Type IV Hypersensitivity

TABLE 19.1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody-mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, for example, hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: Type IV	1. $CD4^+$ T cells (Th1 and Th17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation and macrophage activation 2. Direct target cell killing, cytokine-mediated inflammation

CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

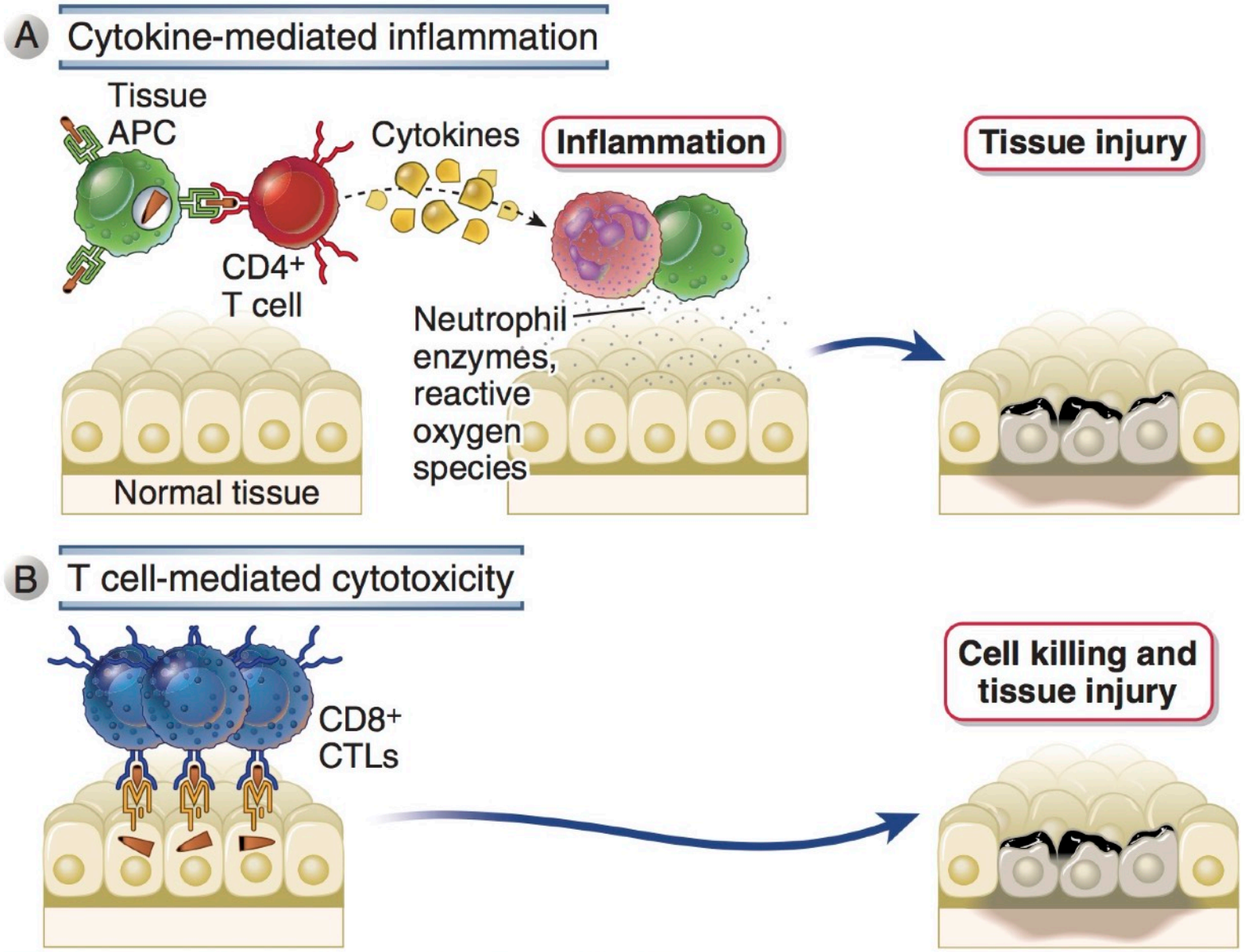


FIGURE 19.5 Mechanisms of T cell–mediated diseases. A, In cytokine-mediated inflammatory reactions, $CD4^+$ T cells (and sometimes $CD8^+$ cells, not shown) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate leukocytes, leading to tissue injury. **B,** In some diseases, $CD8^+$ CTLs directly kill tissue cells. *APC,* Antigen-presenting cell.

Killing by cytotoxic T cells

- release some substances known as perforin, granzyme A,B,C and serglycin and granulysin

- the CTL may release cytokines

Cell-Mediated Immunity

Phagocytosis and killing

- CTLs: Direct cell killing and cytokines release
- NK cells: Direct cell killing
- Macrophages: phagocytosis and release
- Neutrophils: release
- Th cells: cytokines release
- Mast cells: release
- …

Type IV hypersensitivity

DTH (Delayed Type hypersensitivity)
Cell-mediated hypersensitivity

•Is a T cell mediated inflammatory response, in which stimulation of Th cells leads to macrophage activation and localized inflammation and edema within tissues

•This effector T cell response is essential for the control of intracellular and other pathogens.

Examples of Microbial-Induced DTH

- Viruses (destructive skin rashes)
  - smallpox
  - measles
  - herpes simplex
- Fungi
  - candidiasis
  - dematomycosis
  - coccidioidomycosis
  - histoplasmosis
- Parasites (against enzymes from the eggs lodged in liver)
  - leishmaniasis
  - schistosomiasis

How Important is the DTH Response?

- The AIDS virus illustrates the **vitally** important role of the cellular response in protecting against various intracellular pathogens.

- The disease cause severe depletion of CD4+ T cells, which results in a loss of the cellular response.

- AIDS patients develop life-threatening infections from intracellular pathogens that normally would not occur in individuals with intact cellular responses.

Type IV hypersensitivity

- DTH (Delayed type hypersensitivity)
- Is a T cell mediated inflammatory response, in which stimulation of T cells leads to macrophage activation and localized inflammation and edema within tissues.
- This effector T cell response is essential for the control of intracellular and other pathogens.

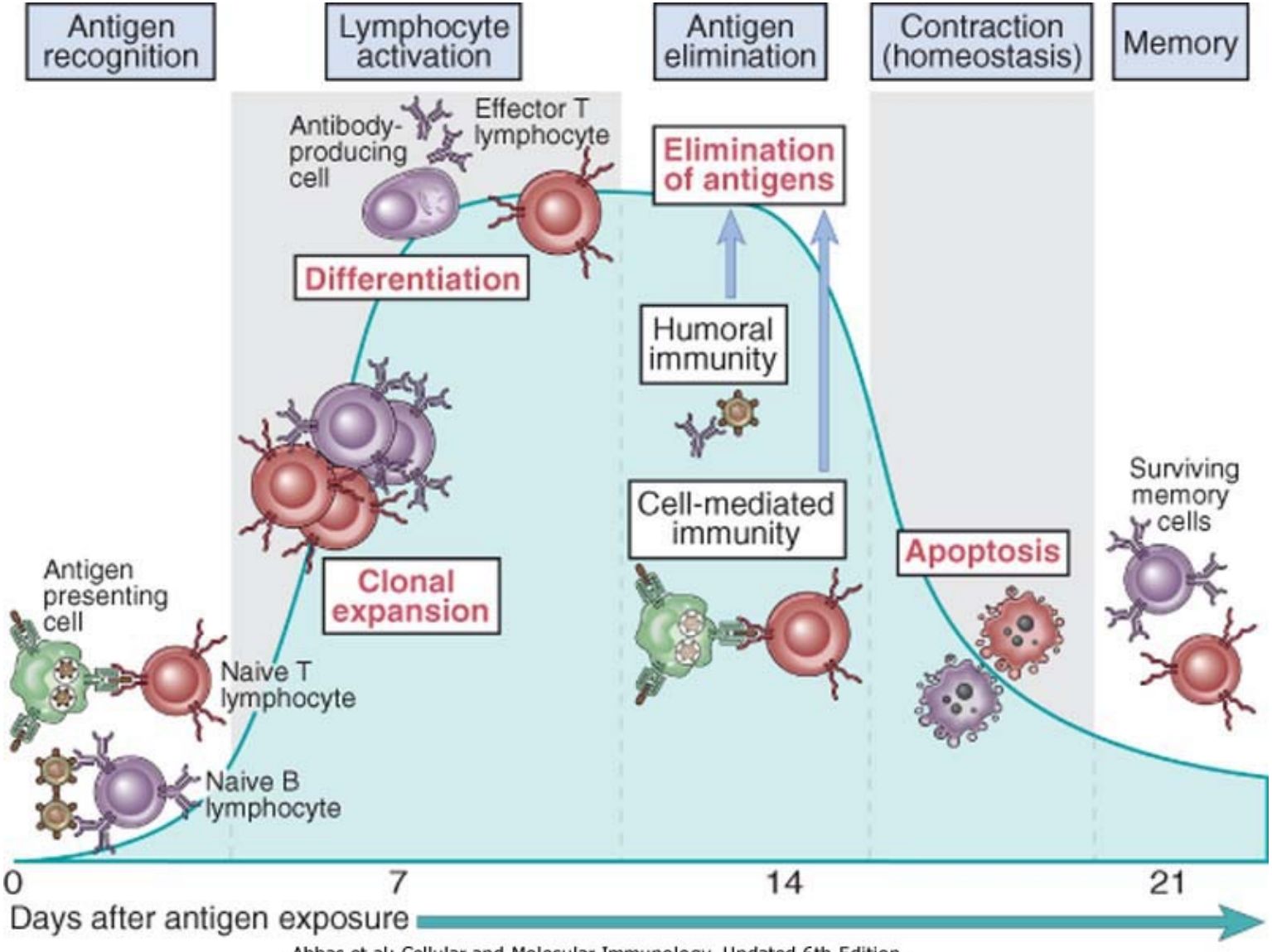
- **If the response is excessive or against self Ags it can damage host tissues**

Type IV Hypersensitivity

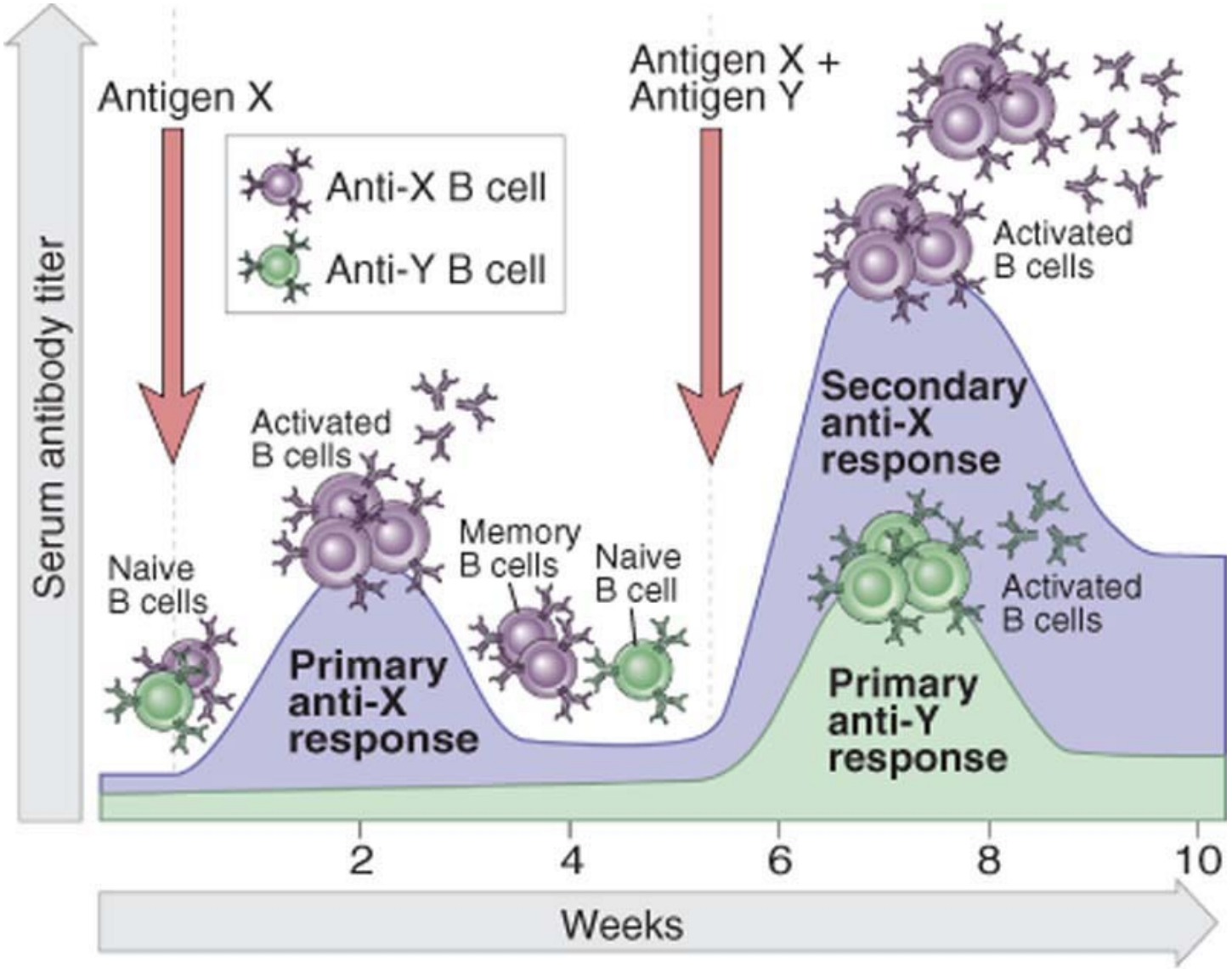
What is delayed type hypersensitivity (DTH)?

- A hypersensitive response mediated by sensitized T cells, which release various cytokines and chemokines
- Generally occurs “at least” 2-3 days after T cells interact with antigen

Phases of adaptive immune response



Timing for immune response



Phases of the DTH Response

1. **Sensitization** – TH1 cells triggered by contact with APC

Stages of Type IV DTH
sensitization-Effector stage

- **Th1** memory cells production. Then they have to be activated to produce cytokines.
  - IFN-γ, TNF-α, and TNF-β which cause tissue destruction, inflammation.
  - IL-2 that activates Th cells and CTLs.
  - Chemokines- for macrophage recruitment.
  - IL-3, GM-CSF for increased monocyte/macrophage

Phases of the DTH Response

1. **Sensitization** – TH1 cells triggered by contact with APC
2. **Effector response** – produces huge influx of activated MØ
    1. Activated MØ is more efficient at antigen-presentation
    2. Release of lytic enzymes lead to non-specific destruction of cells
    3. Works well against intra-cellular pathogens
    4. If pathogen/particle lingers -> can lead to **granuloma** formation
        1. Ex: *Mycobacterial* pathogens in TB and Leprosy

Stages of Type IV DTH
Effector stage

- Inflamed area becomes red and fluid filled can form lesion.
  - From tissue damage there is activation of clotting cascades and tissue repair.

- Continued exposure to antigen can cause chronic inflammation and result in granuloma formation.

Tissue damages of cellular response (type IV HyperSensitivity)

There are 3 variants of type IV HS reaction

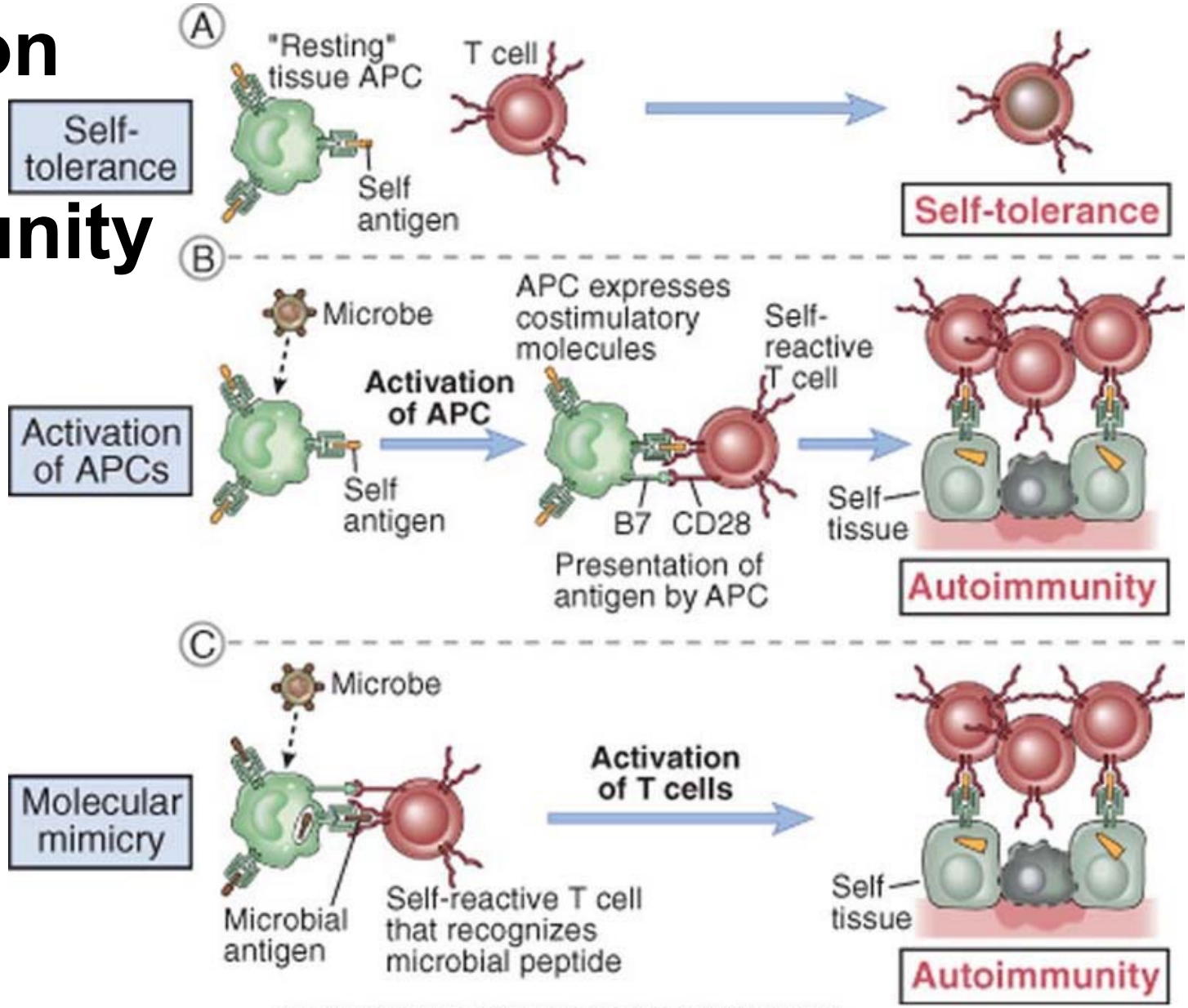
- Contact HS
- Tuberculin type HS
- Granulomatous HS

Type	Reaction time	Clinical appearance	Histology	Antigen and site
contact	48-72 hr	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, heavy metals, *etc.*)
tuberculin	48-72 hr	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, lepromin, *etc.*)
granuloma	21-28 days	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, leprosy, *etc.*)

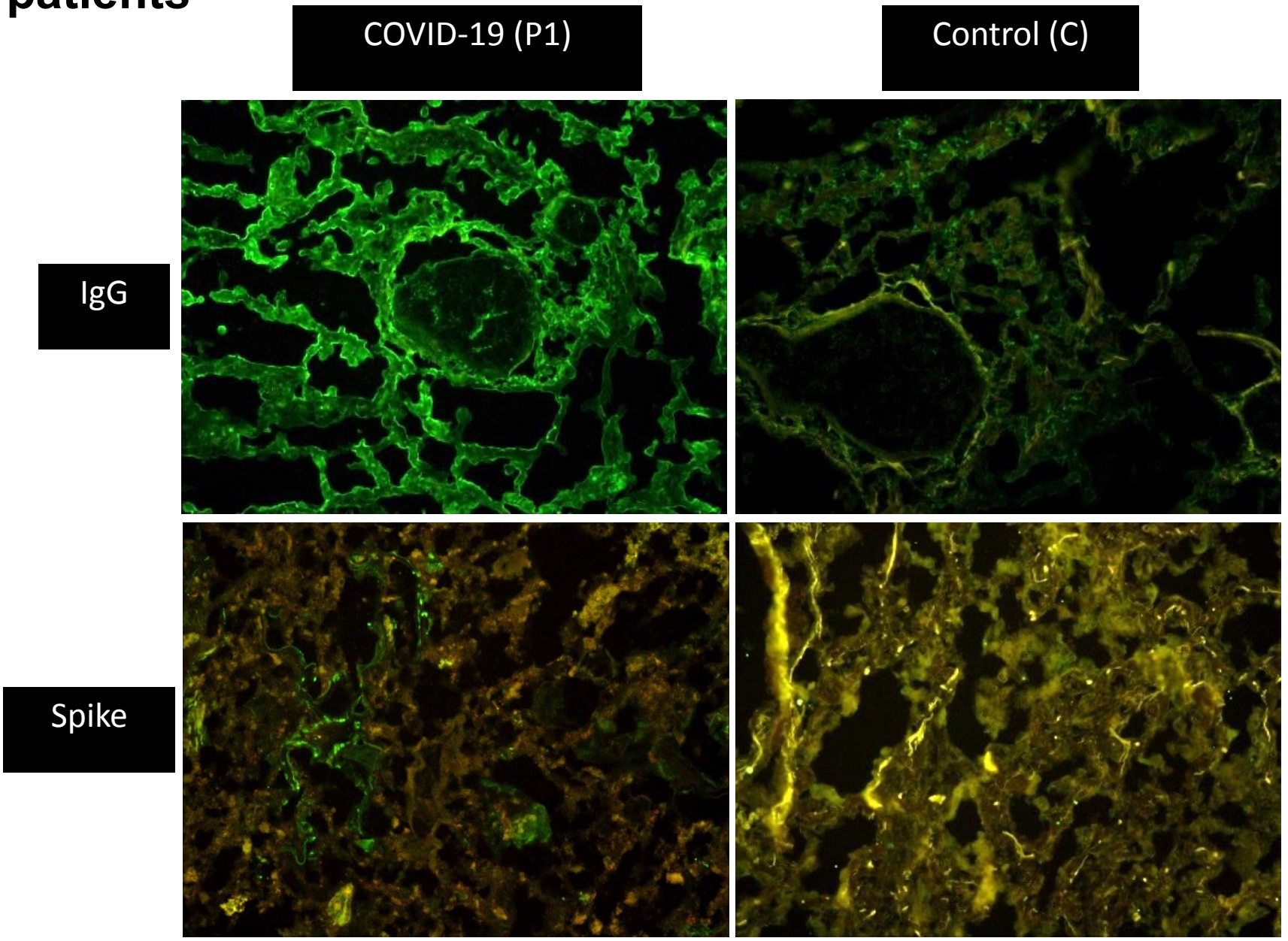
Tissue damages of cellular response (type IV HyperSensitivity)

Different “problems” happened if the antigen in not eliminated or confined…. like in autoimmune diseases

Infection and autoimmunity



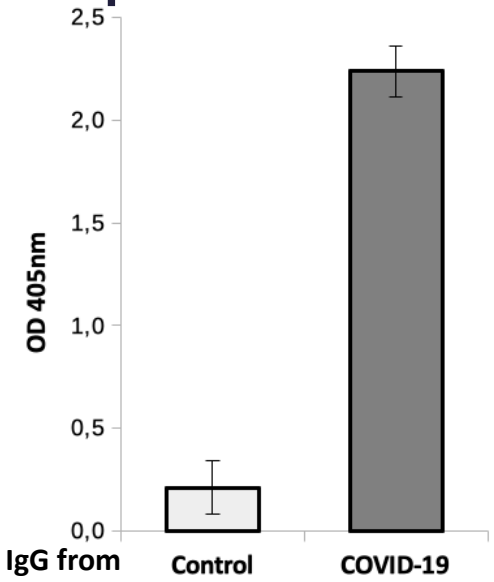
IgG vs spike protein in lungs from COVID-19 or control patients



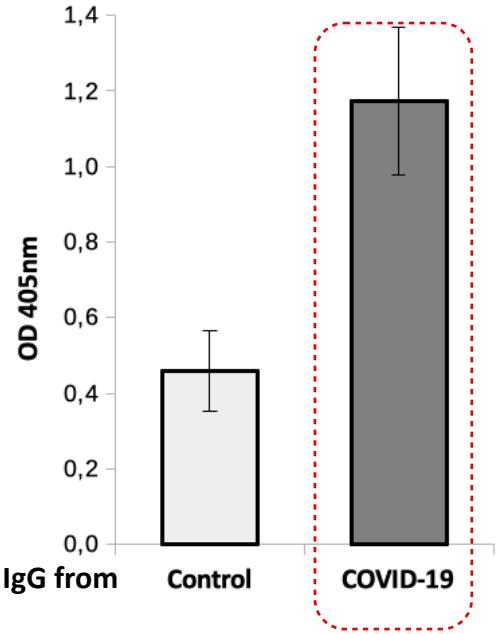
Evaluation of autoantibodies in lungs from COVID-19 or control patients

Lung sections → RIPA buffer → lysed tissues → Protein A column → 1. Antibodies from tissues; 2. Tissue proteins

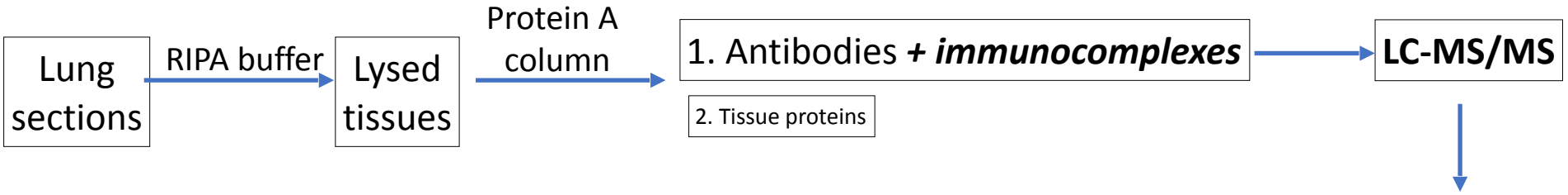
ELISA (IgG) on COVID-19 tissue proteins



ELISA (IgG) on Control tissue proteins

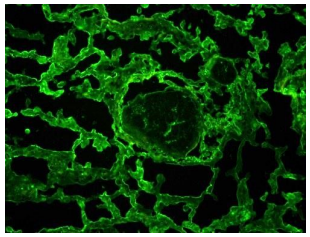


Evaluation of antibody targets in lungs from COVID-19 and control patients



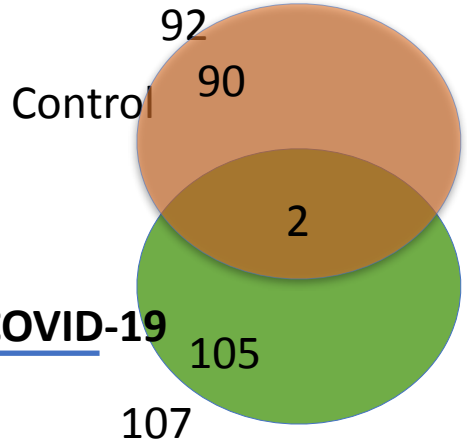
List of membrane proteins specific in COVID-19 samples

Entry	Name	Entry	Name	Entry	Name
P00918	CA2	Q9UBX5	FBLN5	O96009	NAPSA
P62937	PPIA	P08311	CTSG	P16452	EPB42
P06702	S100A9	P07900	HSP90AA	P21810	BGN
P37802	TAGLN2	P21980	TGM2	P11166	SLC2A1
P27105	STOM	Q01518	CAP1	Q6UX06	OLFM4
Q08431	MFGE8	P02792	FTL	P17931	LGALS3
P05109	S100A8	P60981	DSTN	Q9NZN	EHD2
P26447	S100A4	P60842	EIF4A1	P05023	ATP1A1
P11021	HSPA5	P14555	PLA2G2A	P06744	GPI
Q12805	EFEMP1	P15311	EZR	P18428	LBP
P60953	CDC42	P11142	HSPA8	O75131	CPNE3
P07237	P4HB	P27797	CALR	P12111	COL6A3
P08238	HSP90AB	P07988	SFTPB	P98160	HSPG2
P60660	MYL6	P29401	TKT	P02461	COL3A1
P63244	GNB2L1	P07585	DCN		
P23142	FBLN1	P00488	F13A1		



46 proteins on membrane

Analysis of proteins present in 3/3 samples



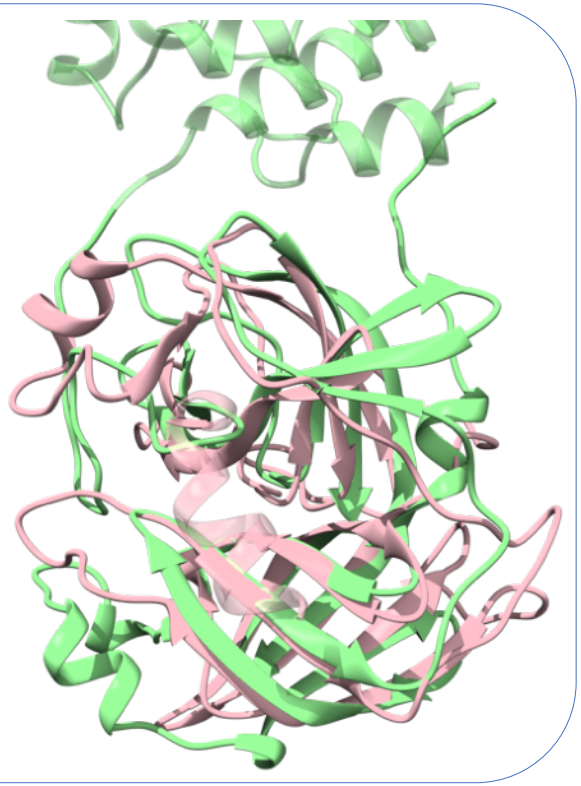
Comparison of antibody targets and SARS-CoV-2 proteins to evaluate molecular mimicry

46 protein targets of **Abs** → Structure from crystal in literature or from Alphafold

18 protein structures from **SARS-CoV-2** → Structure from crystal in literature or from Alphafold

Cathepsin-G (pink)

3CLproteinase (green)



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P27105	STOM	Q01518	CAP1	Q6UX06	OLFM4
Q08431	MFGE8	P02792	FTL	P17931	LGALS3
P05109	S100A8	P60981	DSTN	Q9NZN4	EHD2
P26447	**S100A4**	**P60842**	**EIF4A1**	P05023	ATP1A1
P11021	HSPA5	P14555	PLA2G2A	P06744	GPI
Q12805	EFEMP1	**P15311**	**EZR**	P18428	LBP
P60953	CDC42	**P11142**	**HSPA8**	O75131	CPNE3
P07237	P4HB	P27797	CALR	P12111	COL6A3
P08238	HSP90AB1	P07988	SFTPB	P98160	HSPG2
P60660	MYL6	P29401	TKT	P02461	COL3A1
P63244	GNB2L1	P07585	DCN		
P23142	FBLN1	P00488	F13A1		

1. CTSG: **Cathepsin G**

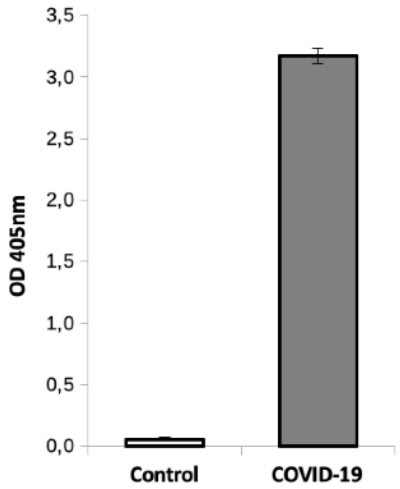
2. S100A8/ A9: **Calprotectin**

3. P4HB: **Protein disulfide-isomerase (PDI)**

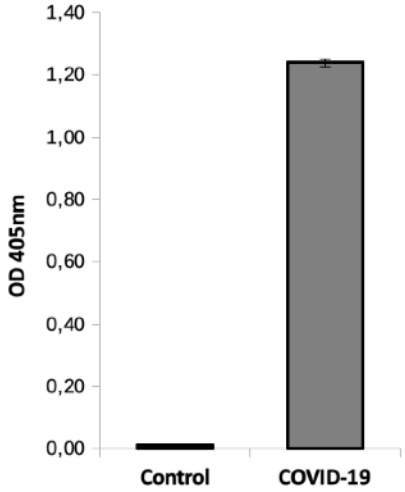
Evaluation of the presence of autoantibodies in COVID-19 or control samples

Lung Abs

1. CTSG: **Cathepsin G**



2. S100A8/ A9: **Calprotectin**



3. P4HB: **PDI**

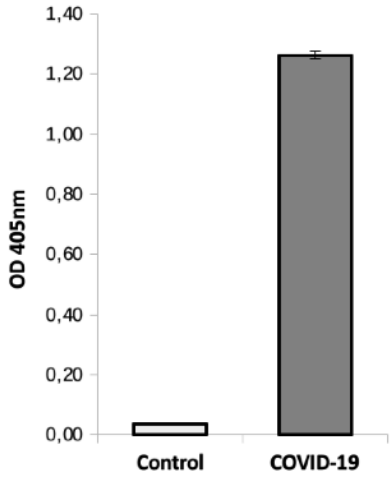


TABLE 19.4 T Cell–Mediated Diseases

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by Th1 and Th17 cytokines. Role of antibodies and immune complexes?
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by Th1 and Th17 cytokines; myelin destruction by activated macrophages
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation; destruction of islet cells by CTLs
Inflammatory bowel disease	Enteric bacteria. Self antigens?	Inflammation mediated by Th1 and Th17 cytokines
Psoriasis	Unknown skin antigens	Inflammation mediated by T cell–derived cytokines

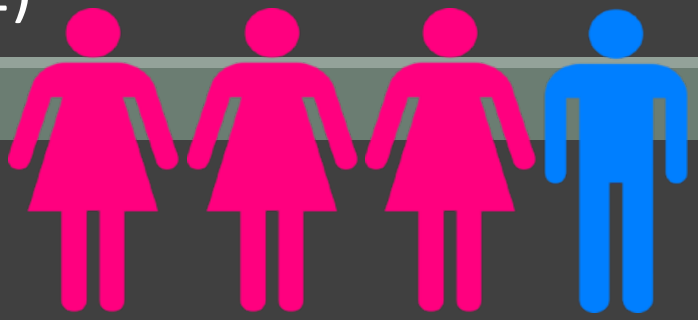
Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred on the basis of the similarity with experimental animal models of the diseases. The roles of Th1 and Th17 cells have been inferred from experimental models and the presence of subset-specific cytokines in human lesions. The cytokines may be produced by cells other than $CD4^+$ T lymphocytes. Ongoing clinical trials targeting these cytokines may provide new information about the contributions of the cytokines in different diseases.

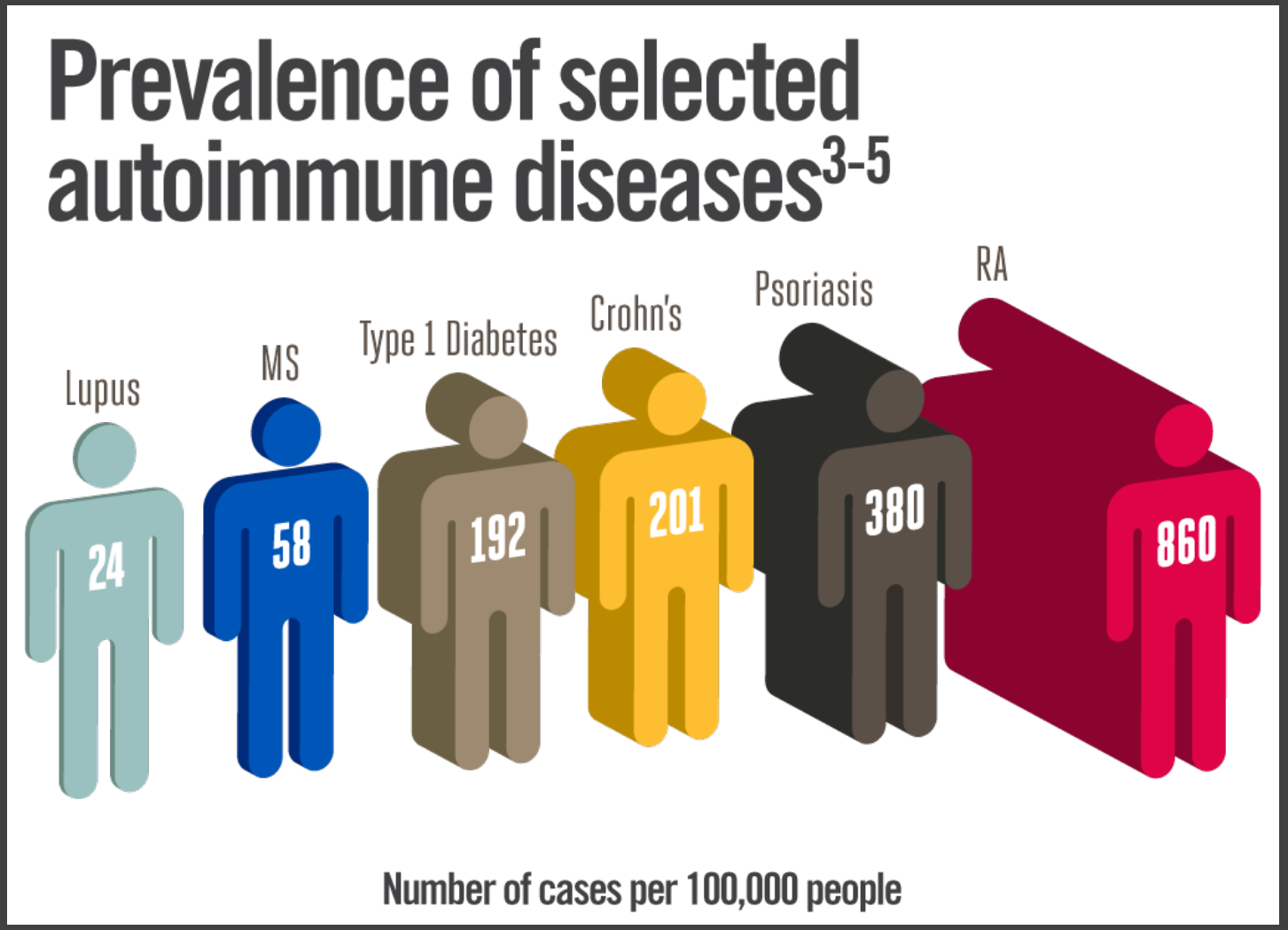
CTLs, Cytotoxic T lymphocytes.

Rheumatoid Arthritis (RA)

- Incidence of 0.5% to 1% in Europe and USA

- Some native Americans have high prevalence (6%)
- Positive family history increase risk 3 to 5 times
- Reduction from urban to rural areas
- More common in women than men (ratio 3:1)





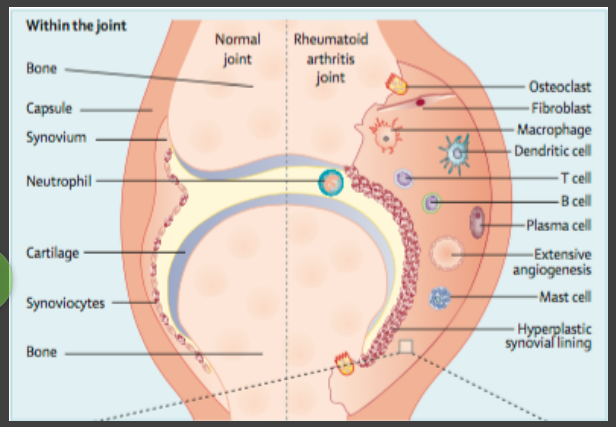
From: https://rheumatoidarthritis.net/what-is-ra/ra-statistics/

Rheumatoid Arthritis (RA)

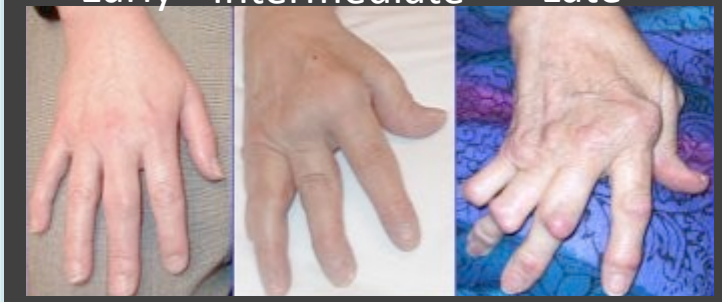
is a chronic autoimmune disease
which cause cartilage and bone damage as well as disability

Clinical manifestations

- Morning stiffness
- Joints swelling
- Articular pain
- Joints deformity
- Extra-articular manifestations



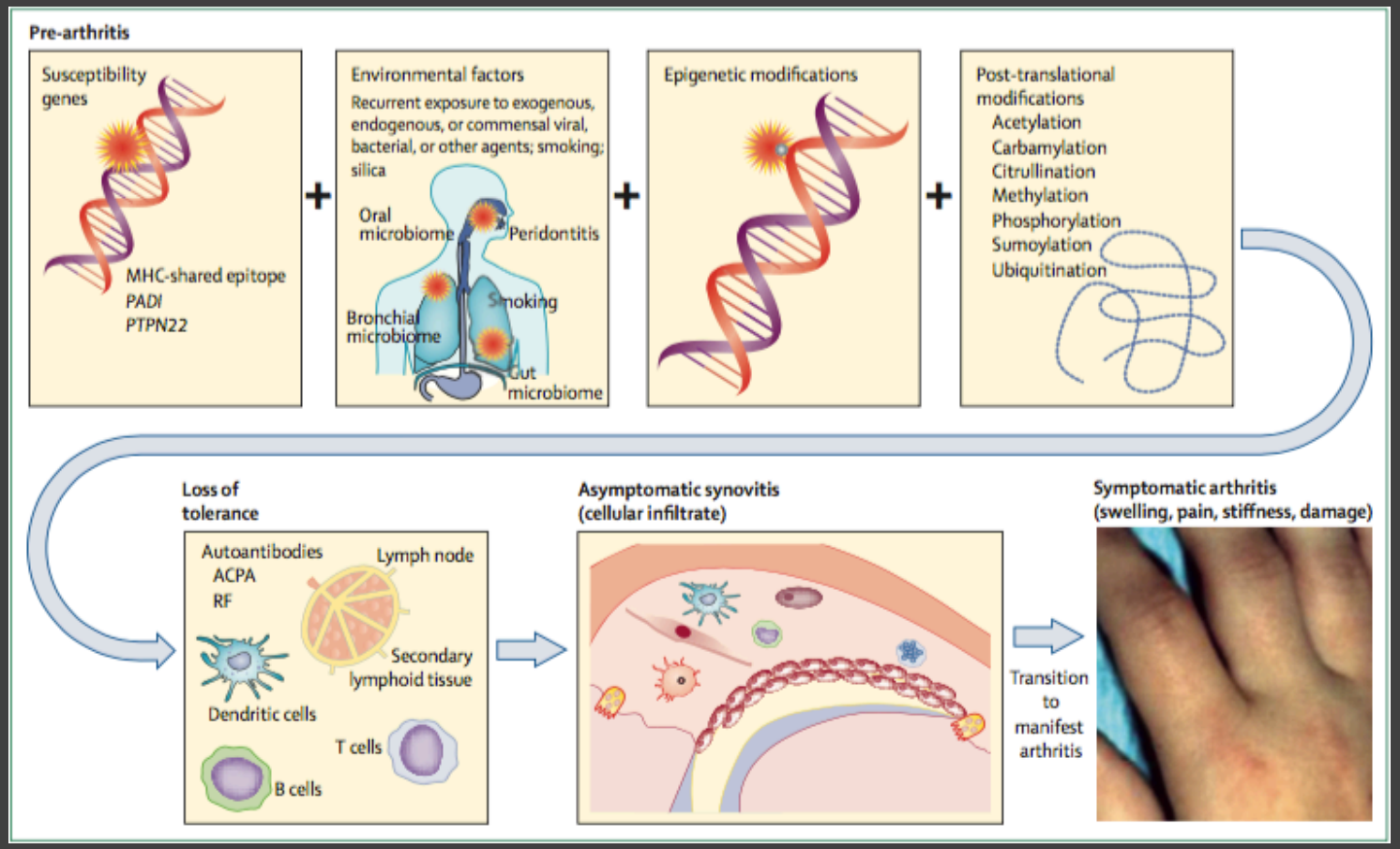
Early Intermediate Late



Josef S Smolen, Daniel Aletaha, Iain B McInnes Lancet, 2016
Adapted from http://www.physio-pedia.com/RA_(Rheumatoid_Arthritis)

Rheumatoid Arthritis (RA)

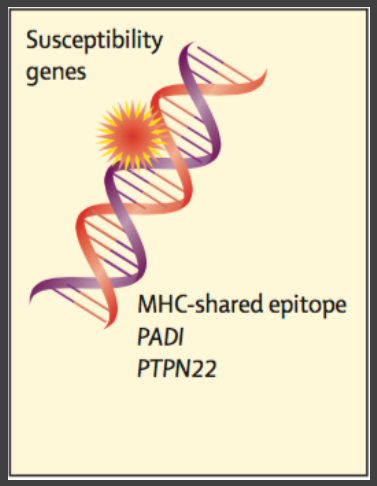
Unknown etiology…just hypothesis

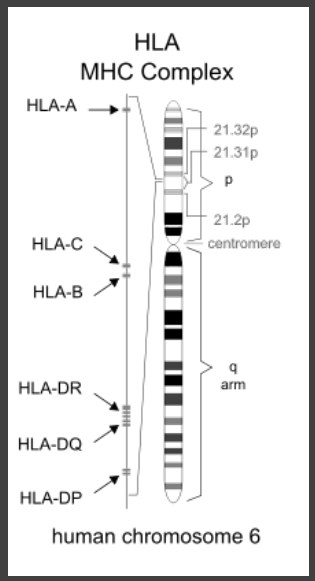


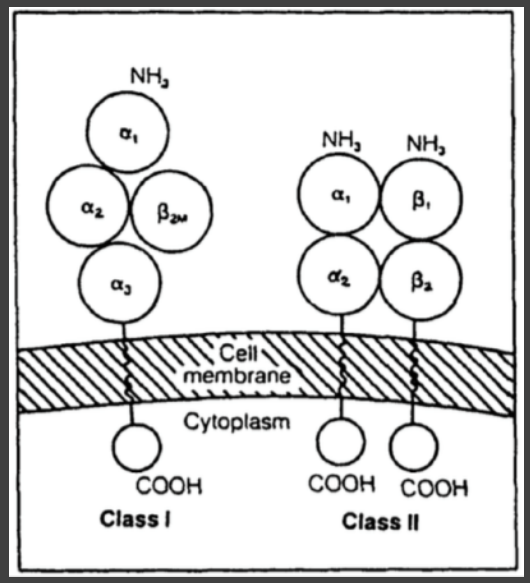
McInnes et al. NEJM 2001

Rheumatoid Arthritis (RA)

Genome wide association studies have characterized more than 100 loci associated with RA risk implicated with immune mechanisms and shared with other pathology



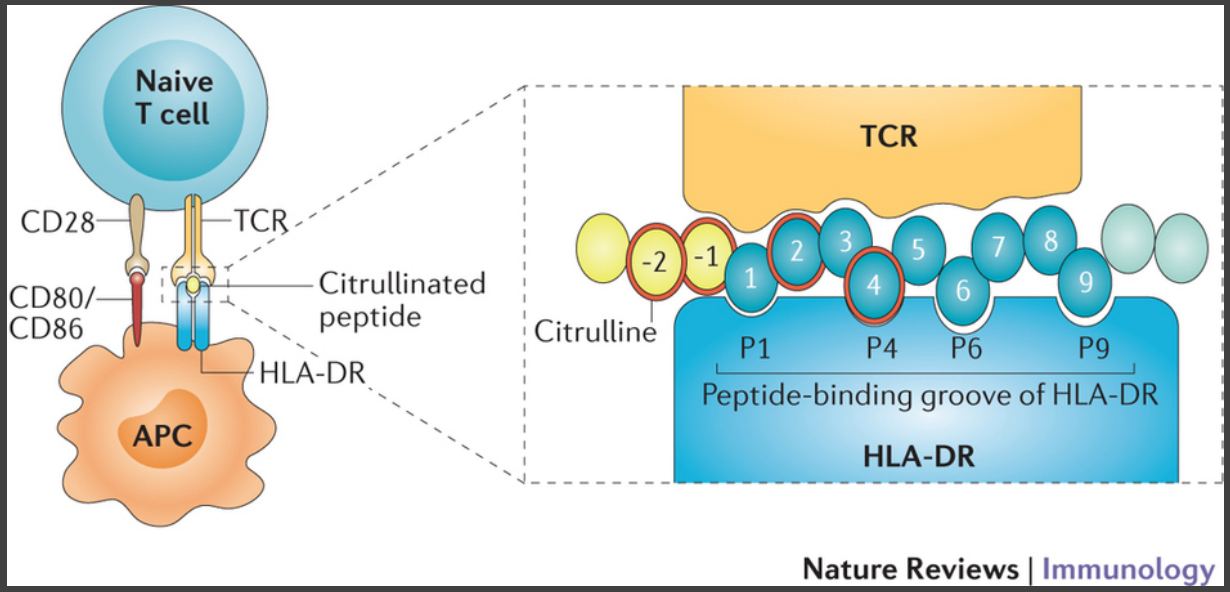




IB McInnes, G Schett - New England Journal of Medicine, 2011
PK Gregersen, J Silver, RJ Winchester - Arthritis & Rheumatism, 1987

Rheumatoid Arthritis (RA)

Specific binding to the RA-associated P4 pocket has been demonstrated for peptides from vimentin, fibrinogen, α-enolase, aggrecan and type II collagen



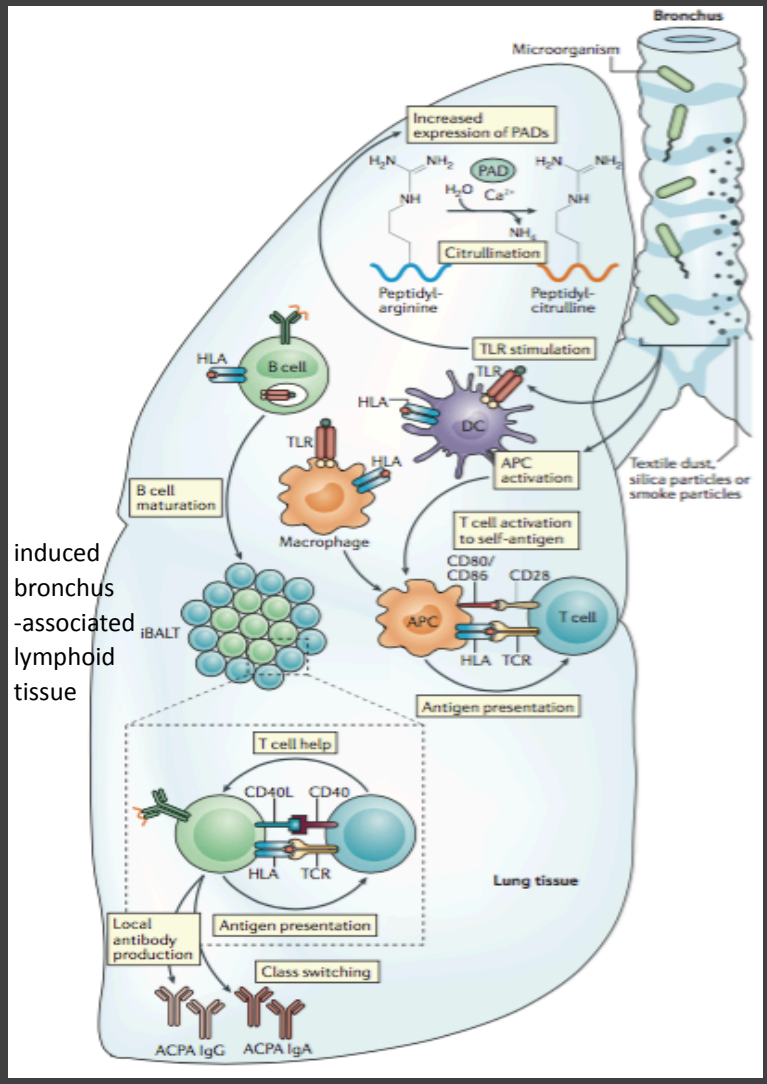
Aminoacids 11, 71 and 74 confer a positive charge to the P4. However, when arginine is converted in a neutral citrulline the peptide is able to fit in the P4

V Malmström et al. Nature Reviews Immunology, 2016

First step

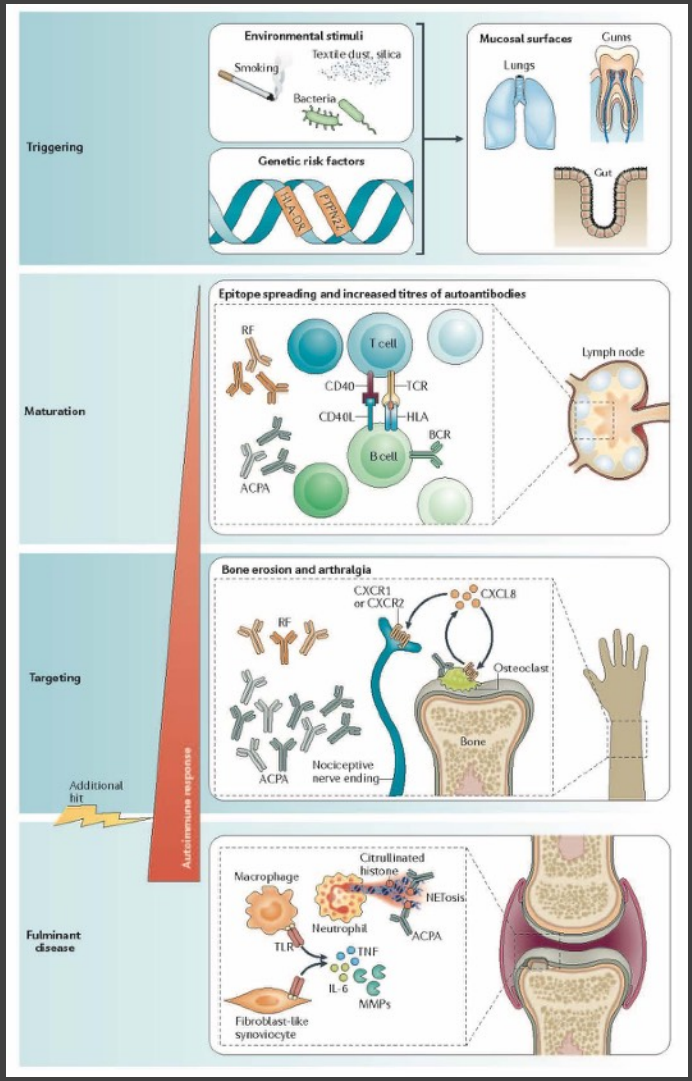
Local early immune activation

…..probably lungs, gums, intestine

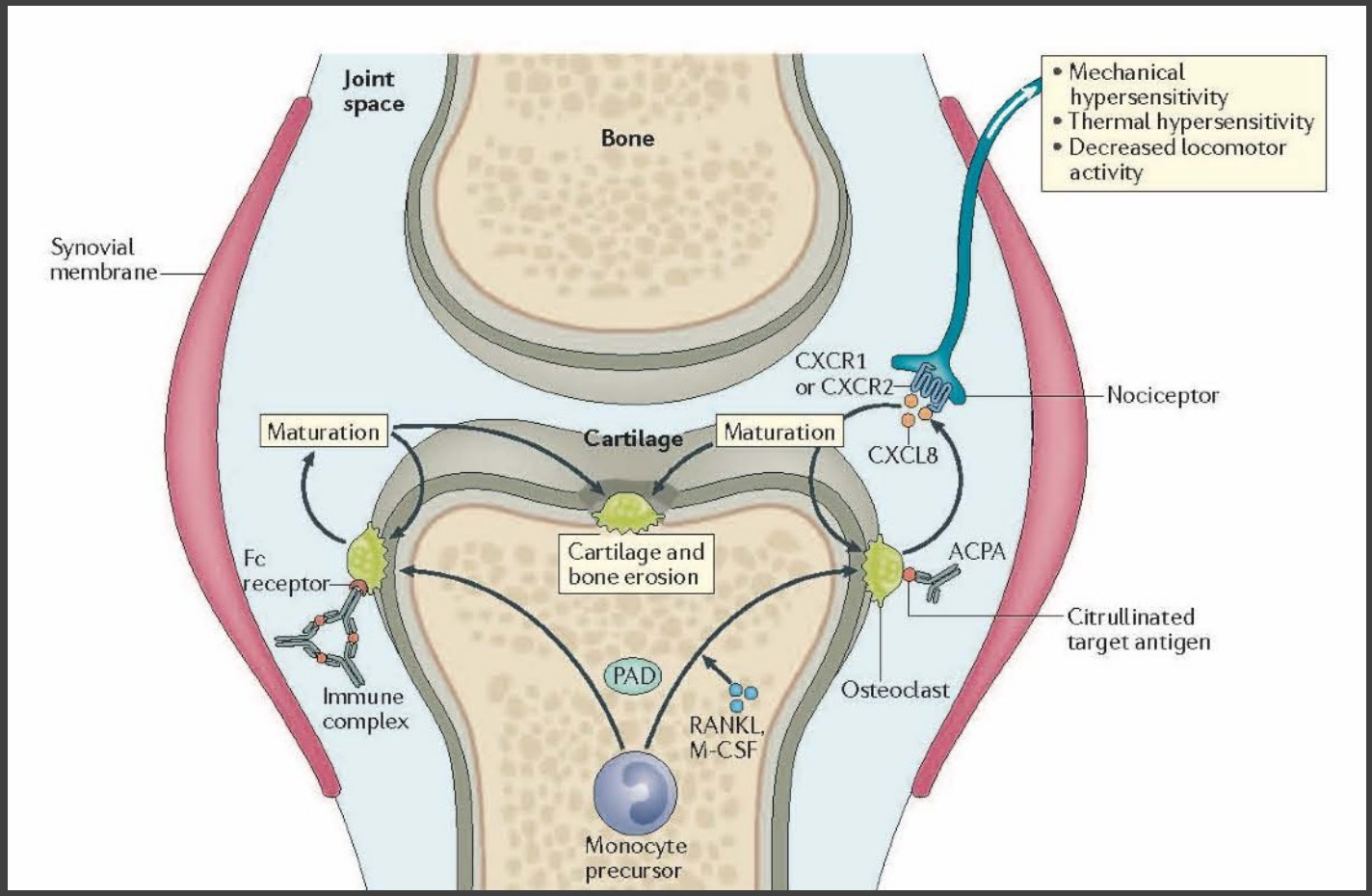


induced bronchus -associated lymphoid tissue

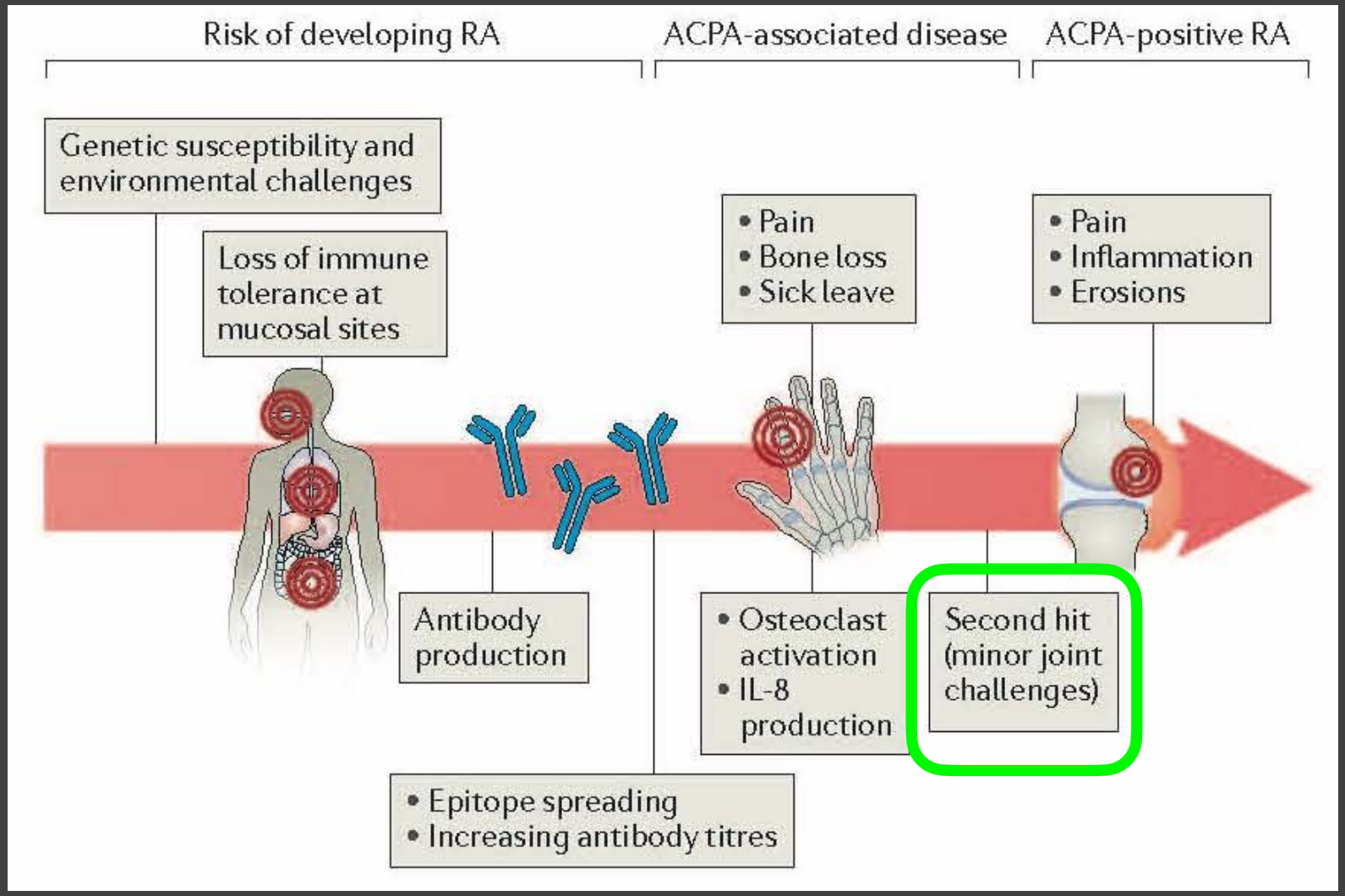
V Malmström et al. Nature Reviews Immunology, 2016



V Malmström et al. Nature Reviews Immunology, 2016



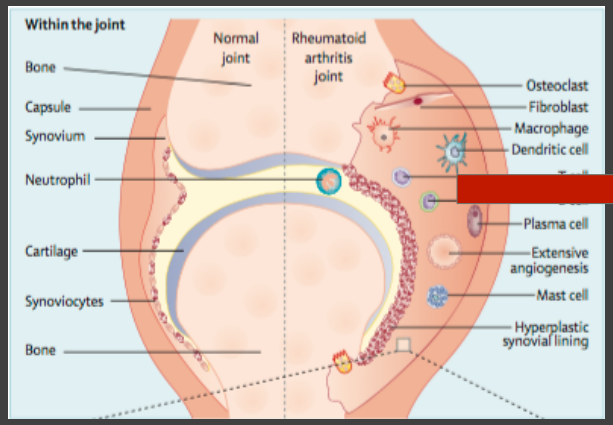
V Malmström et al. Nature Reviews Immunology, 2016



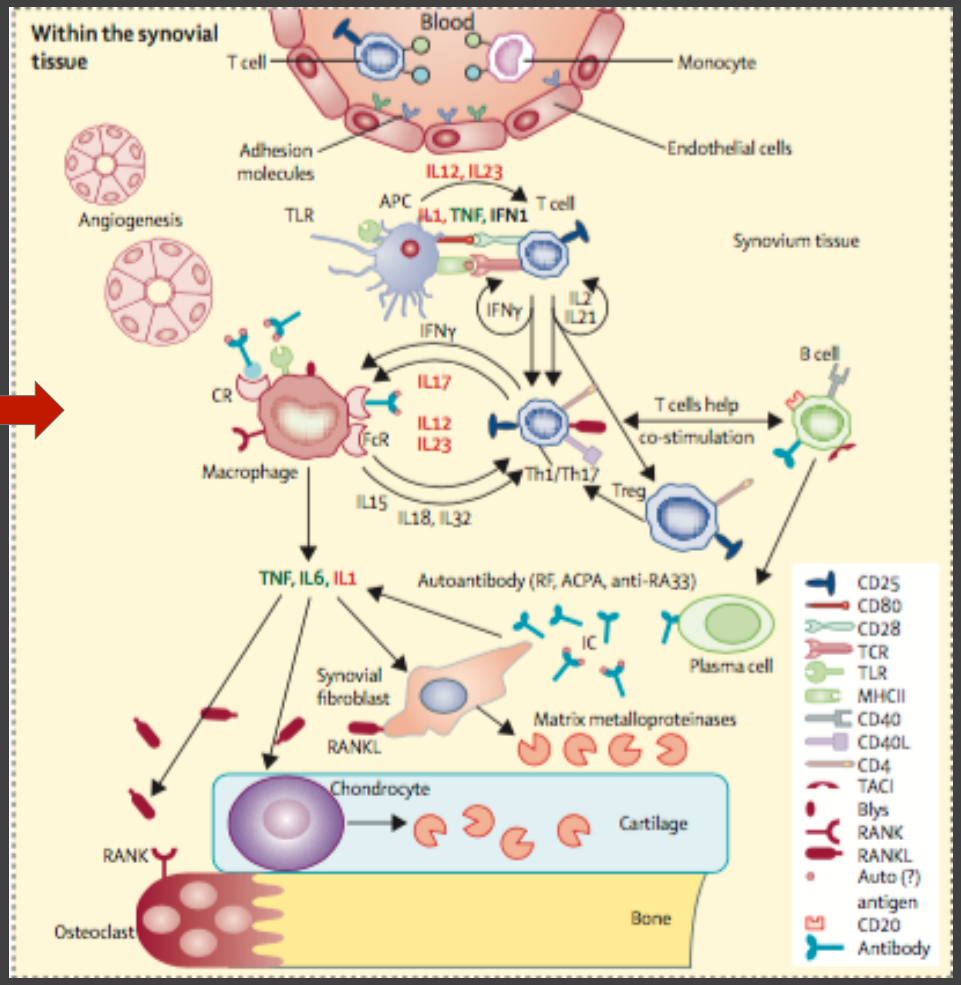
Catrina et al. Nature Review Rheumatology 2017

Rheumatoid Arthritis

Second step

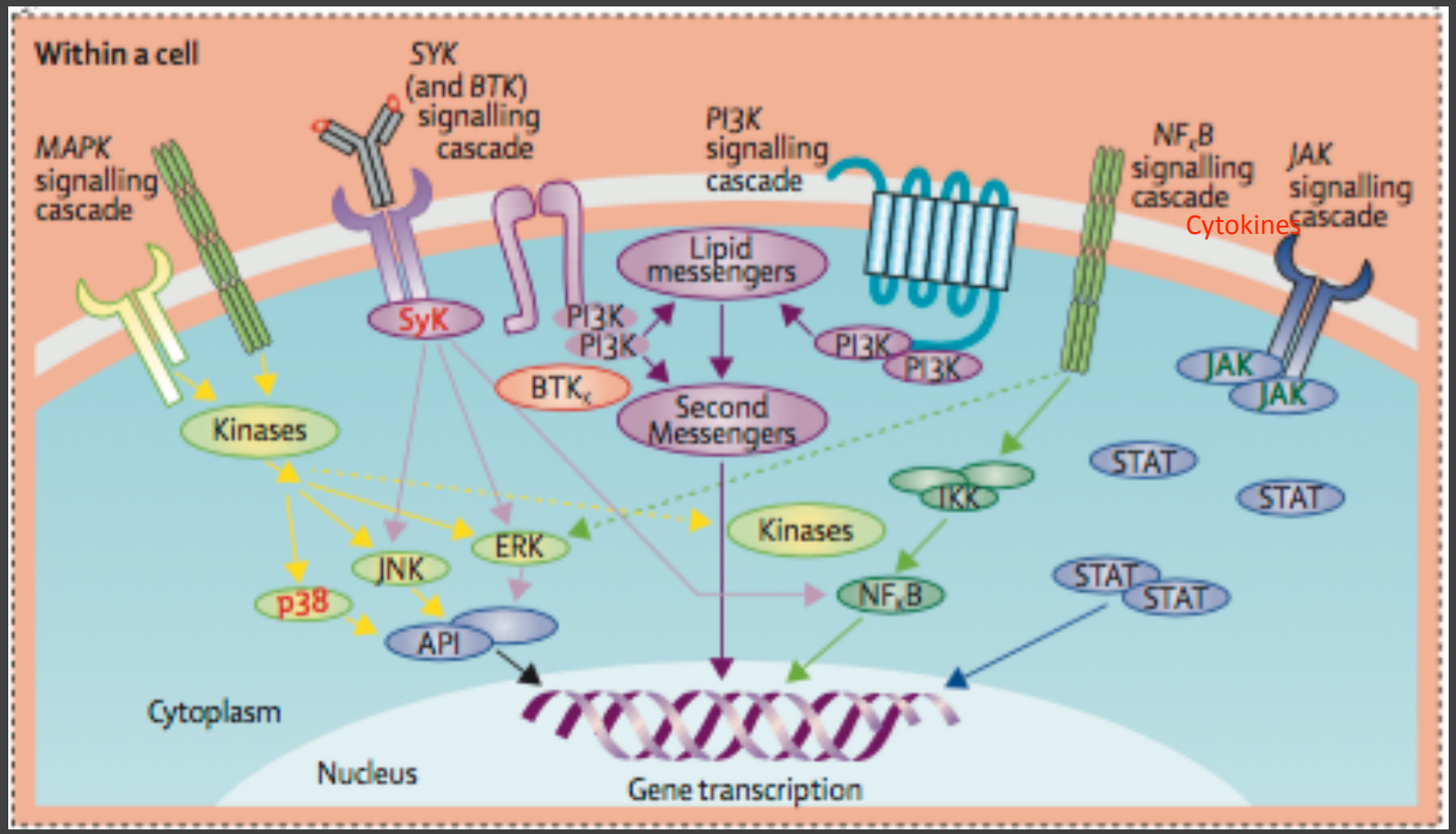


Within the synovial tissue



Josef S Smolen, Daniel Aletaha, Iain B McInnes Lancet, 2016

Rheumatoid Arthritis

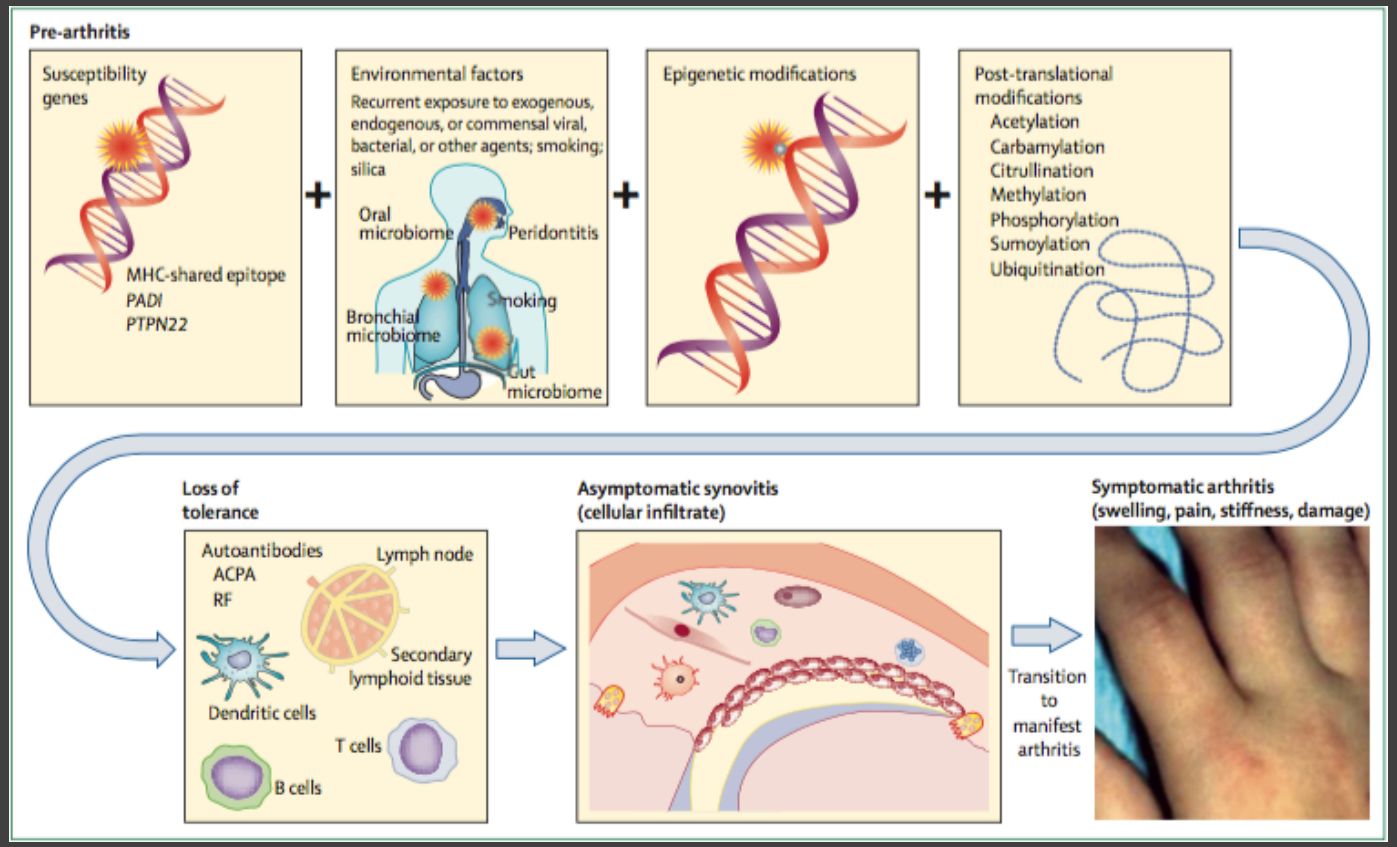


Proliferation, migration, adhesion and cytokines' production

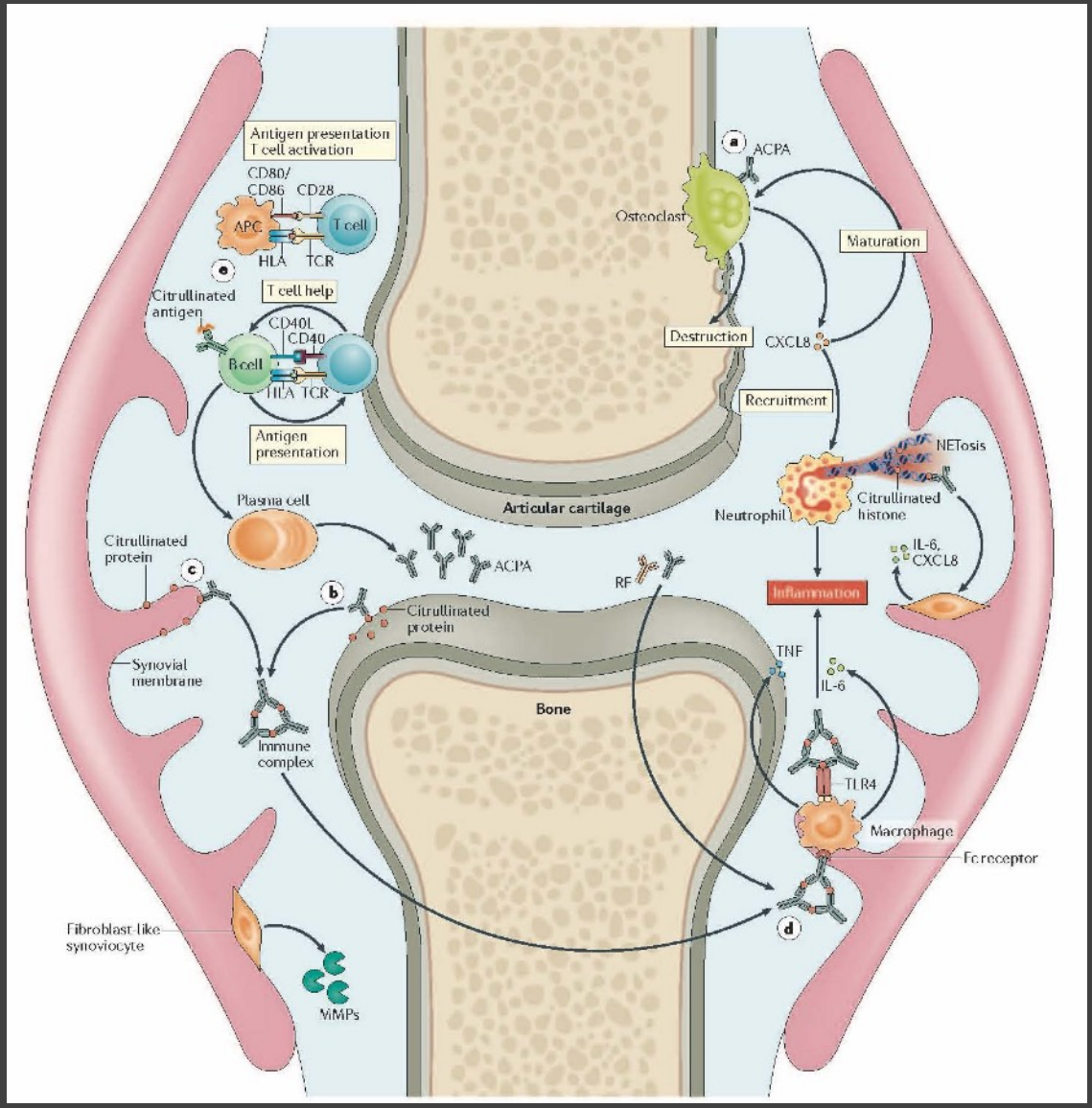
Josef S Smolen, Daniel Aletaha, Iain B McInnes Lancet, 2016

Rheumatoid Arthritis (RA)

Unknown etiology…just hypothesis



IB McInnes et al. NEJM 2001



V Malmström et al. Nature Reviews Immunology, 2016

TABLE 19.5 Examples of Cytokine Antagonists in Clinical Use or Trials

Cytokine or Receptor Targeted	Predicted Biologic Effects of Antagonist	Clinical Indications
TNF	Inhibits leukocyte migration into sites of inflammation	Rheumatoid arthritis, psoriasis, inflammatory bowel disease
IL-1	Inhibits leukocyte migration into sites of inflammation	Rare autoinflammatory syndromes, severe gout, rheumatoid arthritis
IL-6 receptor	Inhibits inflammation, antibody responses?	Juvenile idiopathic arthritis, rheumatoid arthritis
IL-17	Inhibits leukocyte recruitment into sites of inflammation	Psoriasis; possibly rheumatoid arthritis (trials ongoing)
p40 chain of IL-12 and IL-23	Inhibits Th1 and Th17 development	Inflammatory bowel disease, psoriasis
IL-2 receptor (CD25)	Inhibits IL-2–mediated T cell proliferation	Acute graft rejection
IFN-α	May be multiple effects on Th1 differentiation, antibody production	Systemic lupus erythematosus
IL-4/IL-13	Inhibits Th2 differentiation and function, IgE production	Asthma
BAFF	Reduces survival of B lymphocytes	Systemic lupus erythematosus

The table lists examples of antagonists against cytokines (antibodies or soluble receptors) that are approved for clinical use or in trials. Monoclonal antibodies specific for each of the listed targets are in clinical use; soluble TNF receptor and IL-1 receptor antagonists are used as well.

IFN, Interferon; *IL,* interleukin; *TNF,* tumor necrosis factor.

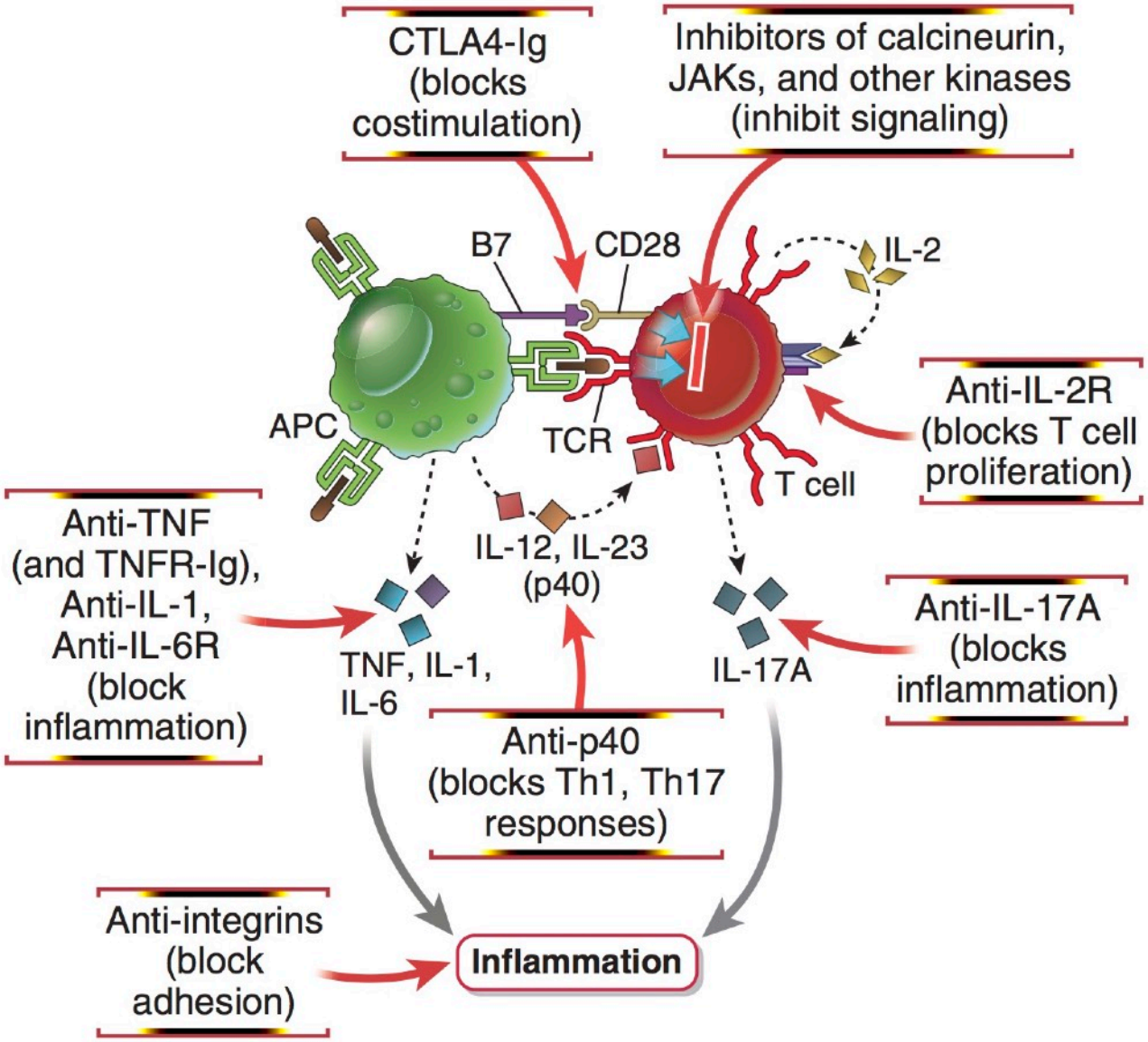


FIGURE 19.9 Novel therapies for inflammatory diseases targeting T cell responses and inflammation. Illustrated are the sites of action of some therapeutic agents that block different components of immune and inflammatory responses. Many of these agents target cytokines and their receptors. B cell depletion by anti-CD20 may also reduce pathologic T cell responses *(not shown).*

Contact hypersensitivity

- Occur within 72 hrs of Ag challenge
- Characterized by an eczematous reaction in the skin at the point of contact with an antigen
- Organic chemicals and inorganic metals such as nickel, chromate and rubber accelerator in latex gloves

Contact Dermatitis

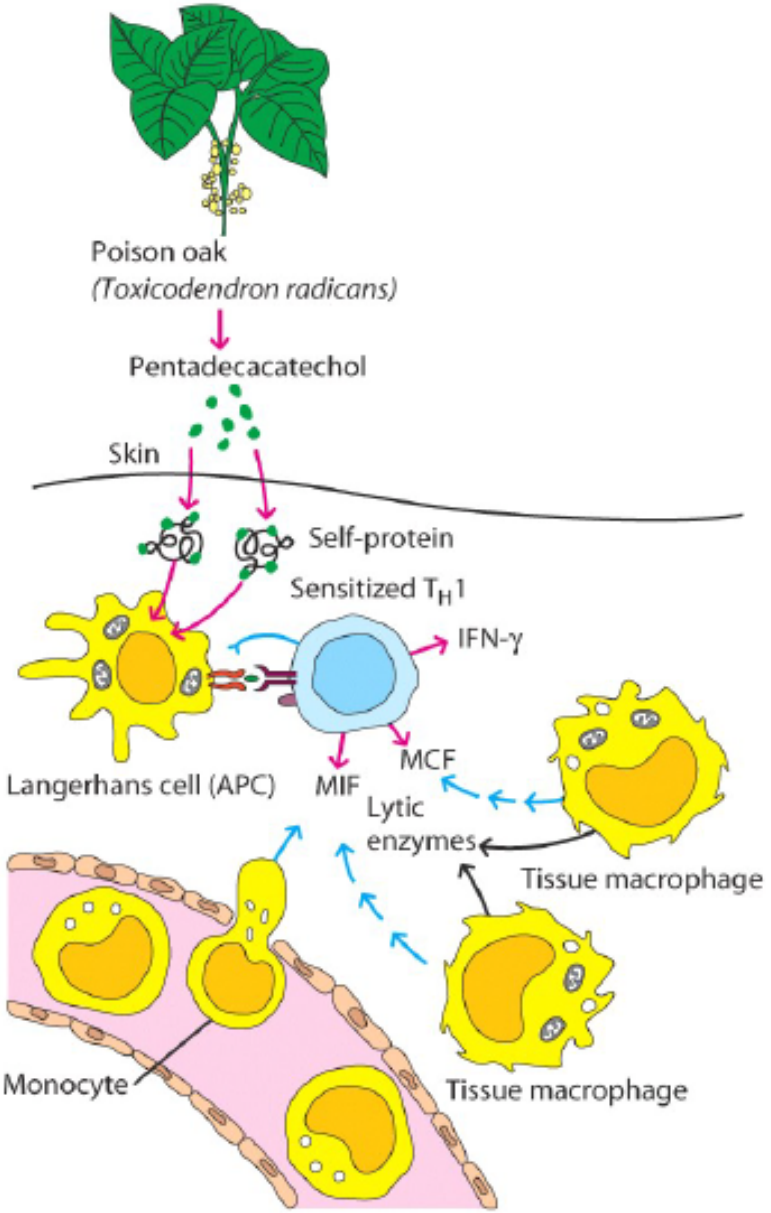
Produced by a variety of substances

Mostly small molecules attach to a protein in the skin

The Ag-protein complex is processed and presented → sensitize TH1 cells

Subsequent exposure activates TH1 cells → 48-72 hrs later MØ infiltrate

Activation of MØ causes the inflammation that characterizes the disorder



Type IV Hypersensitivity

Contact dermatitis

May be caused by metals (zirconium) or poison ivy

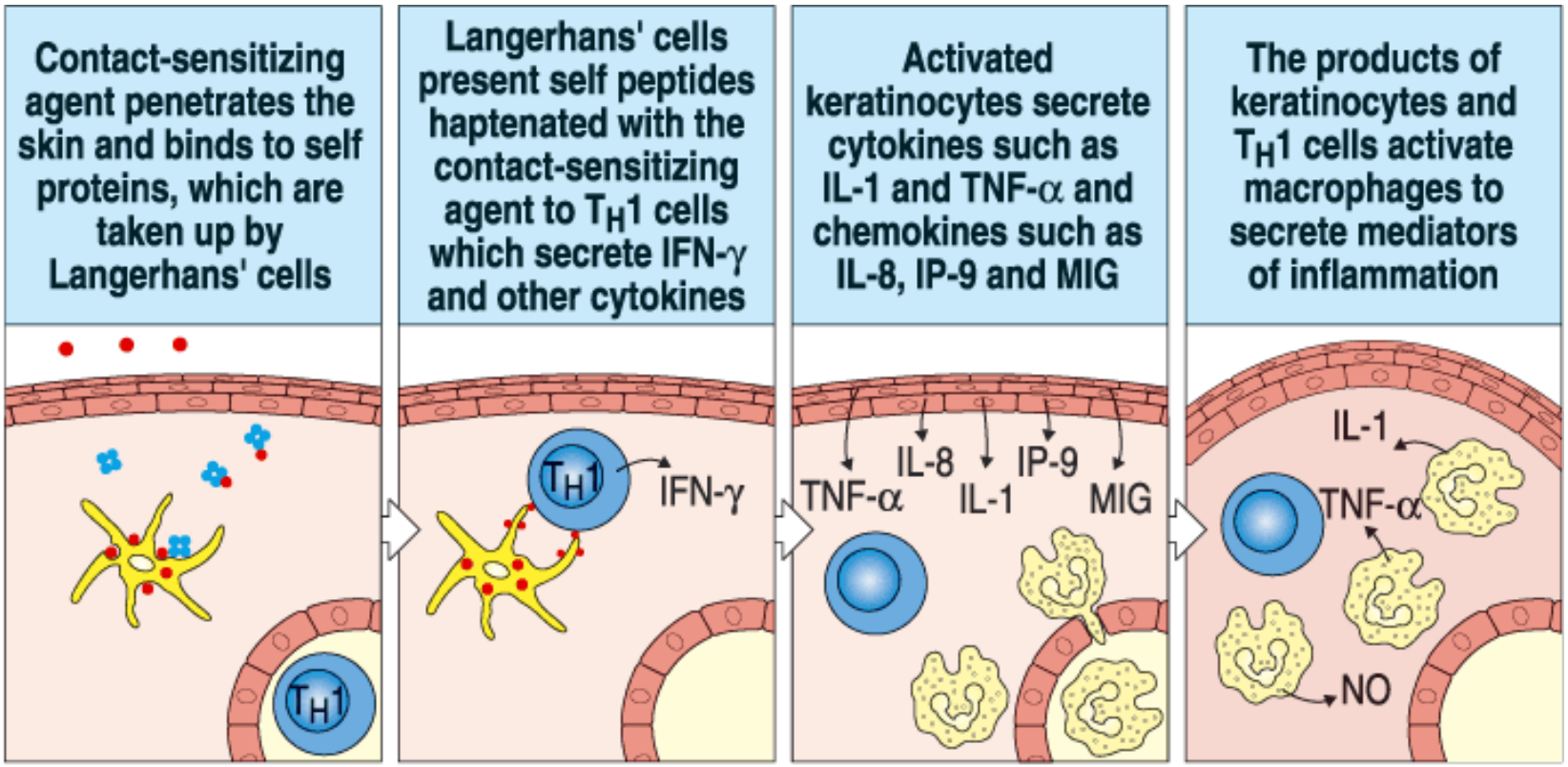
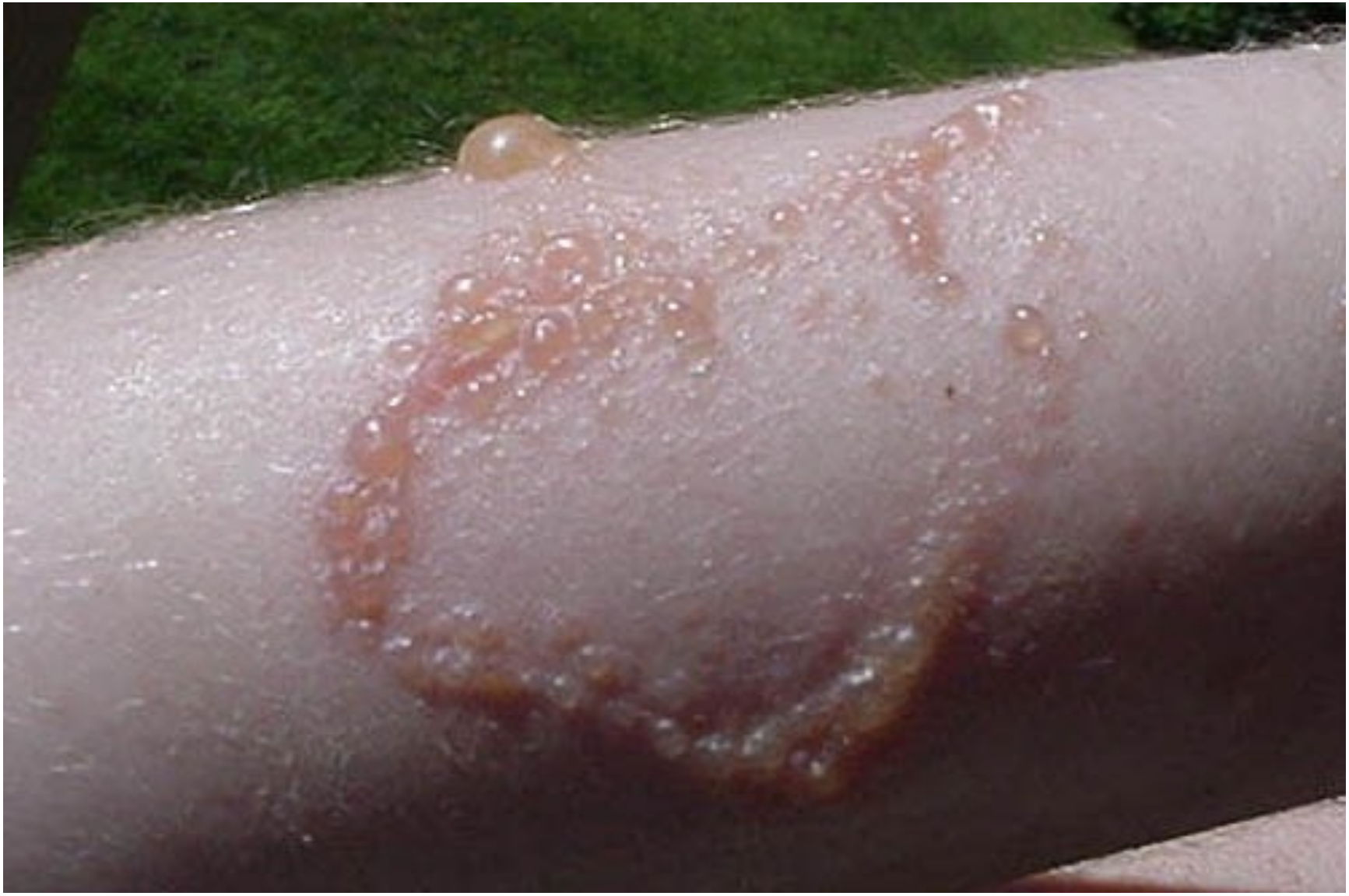
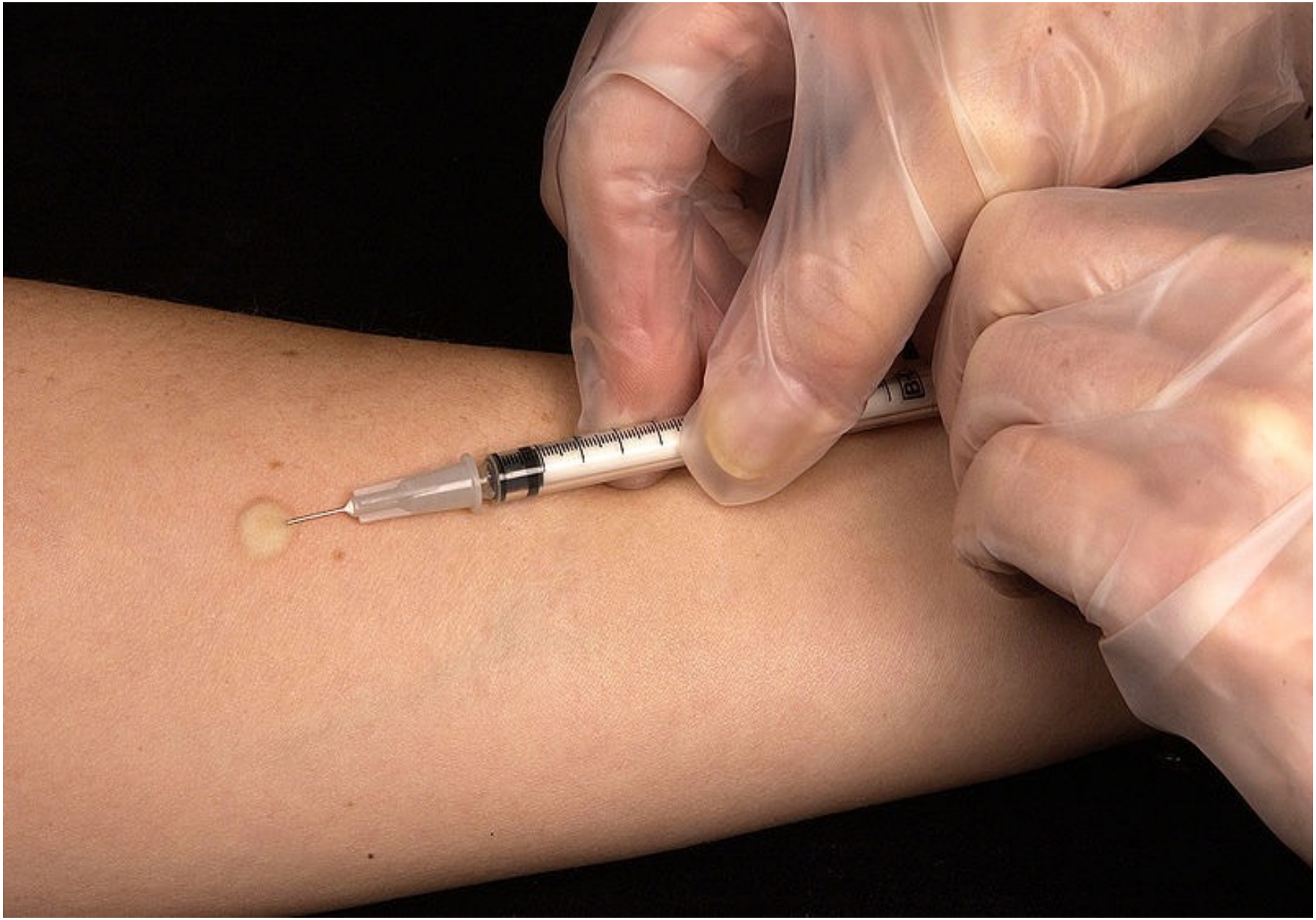


Fig 12.24 © 2001 Garland Science



TUBERCULIN TYPE

- Is induced by soluble antigens from organisms such as Mycobacterium Tuberculosis and Leprae and Leishmania tropica
- Following Intradermal tuberculin challenge, memory T cells are recruited and activated to secrete IFN-γ, which activates macrophages to produce TNF and IL-1
- The initial influx at 4 hrs is neutrophils but replaced at 12 hrs by monocytes and T cells.



Type IV hypersensistivity

(Tubercolin reaction)

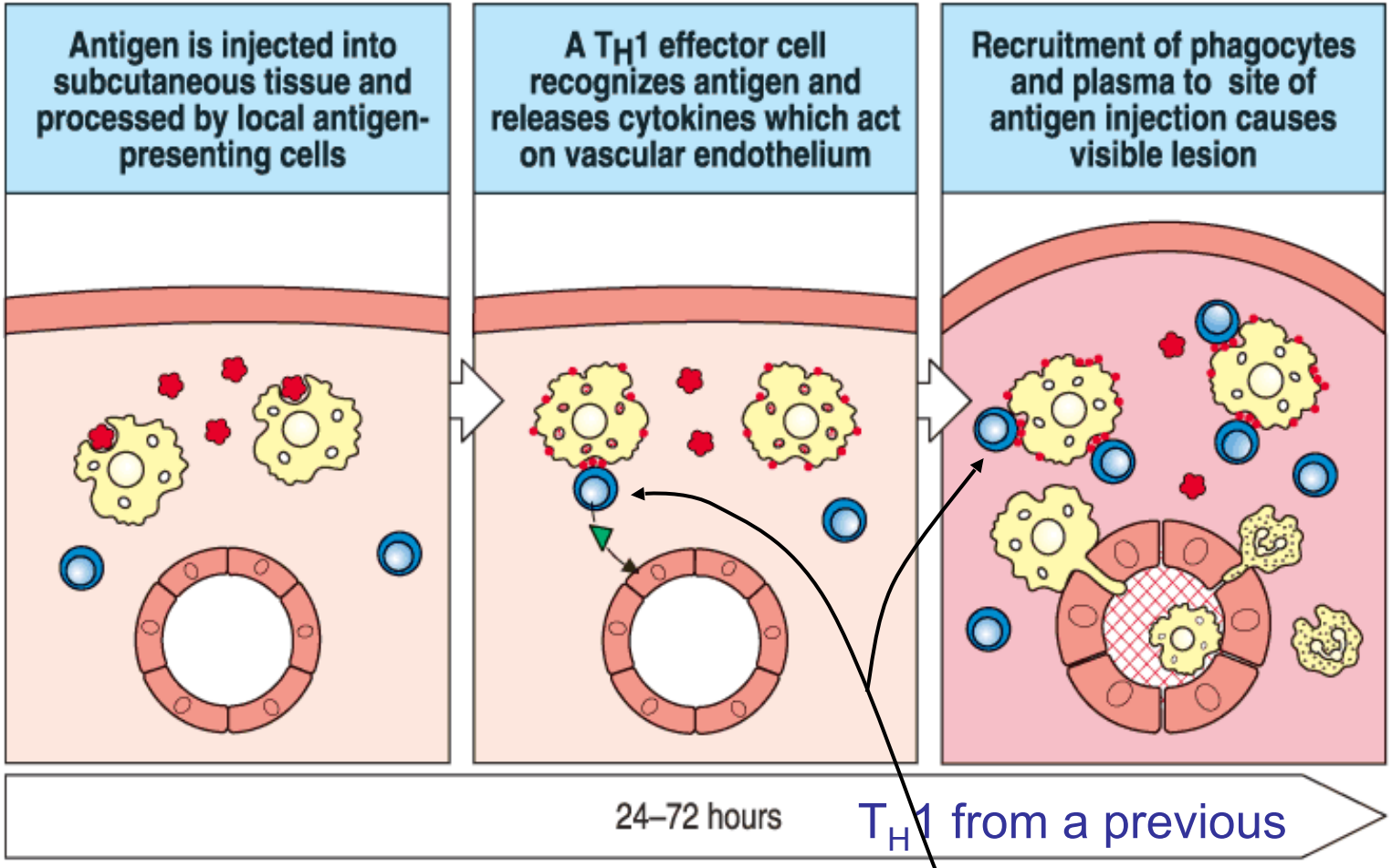
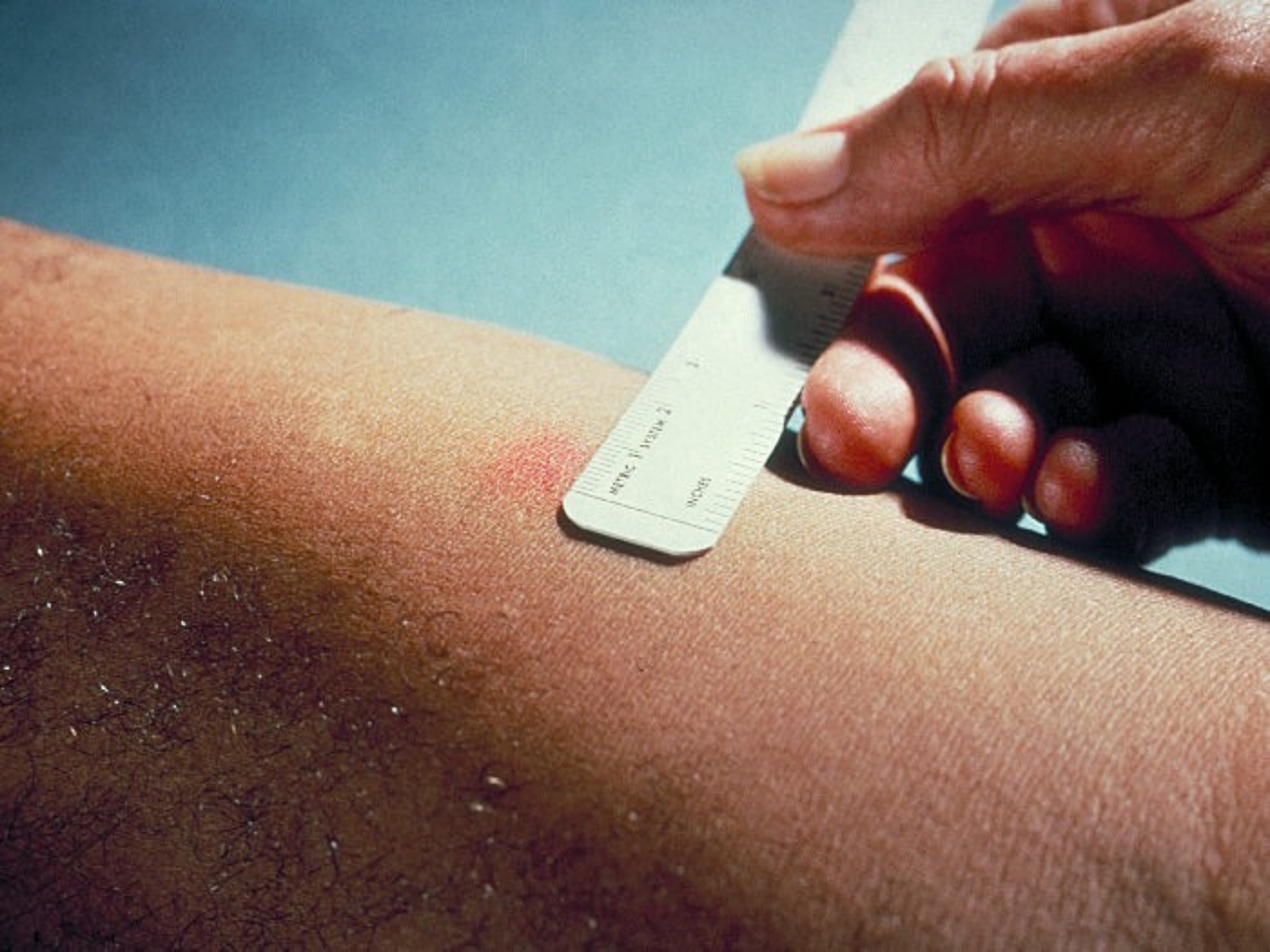


Fig 12.22 © 2001 Garland Science



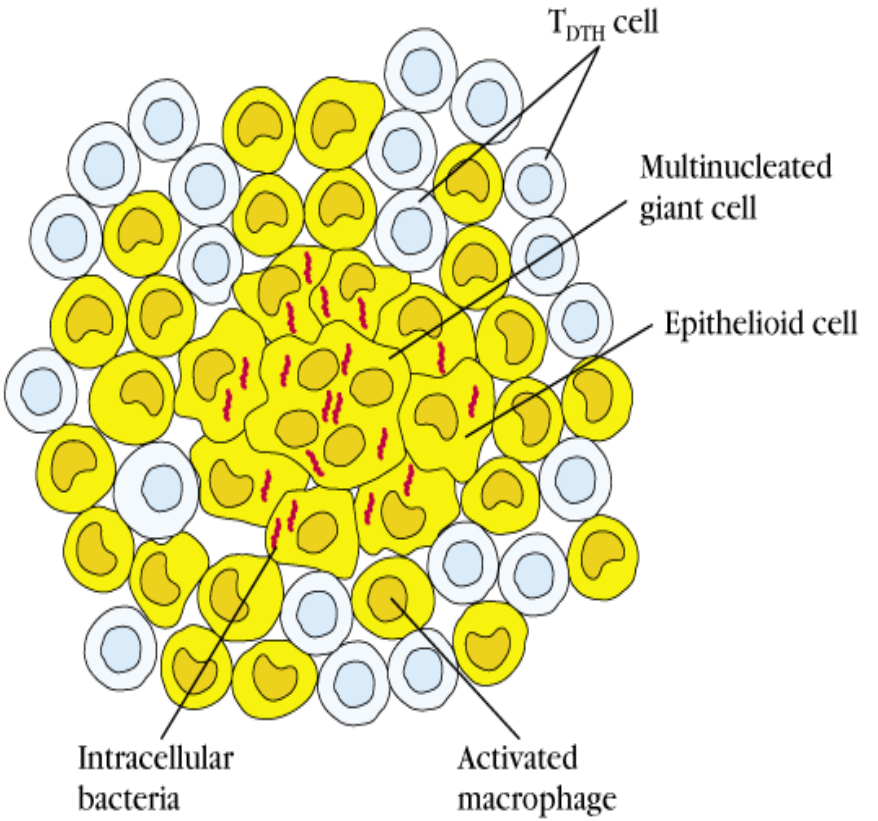
Granulomatous HS

- Clinically the most important form of type IV HS.
- If the Ag persist (intracellular microorg., other particles such as zirconium and beryllium, talc, silica), chronic activation of T cells and macrophages lead to granuloma formation and tissue damage.

What happens if the DTH response is prolonged?

A granuloma develops…

- Continuous activation of macrophages induces the macrophages to adhere closely to one another, assuming an epithelioid shape and sometimes fusing together to form giant, multinucleated cells.



Epitheloid Cell Granuloma Formation

- Large flattened cells with increased endoplasmic reticulum
- Multinucleate giant cells with little ER
- May see necrosis
- Damage due to CD8+ T-cells recognizing antigen-coated macrophages, cytokine-activated macrophages
- Attempt by the body to wall-off site of persistent infection

Granulomatous HS

- Leishmaniasis
- Sarcoidosis
- Leprosy
- Tuberculosis