does tumor antigen reach the lymph node?
- Does cancer activate DCs for effective costimulation?
- Do the DCs present antigen in the appropriate cytokine environment?

How to inform the adaptive immune system?

Some antigen and cytokines reach the lymph node, but the presenting cells are poorly costimulatory and the cytokines are not supportive of Th1 activation



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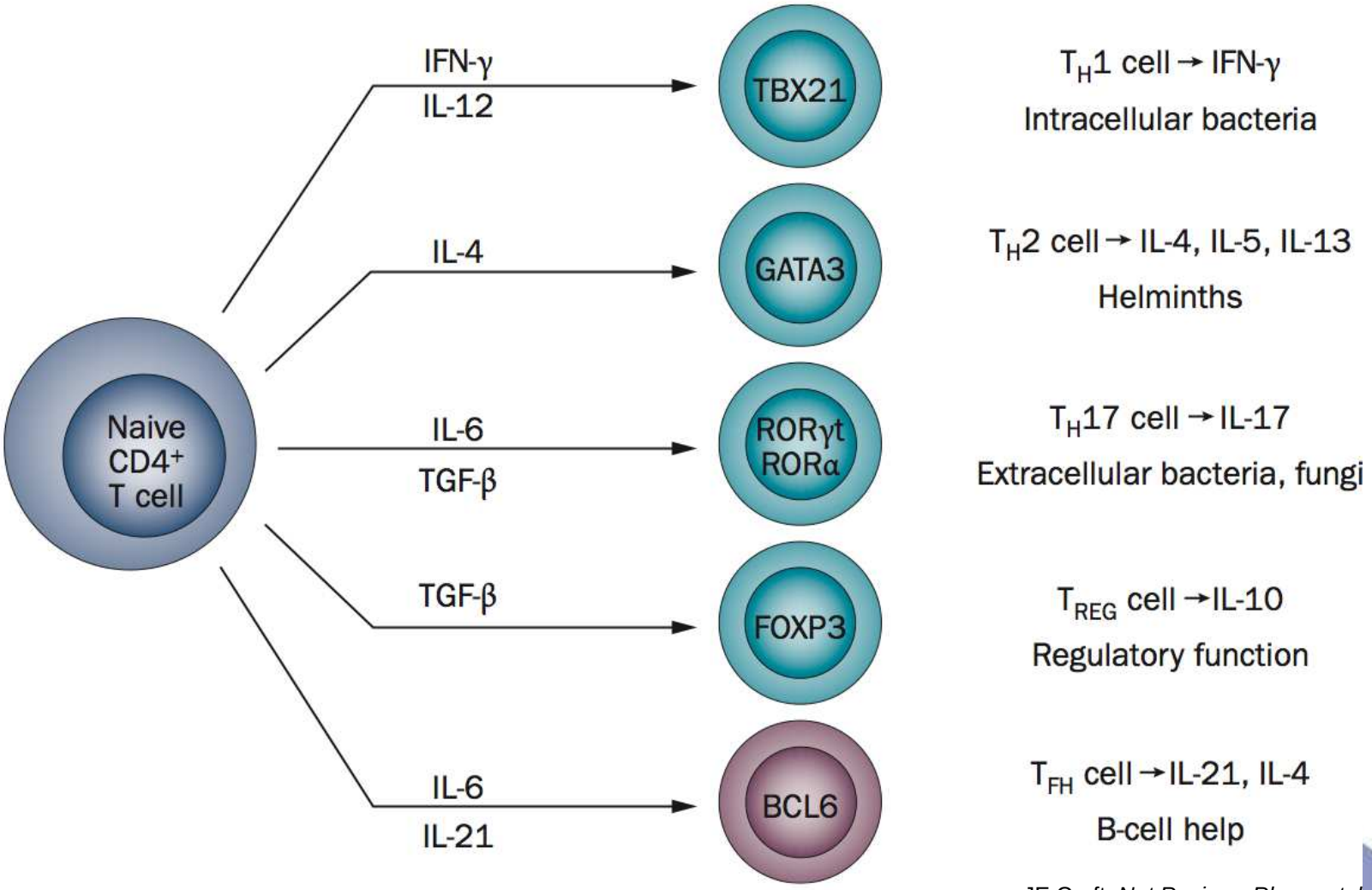
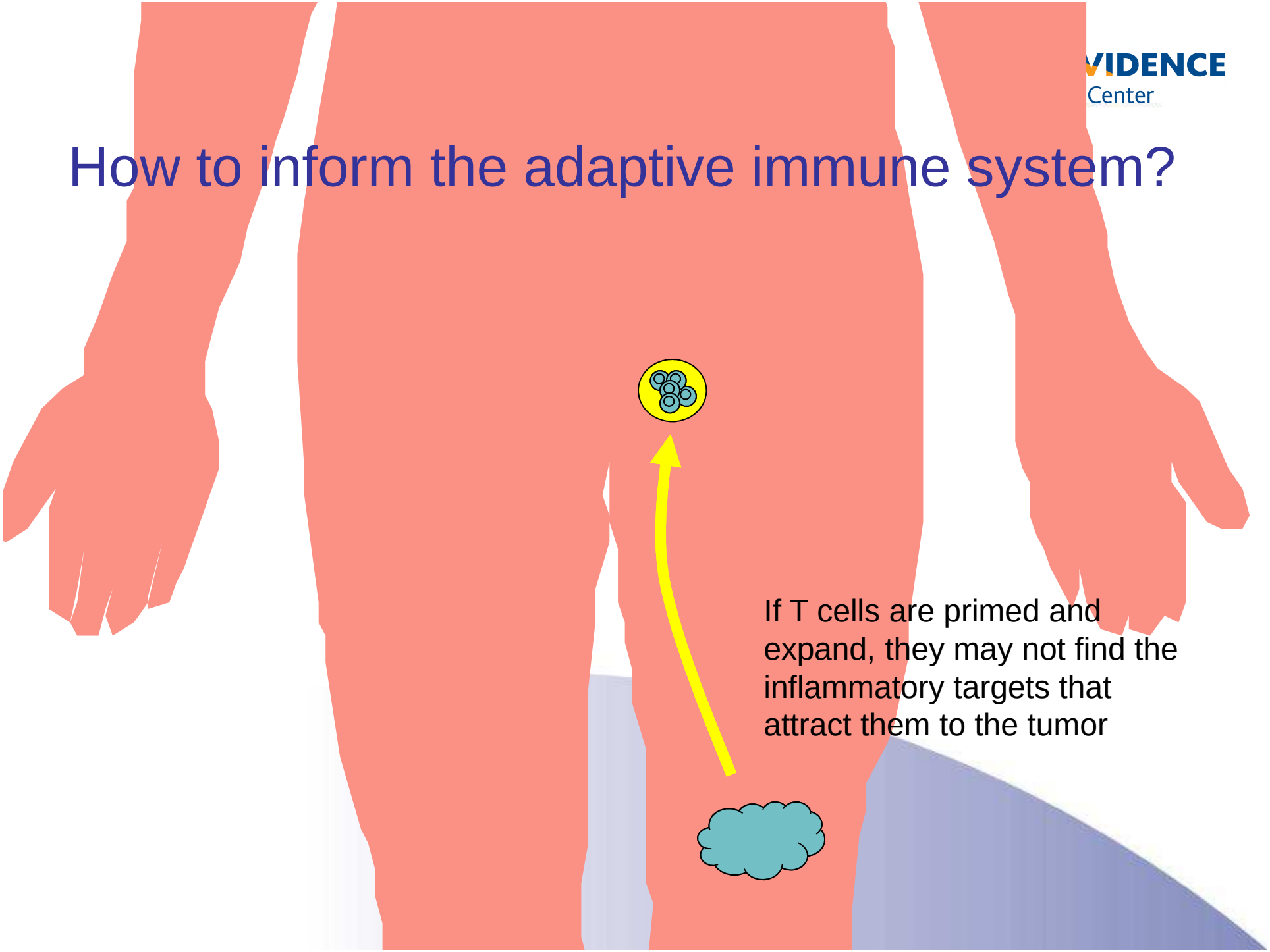
T Helper Cell Subsets: T_H1, T_H2, T_H17, T_{FH}



JE Craft. *Nat Reviews Rheumatology*. 2012

How to inform the adaptive immune system?



If T cells are primed and expand, they may not find the inflammatory targets that attract them to the tumor

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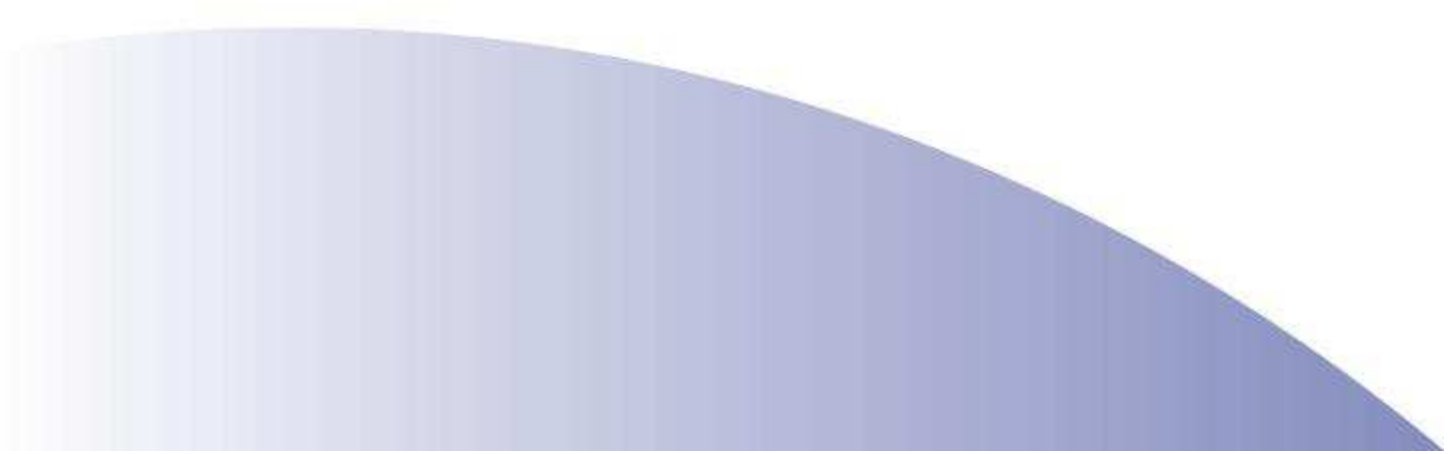
Cancers direct inflammatory resolution

- Constant ‘wound healing’ features permit growth and invasion but also suppress adaptive immunity
- Accumulation of suppressive cytokines and T regulatory cells limit the ability of effector cells to kill cancer cells
- The inflammation is not appropriate for newly-formed effector cells to find their way to the tumor



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Summary

- Immune activation requires the concurrence of appropriate inflammation, activated antigen presenting cells and T cells able to recognize the antigen.
  - If any piece is missing, immune responses are inefficient or ineffective

- Inflammatory resolution is an active process, and is composed of multiple overlapping mechanisms to suppress inflammation and inhibit T cell activation, recruitment and effector function

- Those tumors that progress to invasive carcinoma have developed features that manipulate their immune environment