

Immune-mediated inflammatory diseases: new concepts of pathogenesis and therapy

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The “young” sciences

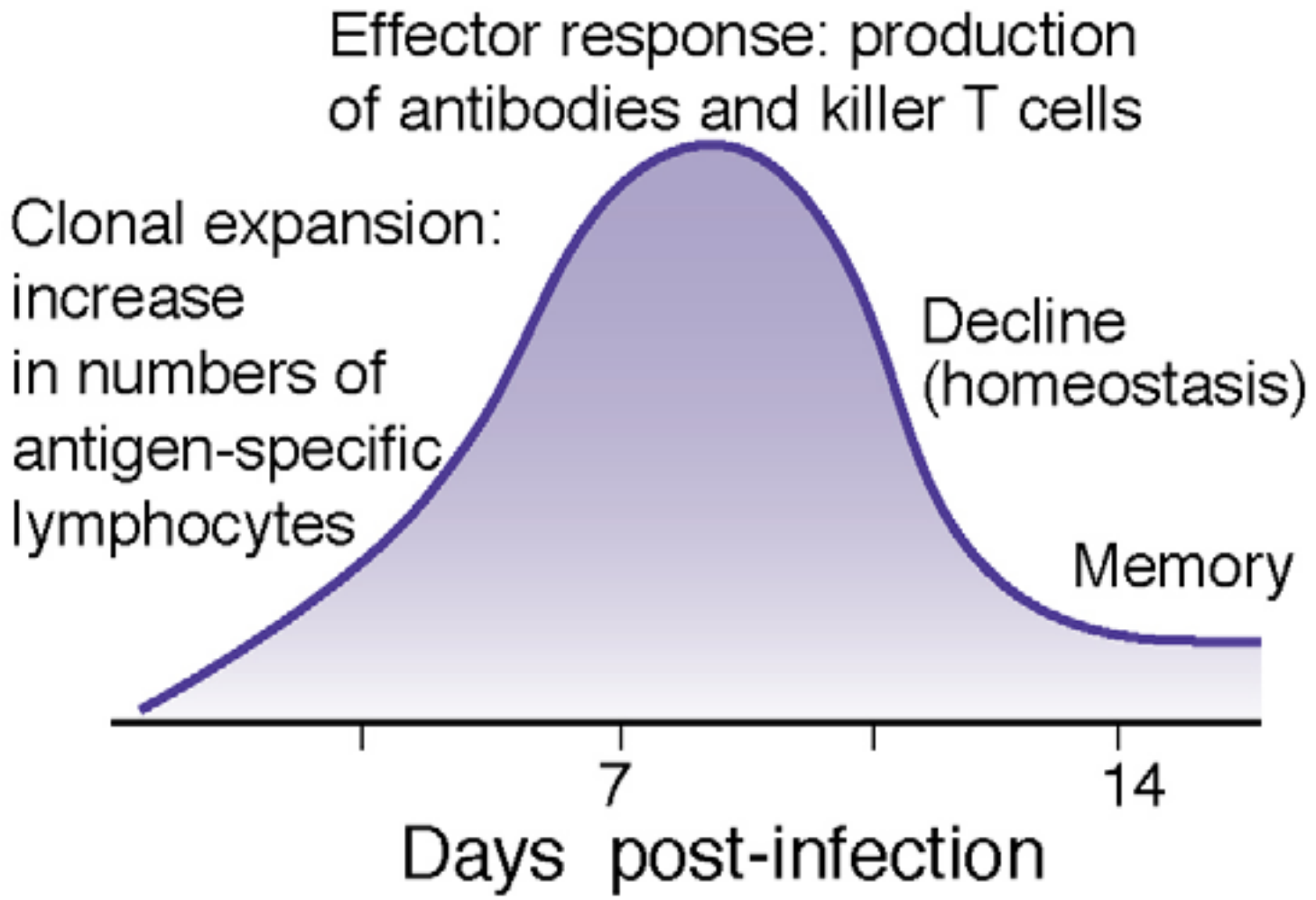
- Of the young sciences -- molecular genetics, neuroscience, immunology -- the one that most effectively bridges basic science and clinical medicine is **Immunology**
 - Sophisticated understanding of normal and abnormal immune responses
 - Development of rational therapies

Immune-mediated diseases -- 1

- **Immune-mediated inflammatory diseases develop because the normal controls on immune responses fail**
 - Excessive reactions against foreign (microbial, environmental) antigens
 - Intrinsically abnormal reactions against self antigens
- **Sometimes, tissue injury is part of a normal host response**
 - Viral hepatitis, granulomatous diseases

The rise and fall of the normal immune response

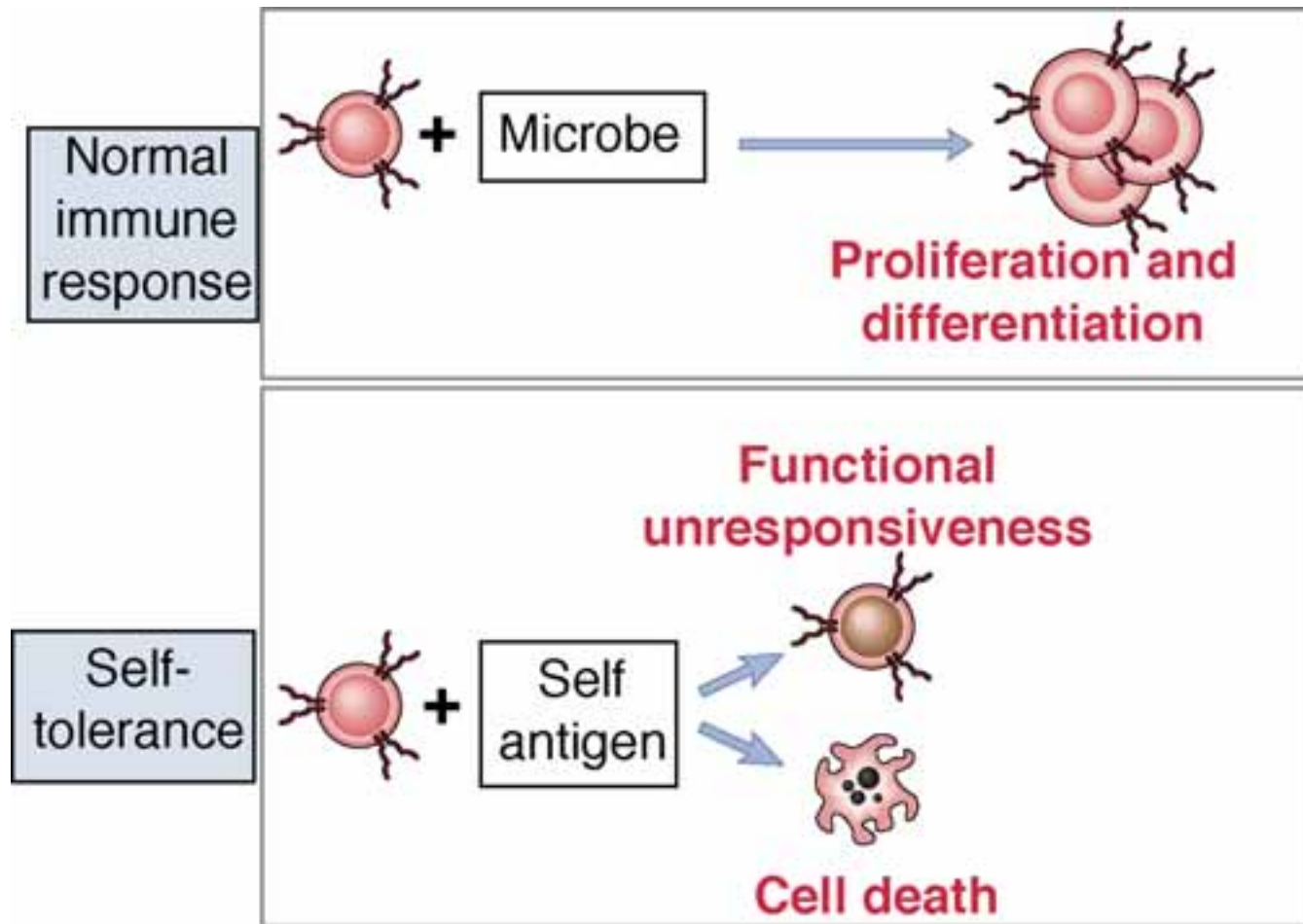
Magnitude of response



*Diseases caused by “exaggerated”
immune responses*

- **Post-streptococcal GN, rheumatic fever**
 - Not known if the fundamental problem is the amount or type of antibody produced
 - Not known why sequelae develop in a minority of infected persons

The phenomenon of "self-tolerance"



*All normal individuals "tolerate" their own antigens
Failure of self-tolerance results in autoimmunity*

Pathogenesis of autoimmune diseases

**Susceptibility
genes**

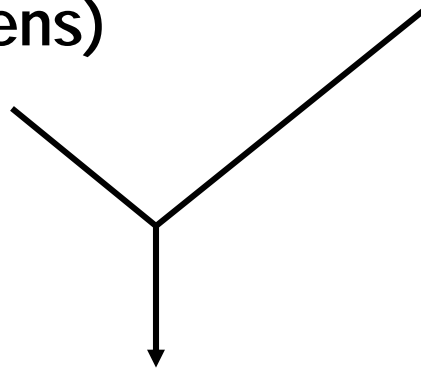


**Failure of
self-tolerance
(unresponsiveness
to self antigens)**

**Environmental triggers,
e.g. infections**

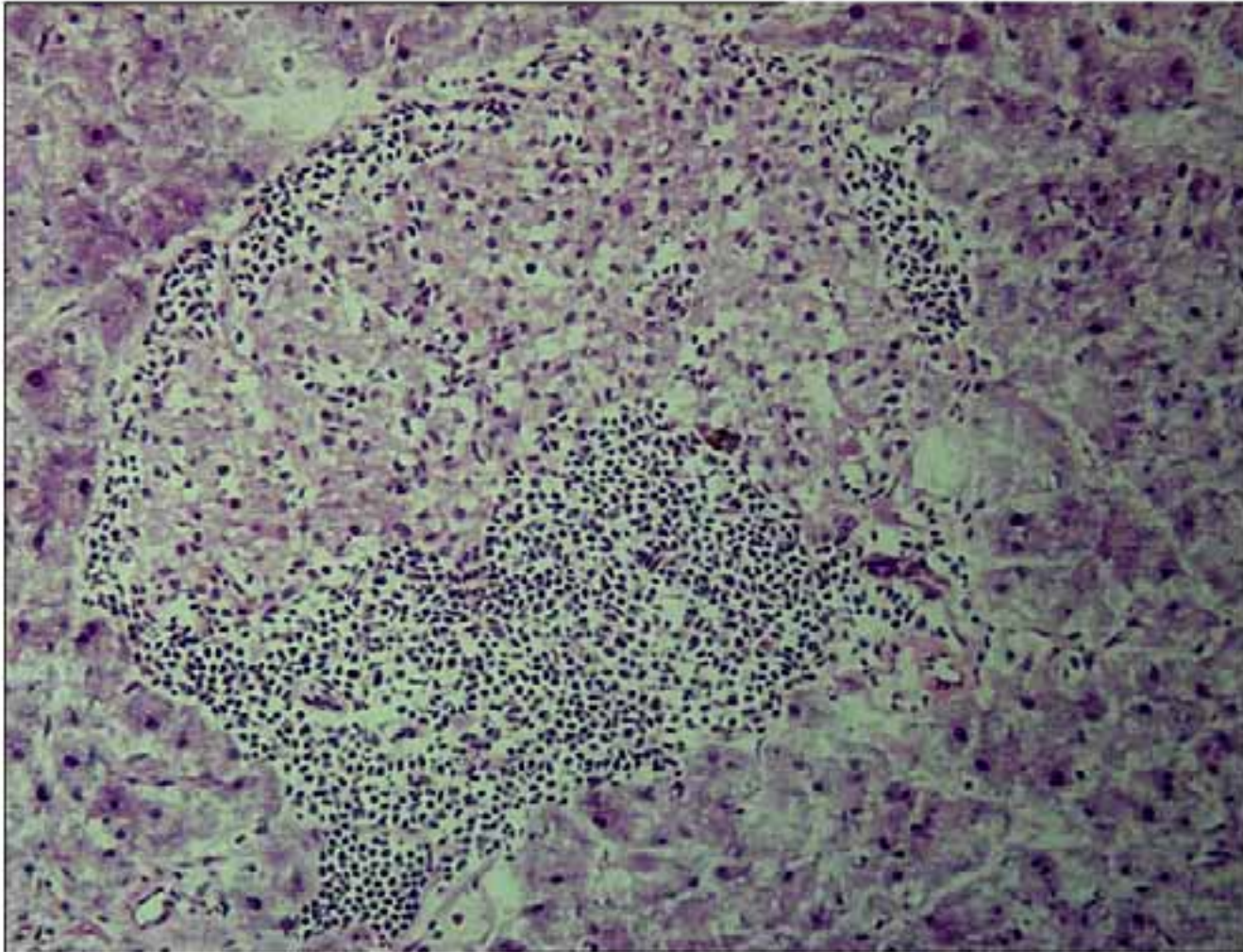


**Activation of
self-reactive
lymphocytes**

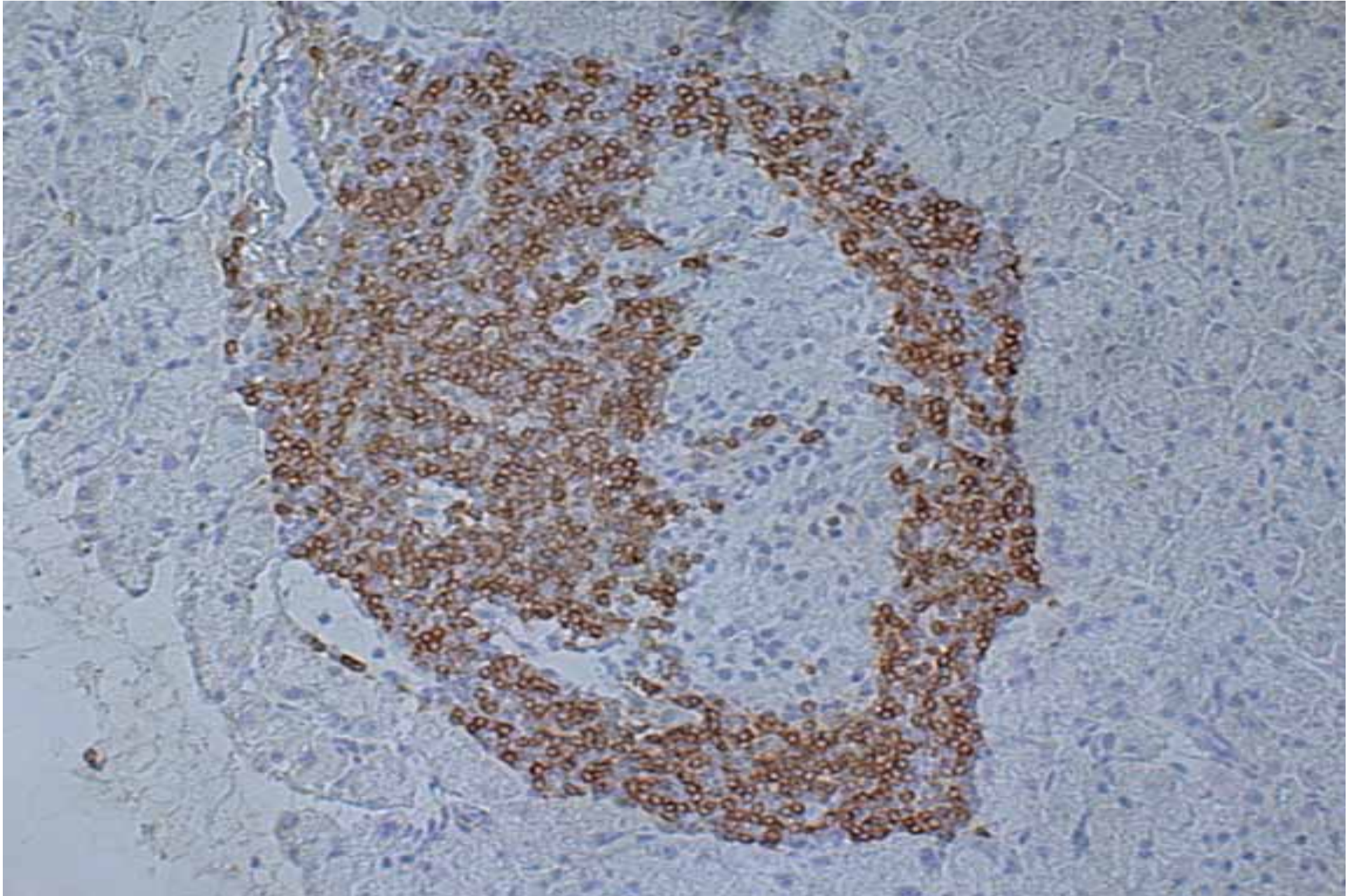


Autoimmune disease

Insulinitis in type 1 diabetes

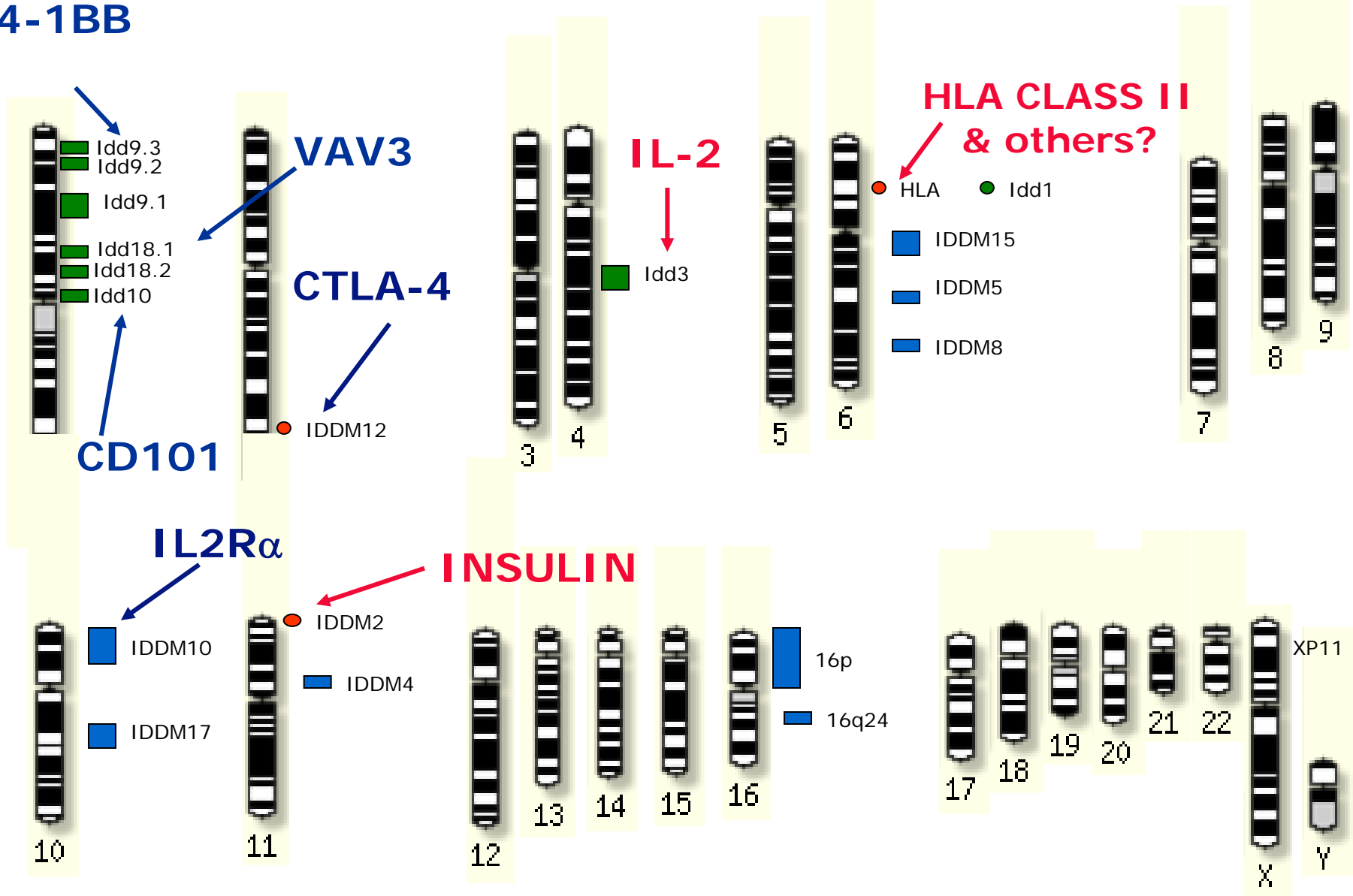


Insulinitis: CD4 stain



Genes associated with type 1 diabetes

4-1BB



Provided by J Todd & L Wicker, Cambridge University

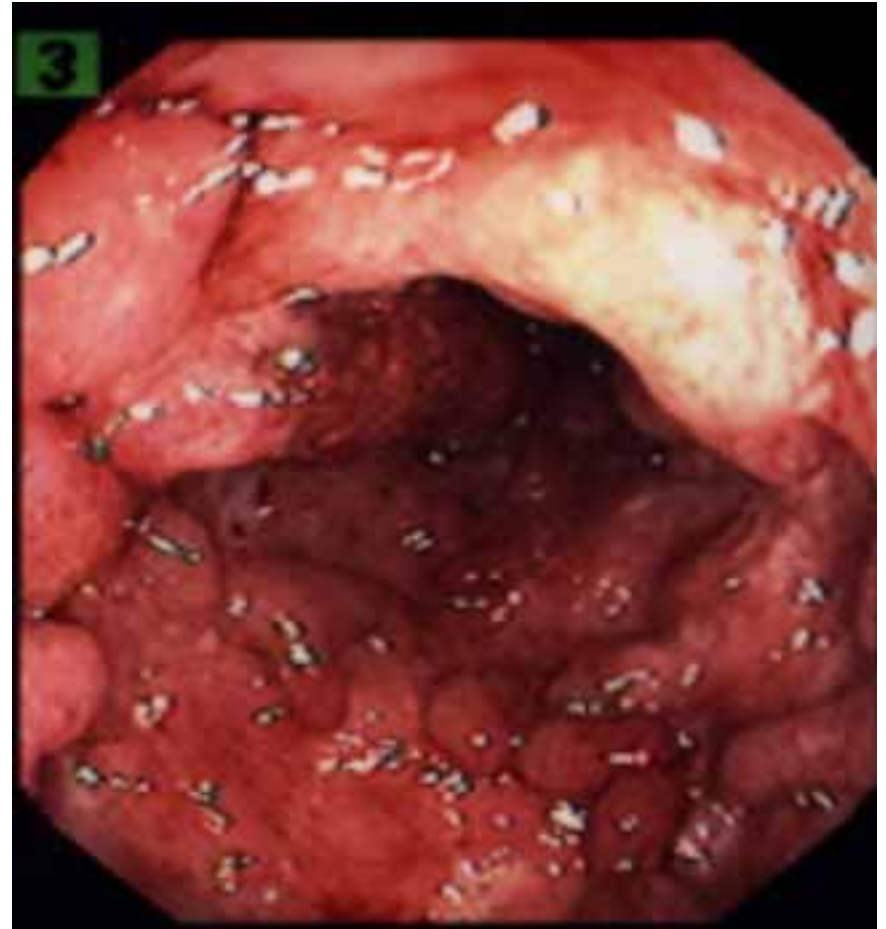
Genetics of autoimmune diseases

- Most autoimmune diseases are complex multigenic traits (numerous associated polymorphisms)
- The hope is that defining the susceptibility genes will provide clues about pathogenesis and suggest new therapeutic targets

Crohn's disease: colitis

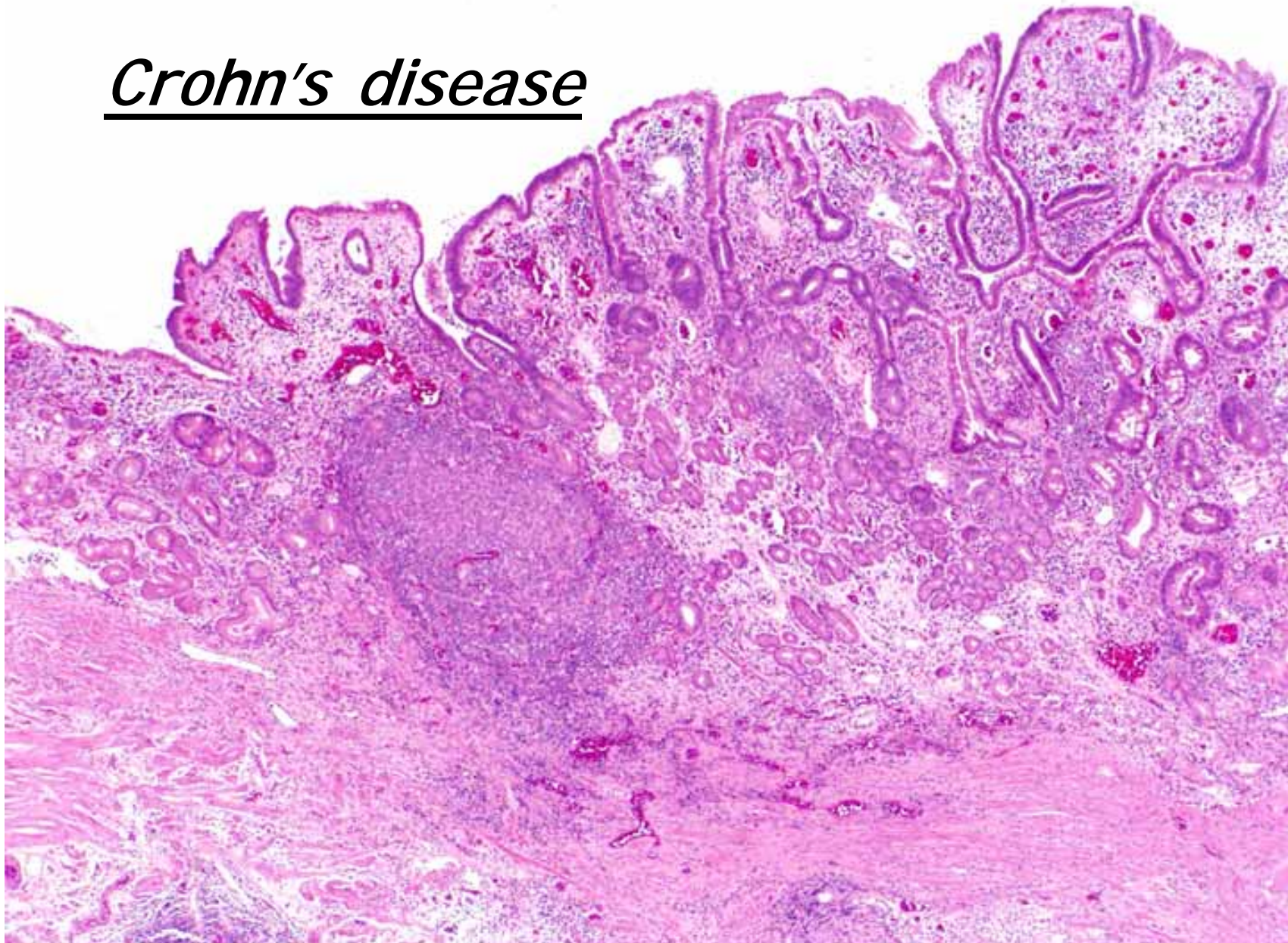


Normal



Inflamed

Crohn's disease

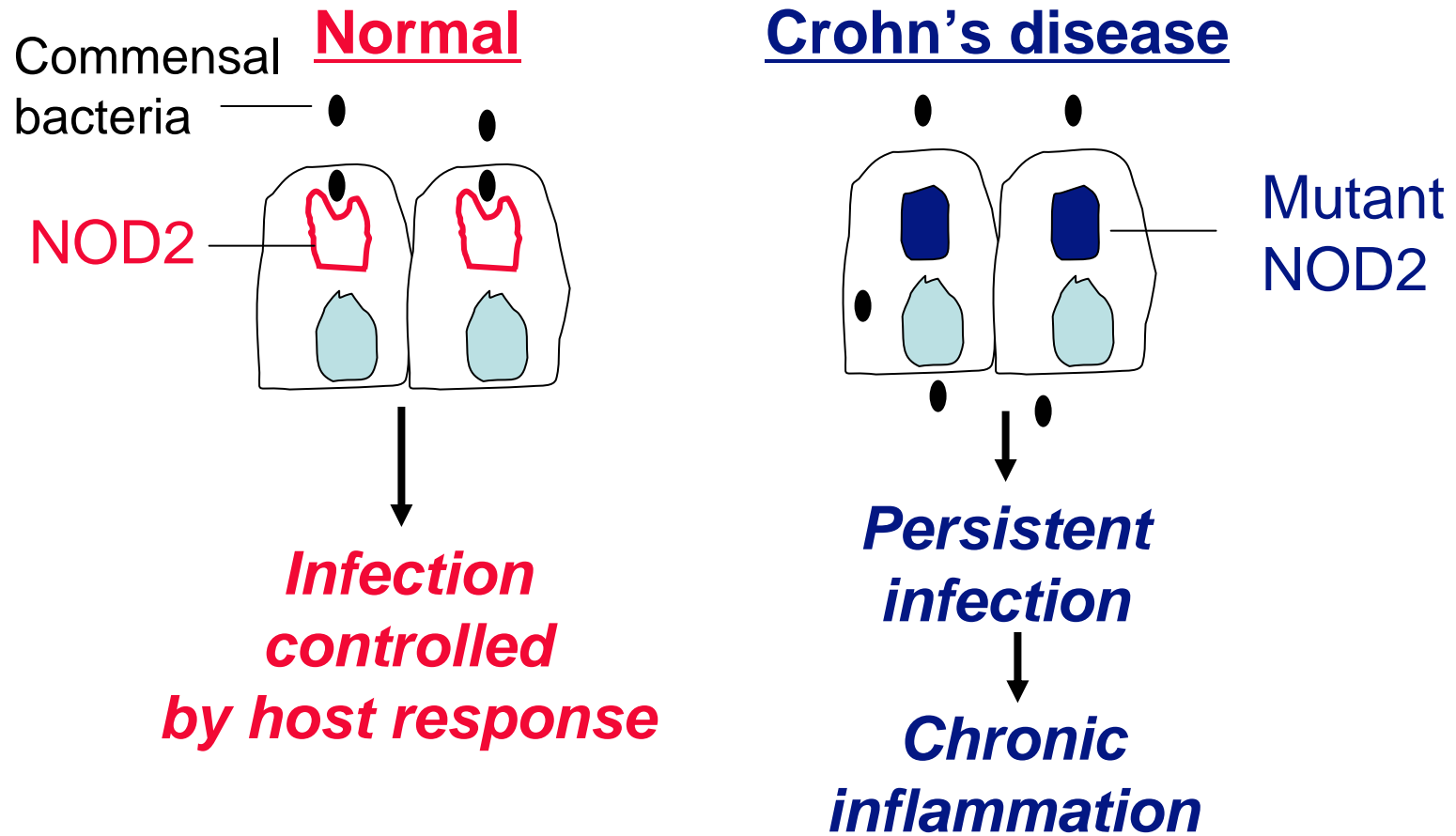


Transmural inflammation, mucosal granulomas

Genes and Crohn's disease

- About 25% of patients with Crohn's disease have mutations in a gene called *NOD2*
- The NOD2 protein is an intracellular receptor for bacterial peptides (e.g. muramyl dipeptide) that triggers protective anti-bacterial host responses

Postulated role of Nod2 in Crohn's disease



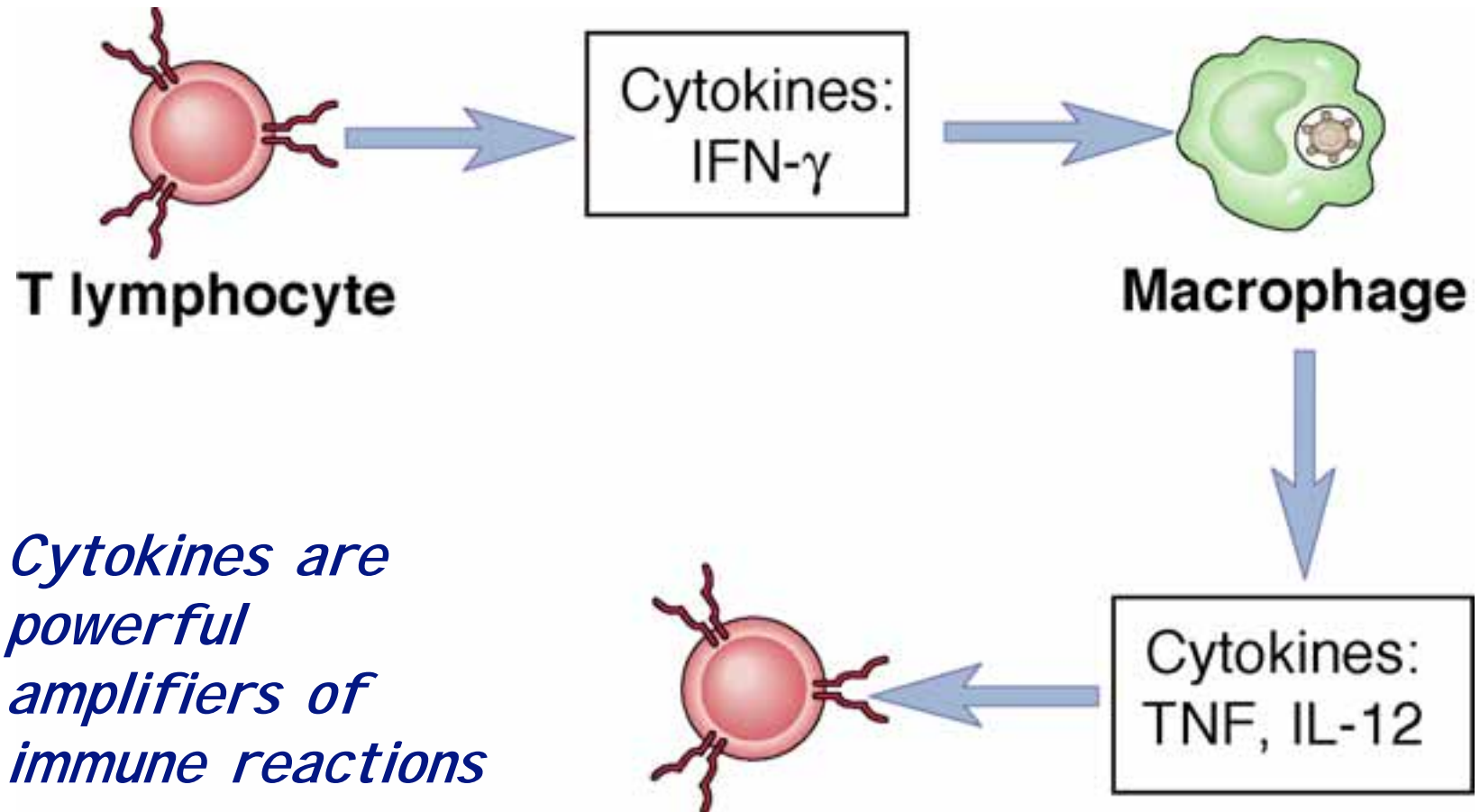
Infection and autoimmunity

- Crohn's disease: association with Nod2 mutation
- In a mouse model of systemic autoimmunity:
 - IBD resolves in germ-free animals
 - Anti-DNA antibody, autoimmune hemolytic anemia persist in germ-free animals
- Role of infection differs in different diseases (sometimes protective -- the "hygiene hypothesis")

Immune-mediated diseases -- 2

- Immunological diseases tend to be chronic and intractable, because --
 - The initiating trigger can often not be eliminated (self antigen, commensal microbes)
 - The immune system contains many built-in amplification mechanisms whose normal function is to optimize our ability to combat infections

Amplification loop in cell-mediated immunity



Cytokines are powerful amplifiers of immune reactions

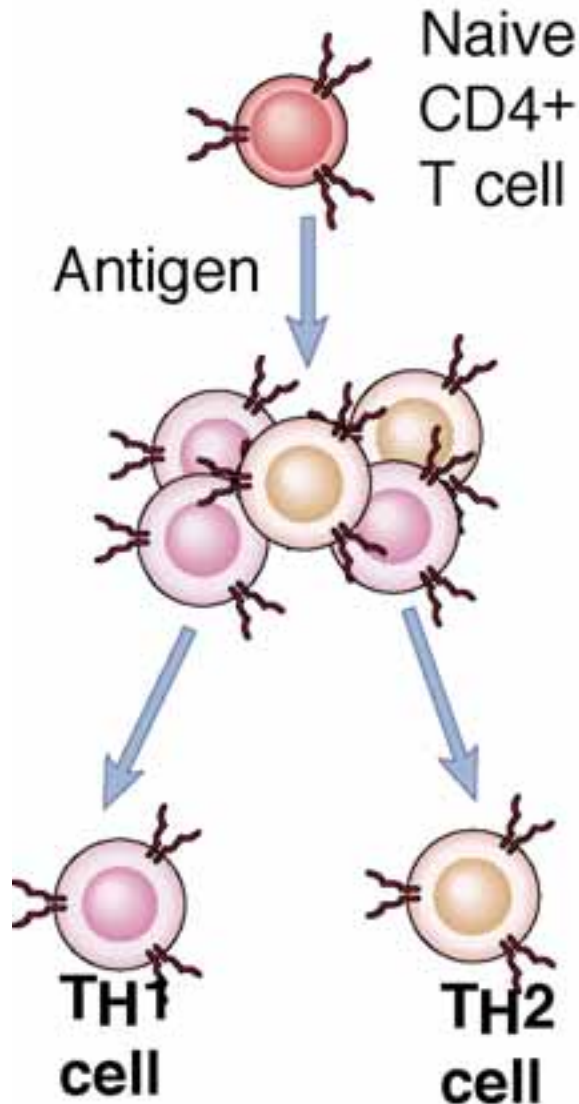
Targeting cytokine networks for therapy

- TNF antagonists for rheumatoid arthritis, IBD
- IL-12 antagonists (and many others) in clinical trials

Immune-mediated diseases -- 3

- The nature of the disease is determined by the type of dominant immune response
 - "Th1 response": destructive inflammation; most autoimmune diseases
 - "Th2 response": IgE-eosinophil-mediated inflammation; allergic reactions

Subsets of CD4+ helper T cells



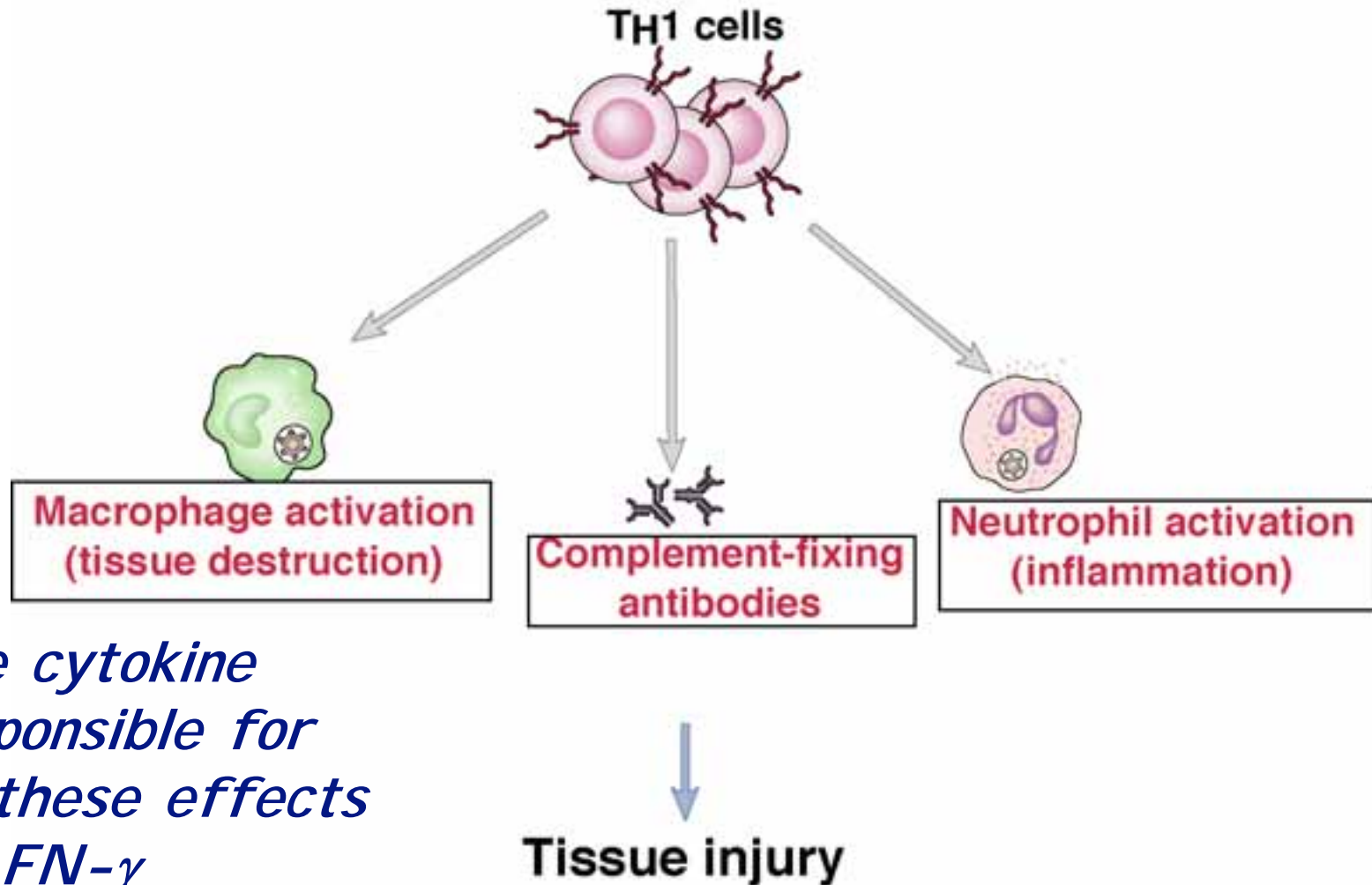
Under different activation conditions, CD4+ helper T cells can differentiate into subpopulations that make different cytokines and perform different functions

Signature cytokines:

TH1 cells: IFN- γ

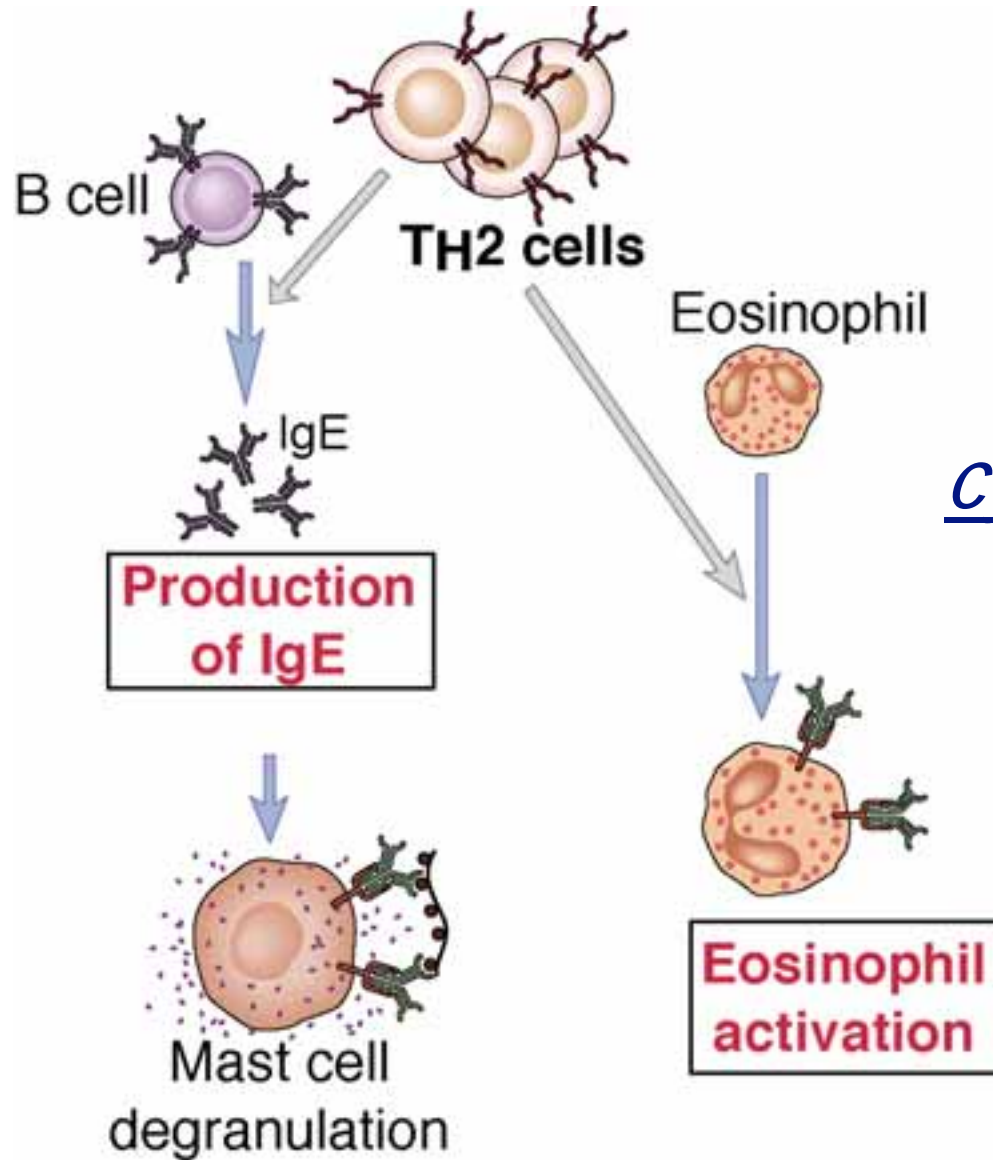
TH2 cells: IL-4, IL-5

TH1 cells are involved in immune-mediated inflammatory diseases



The cytokine responsible for all these effects is $IFN-\gamma$

TH2 cells are involved in allergic diseases



Cytokines involved:

IgE production --

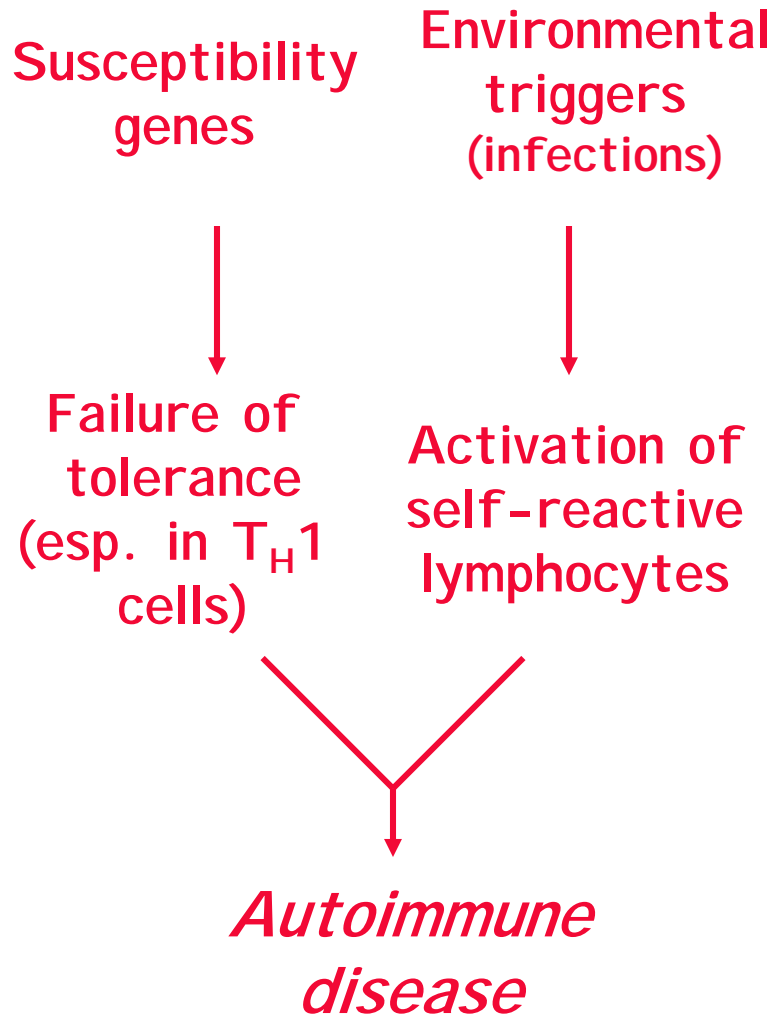
IL4

Eosinophil activation --

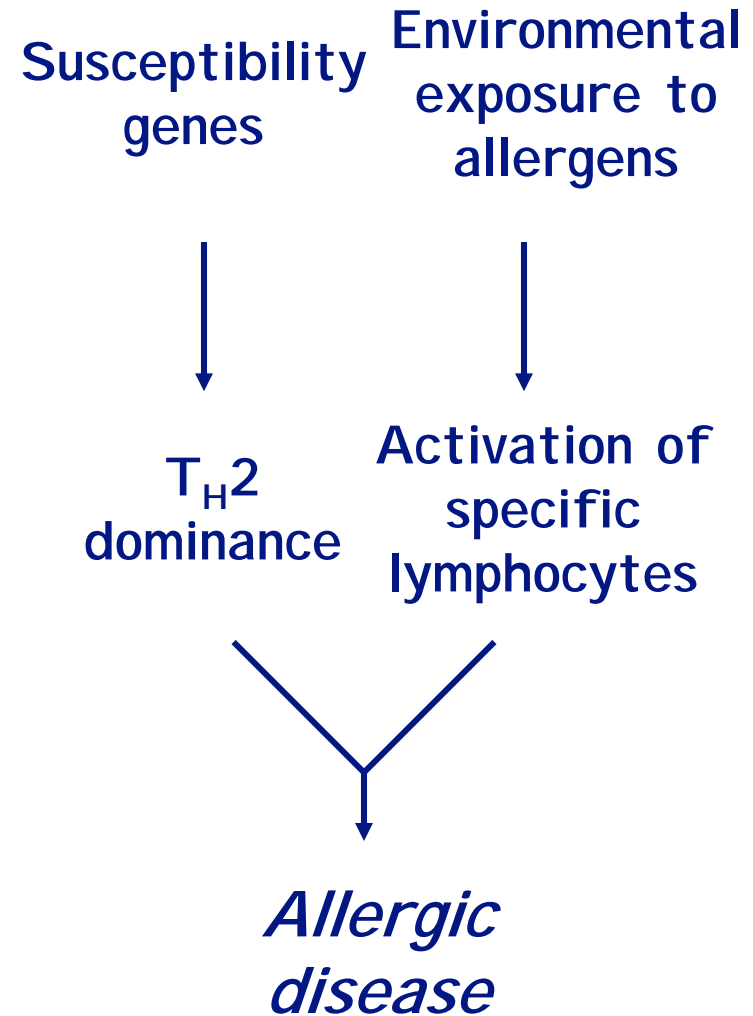
IL-5

Pathogenesis of immunologic diseases

Autoimmunity



Allergy



Immune-mediated inflammatory diseases

- Many of these diseases develop because normal controls in the immune system fail
- These diseases tend to be chronic and difficult to eradicate
- Phenotypic variations in the diseases reflect the dominance of different types of immune responses

The immune system and disease: where have we been and where are we going

- The normal immune response is understood in quite precise molecular detail
 - Value of animal models
- The greatest challenges remaining are to understand why self-tolerance fails to give rise to autoimmune diseases
 - Genetic approaches, clinical trials