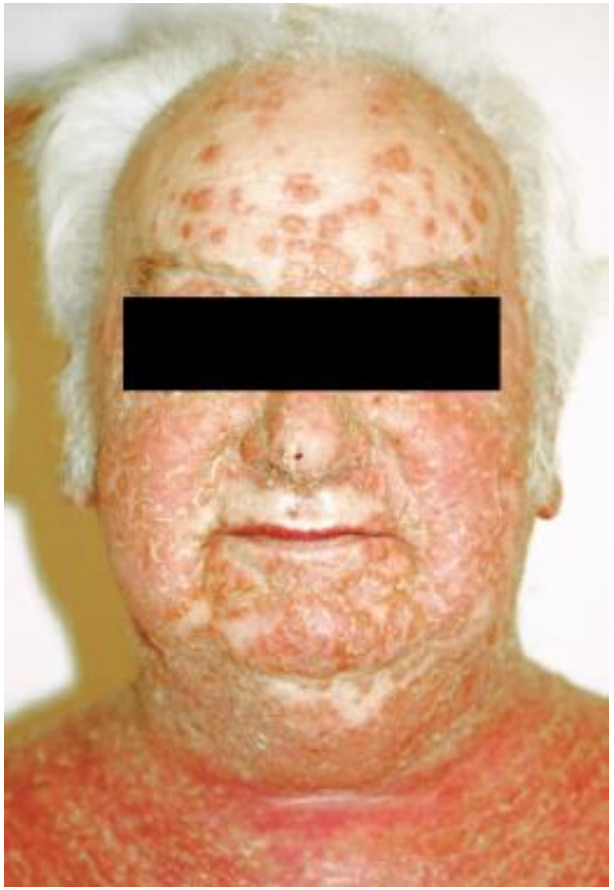
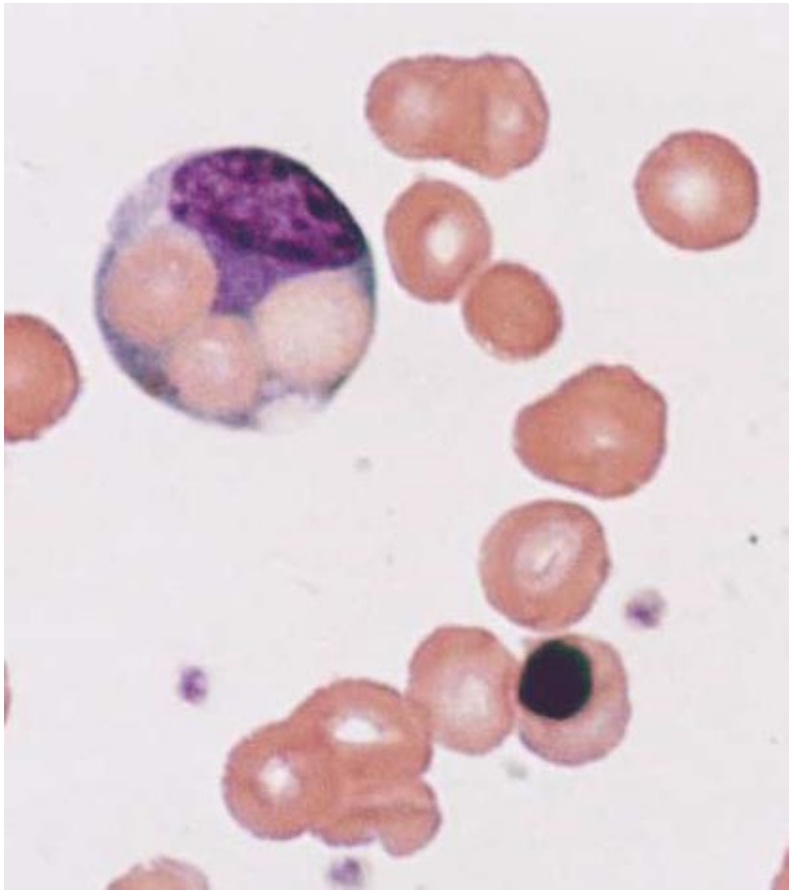
Malattie autoimmuni





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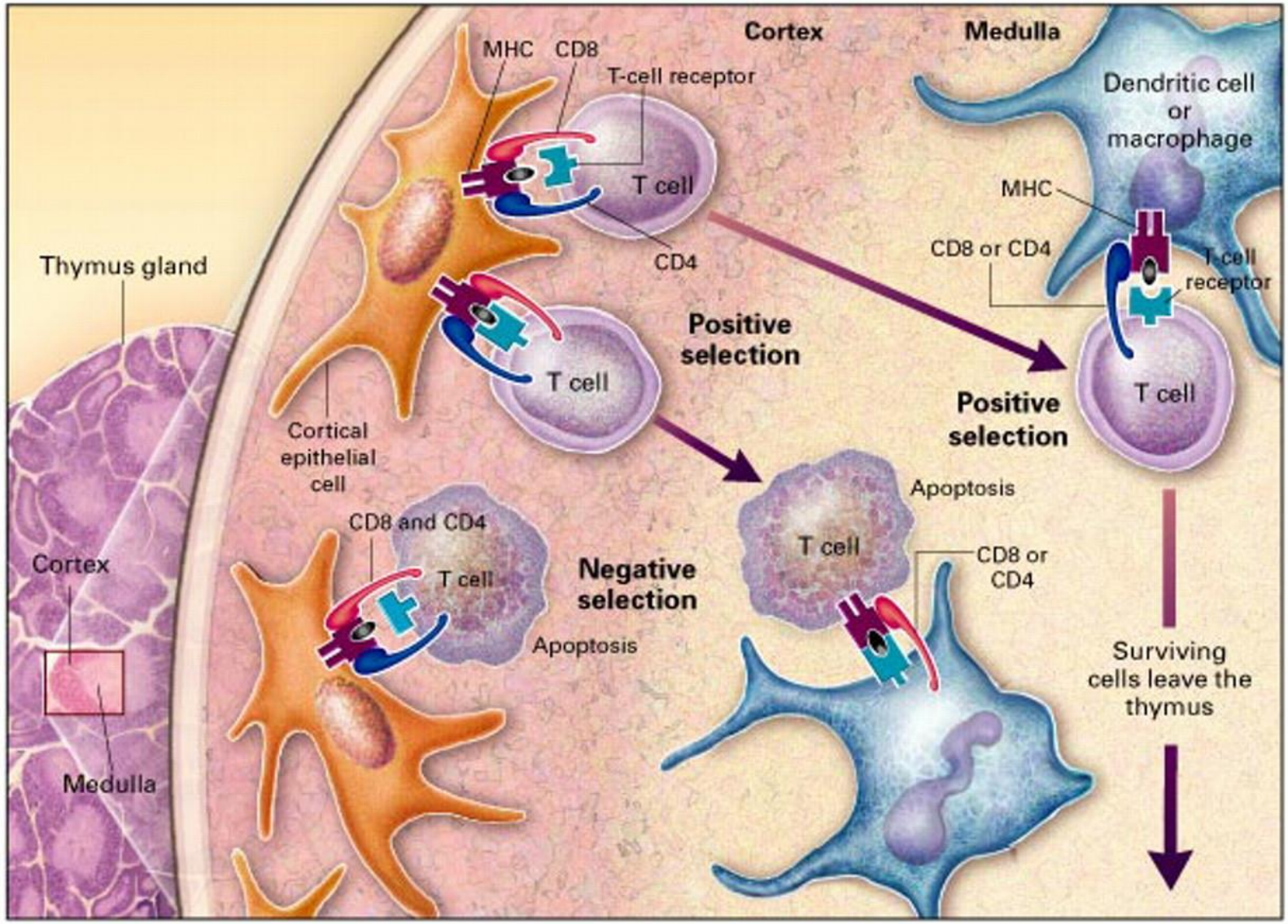
U.O.C. PATOLOGIA CLINICA
ASL LECCE P.O. "VITO FAZZI"

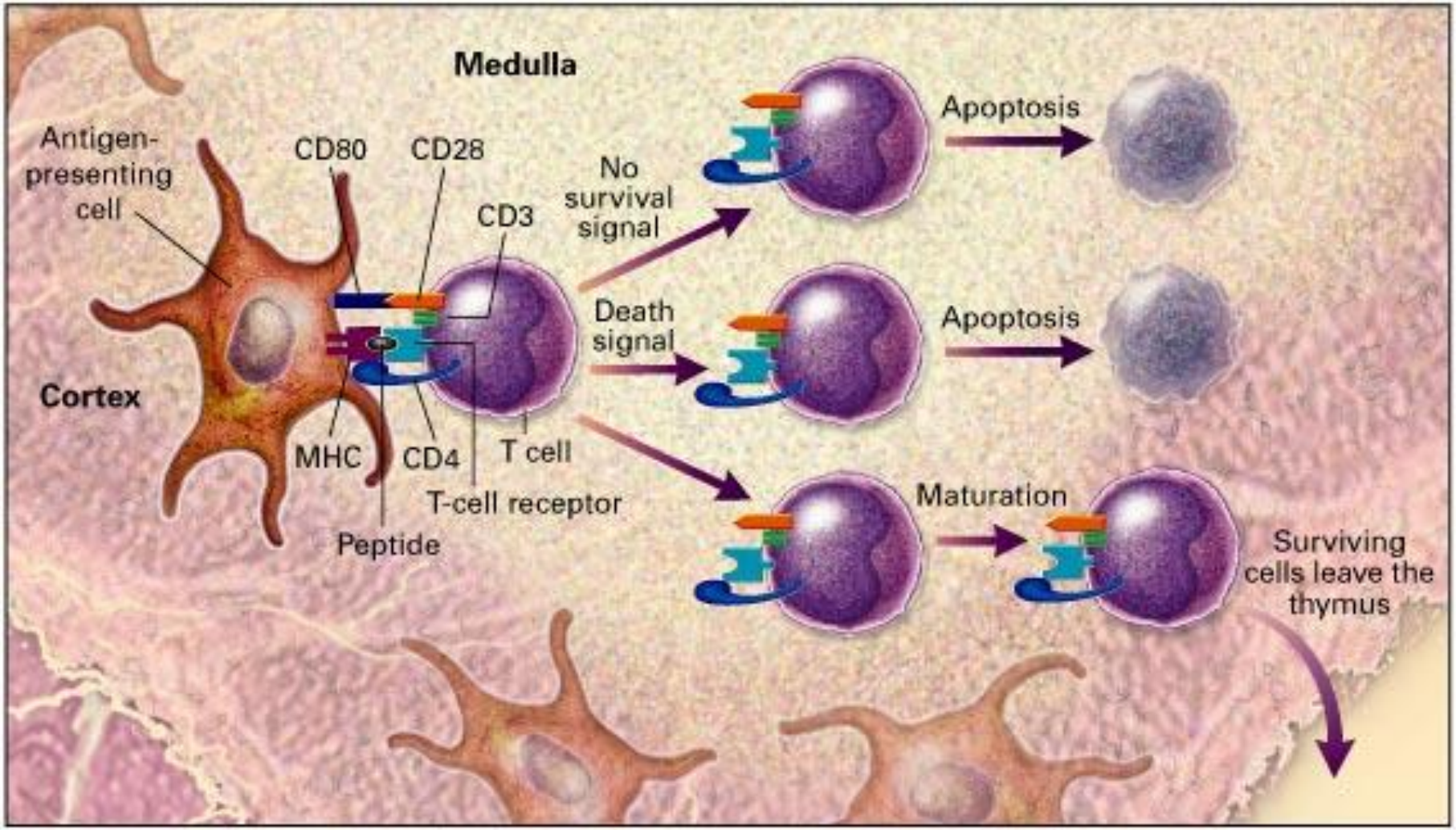
Positive and Negative Selection in the Thymus



The NEW ENGLAND JOURNAL of MEDICINE

Delves P and Roitt I. N Engl J Med 2000;343:37-49

Central Mechanisms of the Induction of Tolerance



Kamradt T and Mitchison N. N Engl J Med 2001;344:655-664

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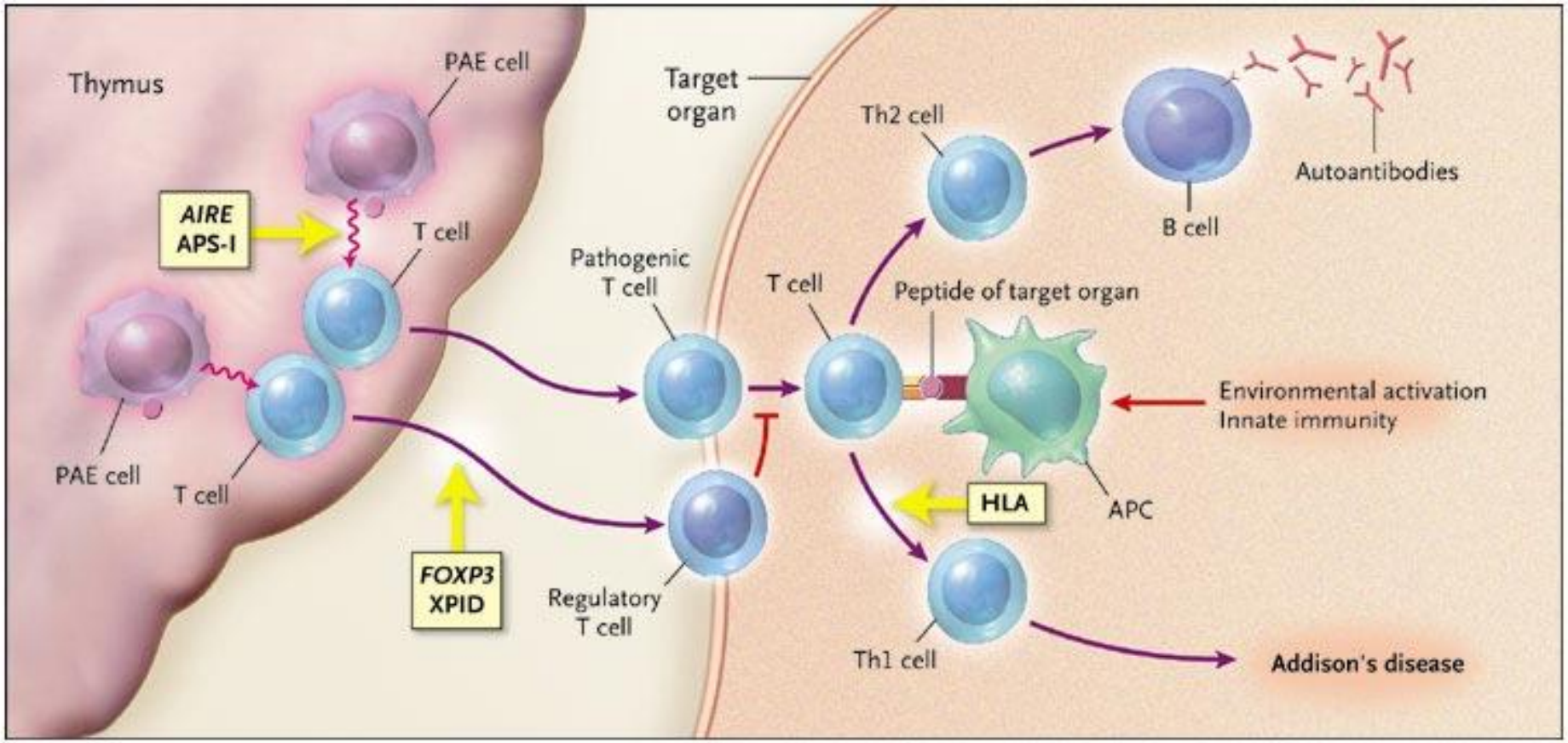
Pathogenic Model of Autoimmune Polyendocrine Syndrome Disorders



Eisenbarth G and Gottlieb P. N Engl J Med 2004;350:2068-2079

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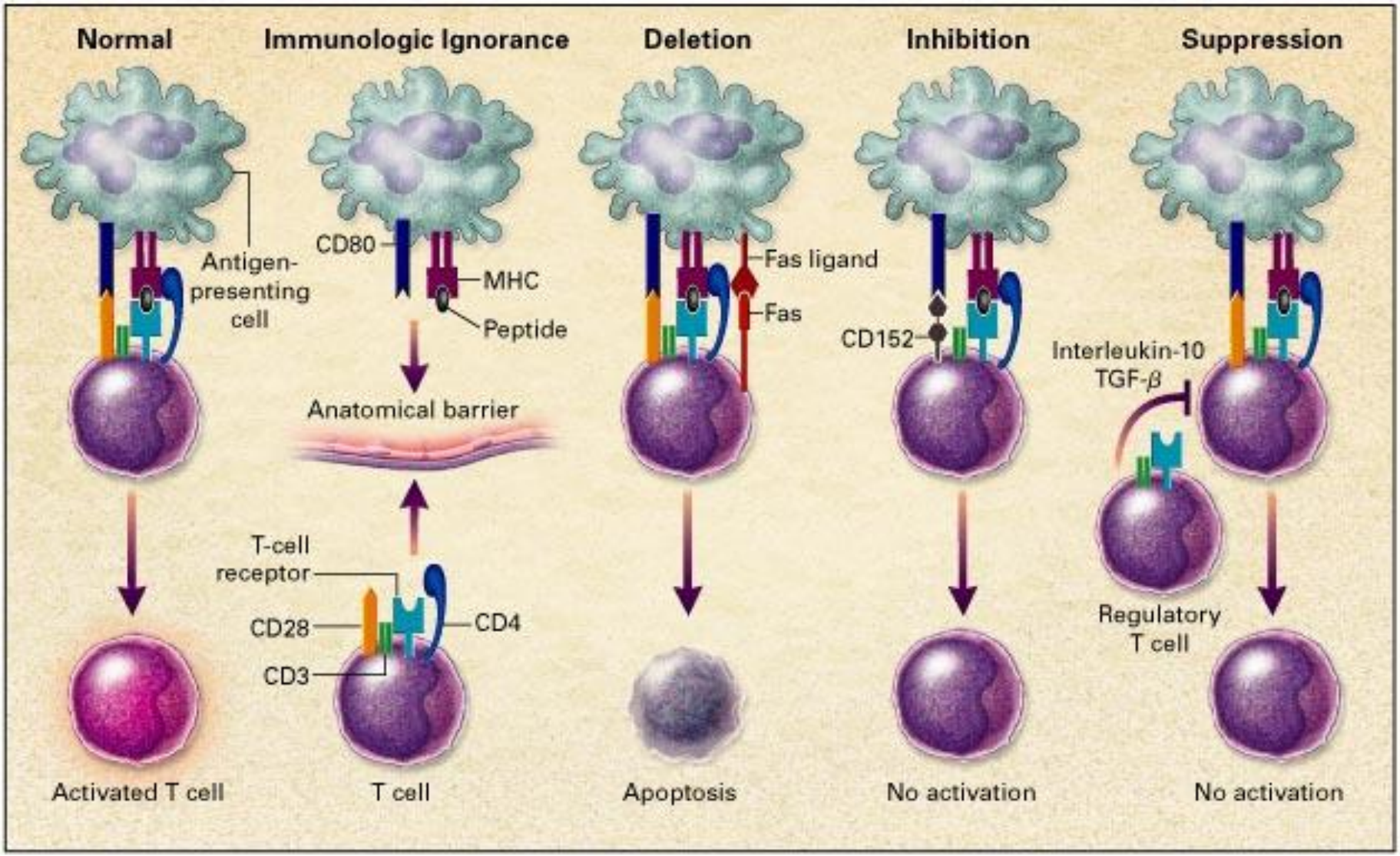
Peripheral Mechanisms of the Induction of Tolerance



Kamradt T and Mitchison N. N Engl J Med 2001;344:655-664

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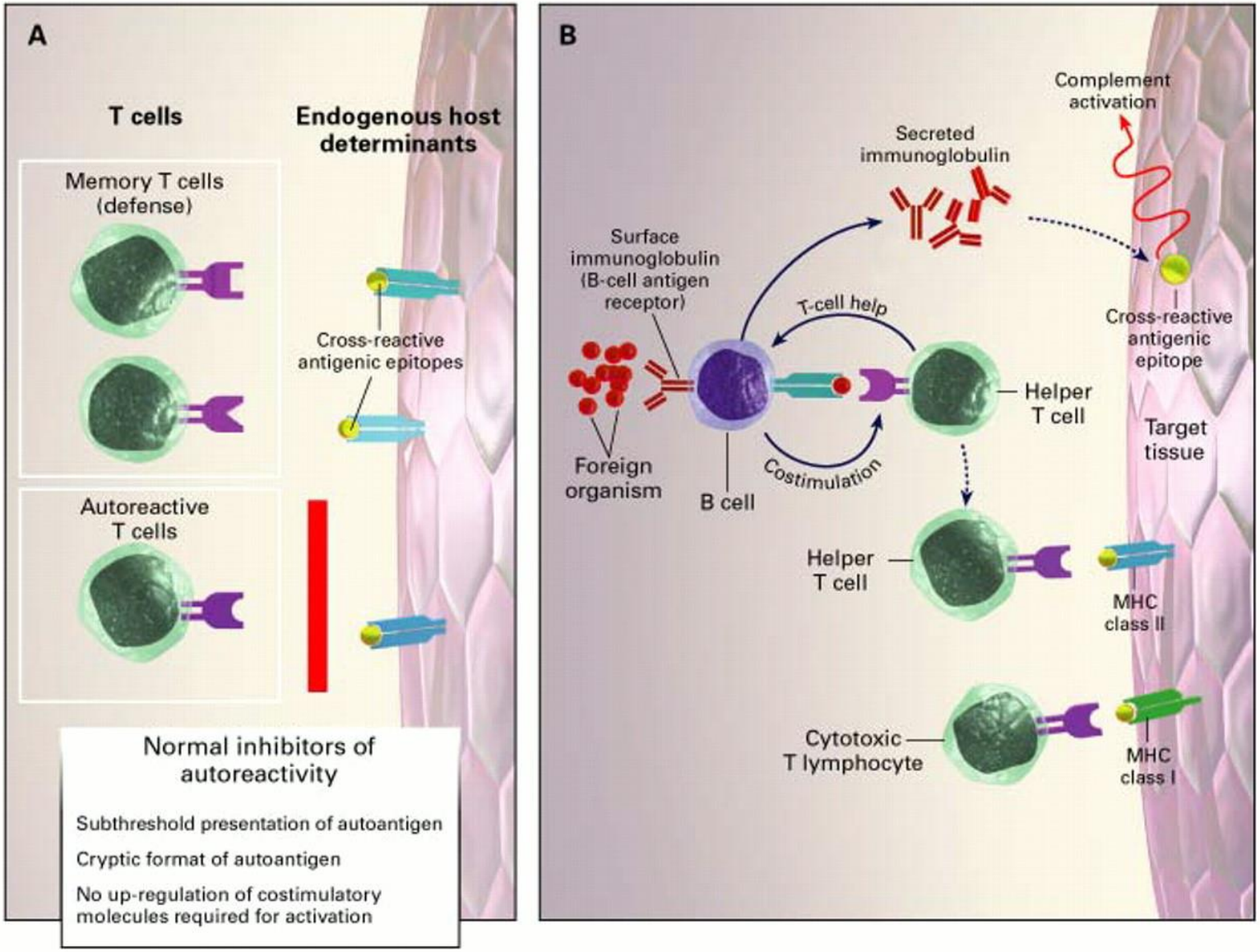
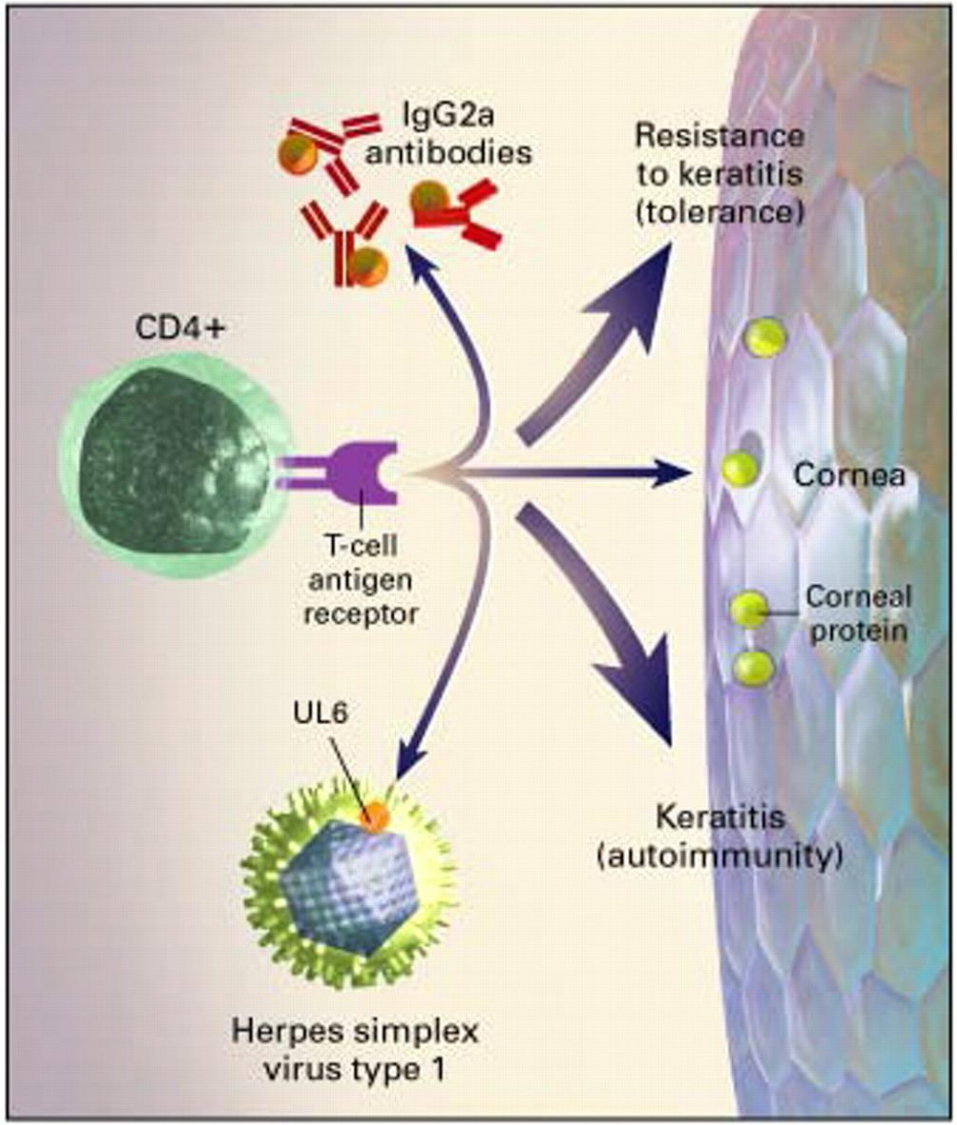
The Peripheral Immune Repertoire and Molecular Mimicry



Albert L and Inman R. N Engl J Med 1999;341:2068-2074

The NEW ENGLAND JOURNAL of MEDICINE

Experimentally Induced Herpes Keratitis



Albert L and Inman R. N Engl J Med 1999;341:2068-2074

The NEW ENGLAND JOURNAL of MEDICINE

Proposed Molecular Mimicry in Autoimmune Diseases

TABLE 1. PROPOSED MOLECULAR MIMICRY IN AUTOIMMUNE DISEASES.*

AUTOIMMUNE DISEASE	PROPOSED AUTOANTIGEN	PROPOSED PATHOGEN OR EPITOPE	IMMUNOLOGIC CROSS-REACTIVITY	ANIMAL MODEL†
Type 1 diabetes mellitus[1-8]	GAD65	Coxsackievirus P2-C	T cell (concept controversial in humans)	LCMV–RIP transgenic mouse
Rheumatoid arthritis[9]	HLA-DRB1	40-kd heat-shock protein (dnaJ)	T and B cells	—
Rheumatoid arthritis[10]	Heat-shock protein 60	*Mycobacterium tuberculosis* heat shock protein 65	T and B cells	Adjuvant arthritis (rat)
Multiple sclerosis[11,12]	Myelin basic protein	Multiple viruses	T cell	LCMV–oligodendrocyte transgenic mouse
Spondyloarthropathies[13-17]	HLA-B27	Multiple gram-negative bacterial proteins	B cell	—
Graves' disease[18,19]	Thyrotropin receptor	*Yersinia enterocolitica*	B cell	—

*LCMV denotes lymphocytic choriomeningitis virus, and RIP rat insulin promoter.

†This model is not specific for cross-reactivity between GAD65 and CoxP2-C.

Albert L and Inman R. N Engl J Med 1999;341:2068-2074

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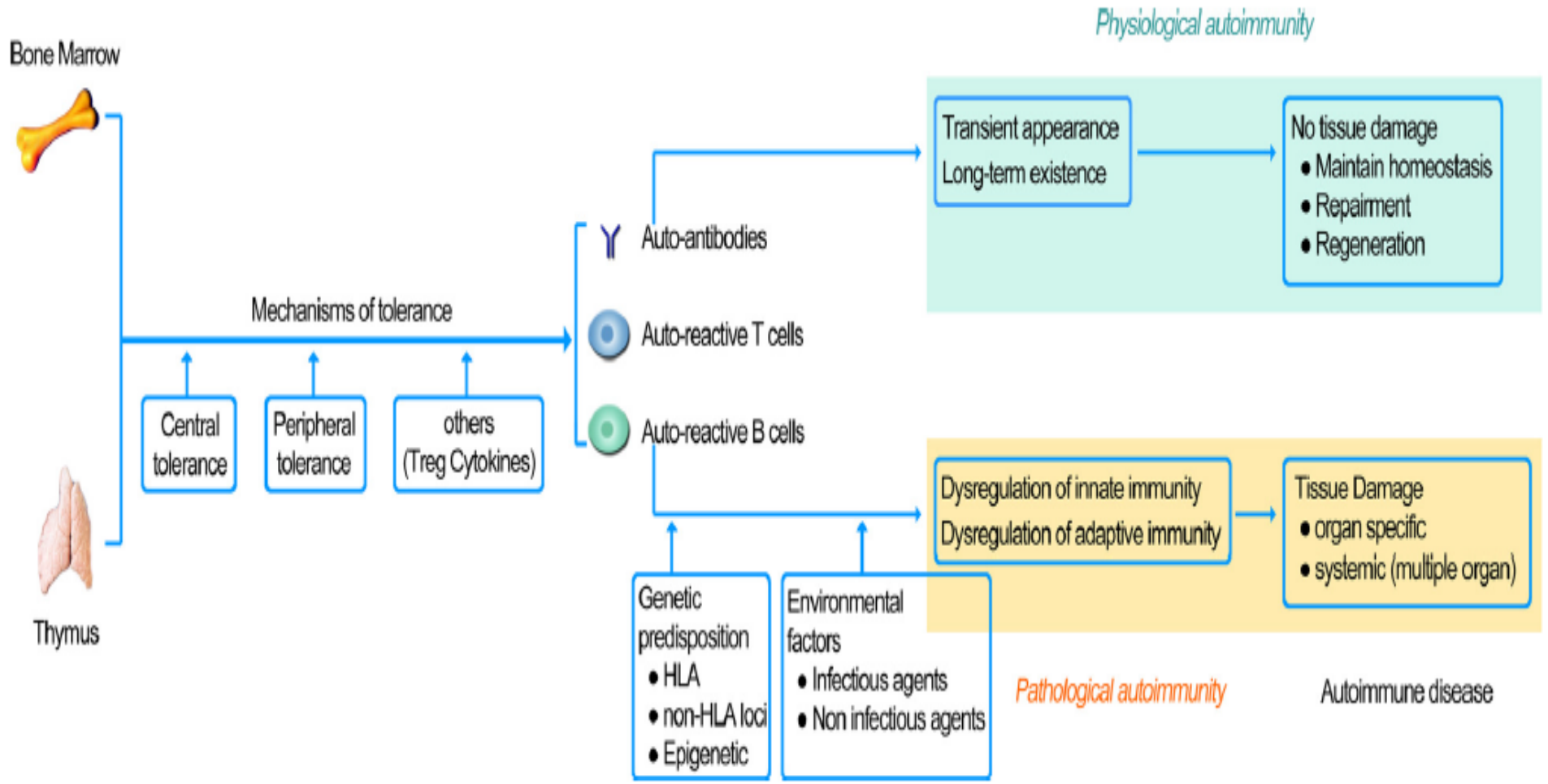
Possibili meccanismi dell'autoimmunità correlata ad infezioni

Mechanisms	Infections	Diseases
Molecular mimicry: Sequence similarities between pathogen-derived peptides and self-peptides	*Streptococcus pyogenes* (bacterial M protein)	Acute rheumatic fever (ARF)
	Escherichia coli (PDC-$E2_{212-226}$, PDC-$E2_{212-226}$), *Pseudomonas aeruginosa* (PDC-$E2_{159-167}$)	PBC
	Helicobacter pylori (H^+, K^+-ATPase α chain)	Gastric autoimmunity, SS, PBC
	EBV (PPPGRRP peptide)	SLE,
	HHV6 (U24)	MS
	Cytomegalovirus; Enteroviruses; Rotavirus	T1D
Epitope spreading: Changes from primary epitope to other epitopes	HCV (polypeptide precursor)	AIH (type 2)
	EBV (*Epstein–Barr virus nuclear antigen-1*)	SLE, MS, RA
	Cytomegalovirus infection	SLE
Bystander activation: Activation of pre-existing autoreactive immune cells	Measles virus	MS
	EBV	MS
Viral persistence and polyclonal activation: Constant presence of viral antigen driving the immune response or epitope spreading	EBV	MS, SLE, RA, SS, PBC, MS
	Enterovirus	T1D

PATHWAY DI SVILUPPO DELLE MALATTIE AUTOIMMUNI



Journal of Internal Medicine, 2015, 278; 369–395

Features of the Autoimmune Polyendocrine Syndromes

Table 1. Features of the Autoimmune Polyendocrine Syndromes.*

Feature	Autoimmune Polyendocrine Syndrome Type I	Autoimmune Polyendocrine Syndrome Type II	X-Linked Polyendocrinopathy, Immune Dysfunction, and Diarrhea
Prevalence	Rare	Common	Very rare
Time of onset	Infancy	Infancy through adulthood	Neonatal period
Gene and inheritance	*AIRE* (on chromosome 21, recessive)	Polygenic	*FOXP3*, X-linked
HLA genotype	Diabetes (risk decreased with HLA-DQ6)	HLA-DQ2 and HLA-DQ8; HLA-DRB1*0404	No association
Immunodeficiency	Asplenism, susceptibility to candidiasis	None	Overwhelming autoimmunity, loss of regulatory T cells
Association with diabetes	Yes (in 18%)	Yes (in 20%)	Yes (in majority)
Common phenotype	Candidiasis, hypoparathyroidism, Addison's disease	Addison's disease, type 1A diabetes, chronic thyroiditis	Neonatal diabetes, malabsorption

* The autoimmune polyendocrine syndromes differ in their prevalence, time of onset, inheritance, immune function, and disease associations. Such differences point to a heterogeneity in their pathogenesis, despite the underlying presence of genetic susceptibility to multiple autoimmune disorders.

Eisenbarth G and Gottlieb P. N Engl J Med 2004;350:2068-2079

The NEW ENGLAND JOURNAL of MEDICINE

Association between the Presence of Various HLA Markers and Selected Autoimmune Diseases

TABLE 1. ASSOCIATION BETWEEN THE PRESENCE OF VARIOUS HLA MARKERS AND SELECTED AUTOIMMUNE DISEASES.

DISEASE	ASSOCIATED HLA MARKER*	RELATIVE RISK OF DISEASE†
Ankylosing spondylitis	B27	87.4
Reactive arthropathy, including Reiter's syndrome	B27	37.0
Rheumatoid arthritis	DR4	4.2
Behçet's syndrome	B51	3.8
Systemic lupus erythematosus	DR3	5.8
Insulin-dependent (type 1) diabetes mellitus	DR3	3.3
	DQB1*0201	2.4
	DR4	6.4
	DQB1*0302	9.5
	DR2	0.19
	DRB*1501‡ DRB*0101‡	
	DQB1*0602	0.15
Idiopathic Addison's disease	DR3	6.3
Graves' disease	DR3	3.7
Hashimoto's disease	DR11	3.2
Postpartum thyroiditis	DR4	5.3
Celiac disease	DR3	10.8
	DQB1*0201‡ DQA1*0501‡	
	DR7, 11	6.0–10.0
	DR7, DQB1*0201‡ DR11, DQA1*0501‡	
Dermatitis herpetiformis	DR3	15.9
Sicca syndrome	DR3	9.7
Myasthenia gravis	DR3	2.5
	B8	3.4
Idiopathic membranous glomerulonephritis	DR3	12.0
Goodpasture's syndrome	DR2	15.9
Multiple sclerosis	DR2	4.1
	DRB1*1501‡ DRB5*0101‡ DQB1*0602‡	
Pemphigus vulgaris (among Ashkenazi Jews)	DR4	14.4
Psoriasis vulgaris	Cw6	13.3
Birdshot retinochoroidopathy	A29	109.0

*Symbols with asterisks indicate alleles, and symbols without asterisks indicate serologically defined antigens. For each disease, the marker or markers with the strongest associations are given. In many cases in which it is difficult to decide whether HLA-DR or DQ markers are responsible for the association, both markers are given.

†The relative risk indicates the frequency of a disease in persons with the HLA marker as compared with persons without the marker. A positive association (i.e., when the HLA marker is more frequent in persons with the disease than in those without it) is indicated by a relative risk of more than 1.0, a negative association by a relative risk of less than 1.0, and no association by a relative risk of 1.0.

‡The risk has not been assessed separately for this allele.

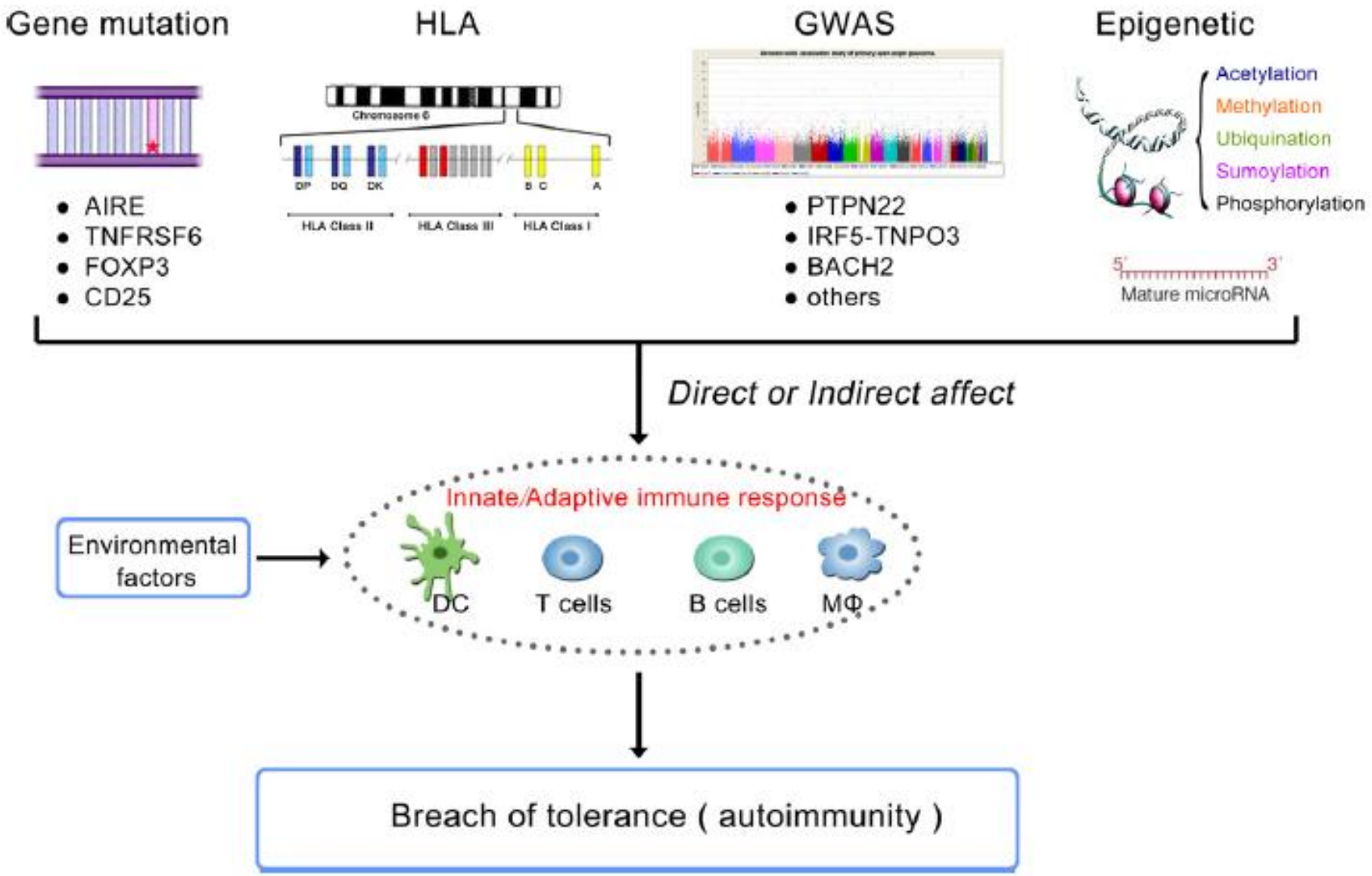
The NEW ENGLAND JOURNAL of MEDICINE

Klein J and Sato A. N Engl J Med 2000;343:782-786

GEOEPIDEMIOLOGIA DI ALCUNE MALATTIE AUTOIMMUNI

Disease	Age at onset (years)	Gender (female/male)	Monozygotic twin concordance[a]	Incidence (per 100 000 person-years)			References
				Europe	North America	Asia and Middle East	
Multiple sclerosis	20–40	2/1	9–31%	0.8–8.7	2.7–7.5	0.7–3.6	[12, 145]
Type 1 diabetes	6–13	1/1	13–48%	>20	10–20	<1	[146, 147]
Primary biliary cirrhosis	50–60	10/1	63%	1.4–3.1	2.7 (USA)	0.34–0.42	[148–151]
Autoimmune hepatitis	<40 (T1) 2–14 (T2)	4/1 (T1) 10/1 (T2)	Only case reports	1.07–3.0	0.5 (USA)	0.08–0.15 (Japan)	[152–154]
Graves' disease	50–60	5/1	17–60%	21–50	38	120	[155, 156]
Crohn's disease	15–30, 60–80	1/1.2	4%	3.1–12.7	6.9–20.2	0.24–1.34	[157–159]
Ulcerative colitis	15–30, 60–80	1/1	6.3–18.8%	4.1–16.5	8.3–19.2	0.36–6.02	[159, 160]
Coeliac disease	Childhood	1/1	75–83%	1.5–8.7 (all ages)	0.9–9.1 (all ages)	Unclear	[161, 162]
Addison's disease	15–45	0.8–2.4/1	Discordant pair	0.56–6.20	1 (USA)	Unclear	[163, 164]
Sjogren's syndrome	40–50	9/1	Only case reports	5.3 (north-west Greece)	3–5 (USA)	6.57	[165–167]
Systemic lupus erythematosus	30–50	9/1	11–25%	1.0–5.0	1.2–8.7	0.9–3.1	[168–170]
Rheumatoid arthritis	44–55	2/1	15–30%	9–36	31–45	8–42	[171–173]

Basi genetiche dell'autoimmunità



Journal of Internal Medicine, 2015, 278; 369–395

Associazioni genetiche ed epigenetiche

Disease	HLA*	Non-HLA loci	Epigenetic aberrations
Multiple sclerosis	HLA class II: DRB1*15:01 DRB1*03:01-DQB1 *02:01 DRB1*13:03-DQB1 *03:01 HLA class I: HLA-A*02:01	L2RA, IL-7Rα, CLEC16A, CD6, CD58, IRF8, **BACH2,** IL-12A, Olig3-TNFAIP3, PTGER4, RGS1, TNFRSF1A	DNA methylation: Hypomethylation of *PAD2* Hypomethylation of *SHP-1* Acetylation: Hyperacetylation of H3 promoter region in white matter miRNA: miR-326, miR-17-5p, 19a/b, miR-20a, miR-92b, **miR-21**, miR-106b, miR-34a, miR-155, miR-326, and others
Type 1 diabetes	HLA class II: DQ2(DRB1 *0301-DQA1 *0501-DQB1*0201) DQ8(DRB1 *04-DQA1 *0301-DQB1 *0302) HLA class I: HLA-A HLA-B: protective effect, DQB1*0602	INS,CTLA4, **PTPN22**, IL-2RA, IFIH1, STAT4, **BACH2**, PTPN2	DNA methylation: HLA, INS, IL-2RB, CD226 Acetylation: Increase H3k9me2 in lymphocyte genes: *TGF-β, NF-kB, IL-6, HLA, CTLA4* miRNA: miR-375, miR-25, miR-326, miR-342, miR-19, miR-510, **miR-21,** and others

Journal of Internal Medicine, 2015, 278; 369–395

Associazioni genetiche ed epigenetiche

Disease	HLA*	Non-HLA loci	Epigenetic aberrations
Primary biliary cirrhosis	HLA class II: DRB1*08, DRB1*11, and DRB1*13 protective	IL-12, IL-12R, IL-7R, CD80, STAT4, TYK2, SOCS1, **IRF5**, SPIB, PLC-L2, IRF8, CXCR5, IKZF3	DNA methylation: *CD40L* miRNA: miR-122-5p, miR-141-3p, miR-26b-5p, miR-506, miR-2, miR-let-7b, miR-505-3p, miR-197-3p, and others
Autoimmune hepatitis	HLA class II: DR3(DRB1*03:01) and DR4 (DRB1*04:01) for AIH-1 DR3(DRB1*03:01) and DR7 (DRB1*07:01) for AIH-2	CTLA-4, TNF-α, TGF-β1, TBX21, VDR, FAS	–

Journal of Internal Medicine, 2015, 278; 369–395

Associazioni genetiche ed epigenetiche

Disease	HLA*	Non-HLA loci	Epigenetic aberrations
Graves' disease	HLA class II: DR3(DRB1*03 or DQA1*0501) HLA class I: HLA-B8	CTLA-4, **PTPN22**, CD25, CD40, FCRL3	DNA methylation: *ICMA1*, *DNMT1*, *MECP2*, *IRF1* miRNA: miR-17, miR-155, miR-146, miR-200a1
Crohn's disease	HLA class II: DR7, DRB3 *03:01, DR4; DR2 and DR3 protective	TLR4, CARD9, IL-23R, JAK2, STAT3, CCR6, ICOSLG, **BACH2,** IRGM, IBD5, DMBT1, XBP1, **PTPN22**, IL-12B	DNA methylation: *CEACAM6*, *VMP1*/ **miR-21**, *HLA* loci miRNA: miR-199a-5p, miR-362-3p, miR-532-3p, miR-505, miR-195, miR-16, miR-93, miR-140, 200c, 532-3p
Ulcerative colitis	HLA class II: DR2, DR15, DR9; DR4 protective	TNFRSF14, PARK7, ERRFI1, CARD9, IL-23R, **IRF5**, RNF186, IL-17, IL-10, PUS10	DNA methylation: *CXCL14 CXCL5*, *GATA3*, *IL-17c*, *IL-4R*, *IFITM1*, *ITGB2*, *S100A9*, *SLPI*, *SAA1*, *STST3* miRNA: miR-29a, miR-505, miR-28-5p, miR-151-5p, miR-340, miR-532-3p, miR-16, miR-21, miR-28-5p, miR-155, miR-188-5p, miR-422a

Associazioni genetiche ed epigenetiche

Disease	HLA*	Non-HLA loci	Epigenetic aberrations
Coeliac disease	HLA class II: DQ2(DRB1 *03:01-DQA1 *05:01-DQB1 *02:01) DQ8(DRB1 *04-DQA1 *03:01-DQB1 *03:02)	IL-2, IL-21, THEMIS, PTPRK, BACH2, **BACH2,** RGS1, MMEL1, SH2B3, IRAQ1	DNA methylation: NF-kB pathway miRNA: miR-449a, miR194-5p, miR-31-5p, miR-192-3p, miR-551a, miR-551b, miR-638, miR-1290, and others
Addison's disease	HLA class II: DR3/DQ2 (DRB1*03:01-DQB1 *02:01) DR4.4/DQ8 (DRB1*04:04-DQA1 *03:01-DQB1*03:02)	UGT2B28, ADAM3A	DNA methylation: Hypomethylated status in CD4+ T cells miRNA: miR-200a

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Associazioni genetiche ed epigenetiche

Disease	HLA*	Non-HLA loci	Epigenetic aberrations
Sjogren's syndrome	HLA class II: DRB1*15, DRB1*03 DRB1*11, DRB1*04 DRB1*08:03 and 16:02 DRB1*12:01 protective	STAT4, IL-12A, TNIP1, **IRF5**, BLK, CXCR5	DNA methylation: Hypomethylated CD4+T, HERVs Acetylation: Acetylation of histone H4 in *AQP5* gene promoter miRNA: miR-146a, miR-155,Let- 7b, **mir-21**
Systemic lupus erythematosus	HLA Class II: DR3(DRB1 *03:01-DRB1*02:01) DR2(DRB1 *15:01-DRB1*06:02) DR8(DRB1 *08:01-DRB1*04:02) DR6(DRB1*13:02 and 14:03) protective HLA Class III: TNF,C2,C4,SCIV2L, CFB, RDBP,DOM3Z, STK19C4A, C4B,	STAT4, IFIH1, **IRF5**, TNFAIP3, **PTPN22**, TNFSF4, IL-10, IL-21, ITGAM, ATG5, TNFAIP3	DNA methylation: *NLRP2*, *CD300LB*, *S1PR3* Hypomethylation in CD4+' Histone modification: Global H3 and H4 hyperacetylation in CD4T miRNA: miR-146a, miR-638, miR- 16, miR-27a, **miR-21**, miR-31, miR-125a, miR- 155, miR-371-5p, miR- 1224-3p, miR-423-5p, miR-15, miR-148a, and others

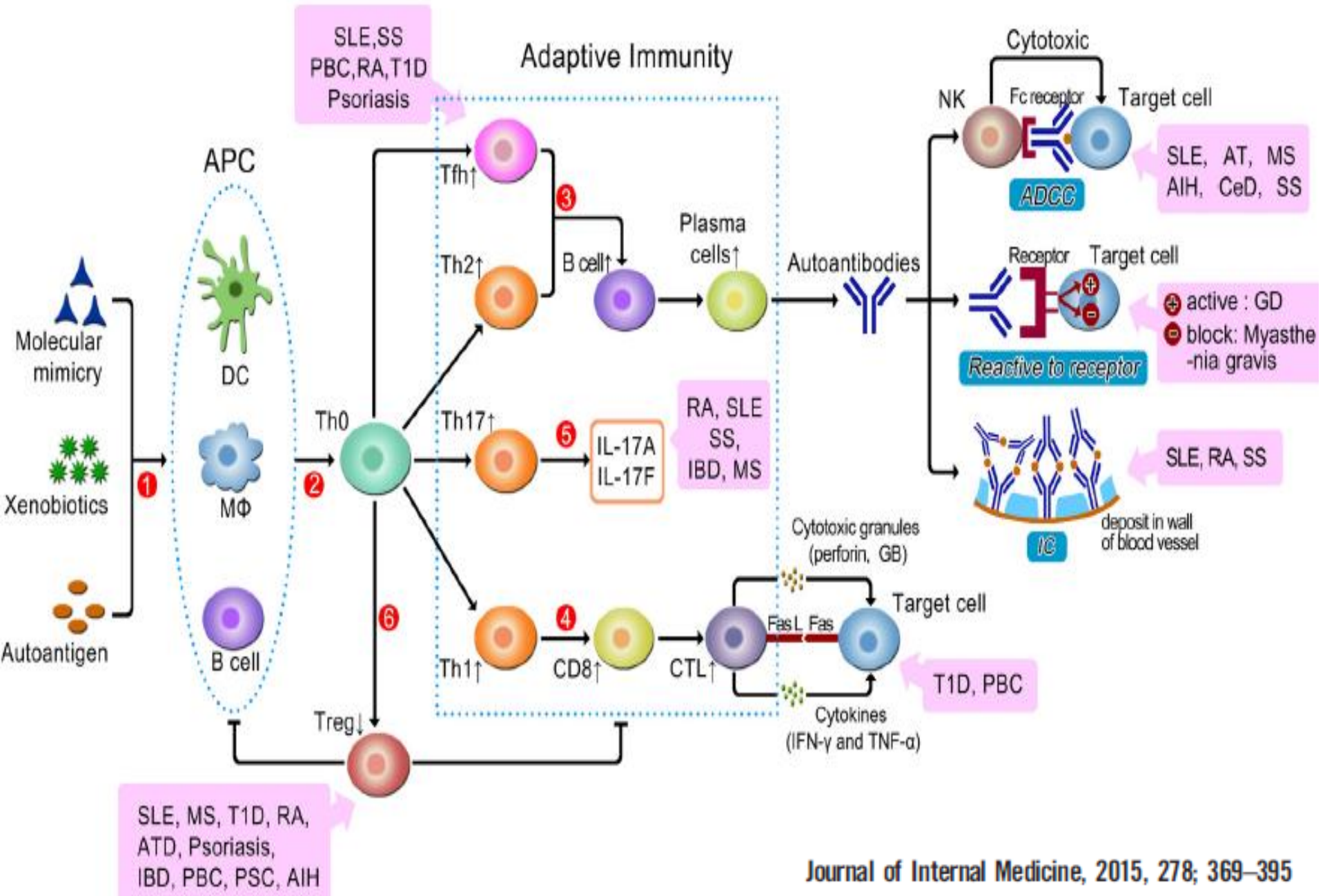
Associazioni genetiche ed epigenetiche

Disease	HLA*	Non-HLA loci	Epigenetic aberrations
Rheumatoid arthritis	HLA Class II: DR4(DRB1*04:01, *04:04,*04:05, *04:02,*04:03,*01:01) DR1 HLA Class III: TNF	PADI4, **PTPN22**, CTLA4, STAT4, TNFAIP3, CD40, IL-2RA, CD28, CCR6, **IRF5**, RUNX1, GATA3	DNA methylation: *C5*, *TET*, *APOBEC*, *IL-6* promoter, *CD40L* promoter, *CXCL12* Histone modification: Alteration of histone modification in PBMCs and synovium/ synoviocytes HDAC inhibitors miRNA: miR-146a, miR-155, miR-223, miR-124, miR-34, miR-346, miR-203a, miR-363, miR-498, miR-let-7a, miR-323-3p, miR-140, miR-132, miR-16, and others

miR, microRNA; HDAC, histone deacetylase; PBMC, peripheral blood mononuclear cell; HLA, human leucocyte antigen. The genes highlighted in bold text were found in more than three different autoimmune diseases, respectively.

Journal of Internal Medicine, 2015, 278; 369–395

Disregolazione del sistema immunitario nelle malattie autoimmuni



Journal of Internal Medicine, 2015, 278; 369–395

Principali malattie autoimmuni organo e non organo specifiche

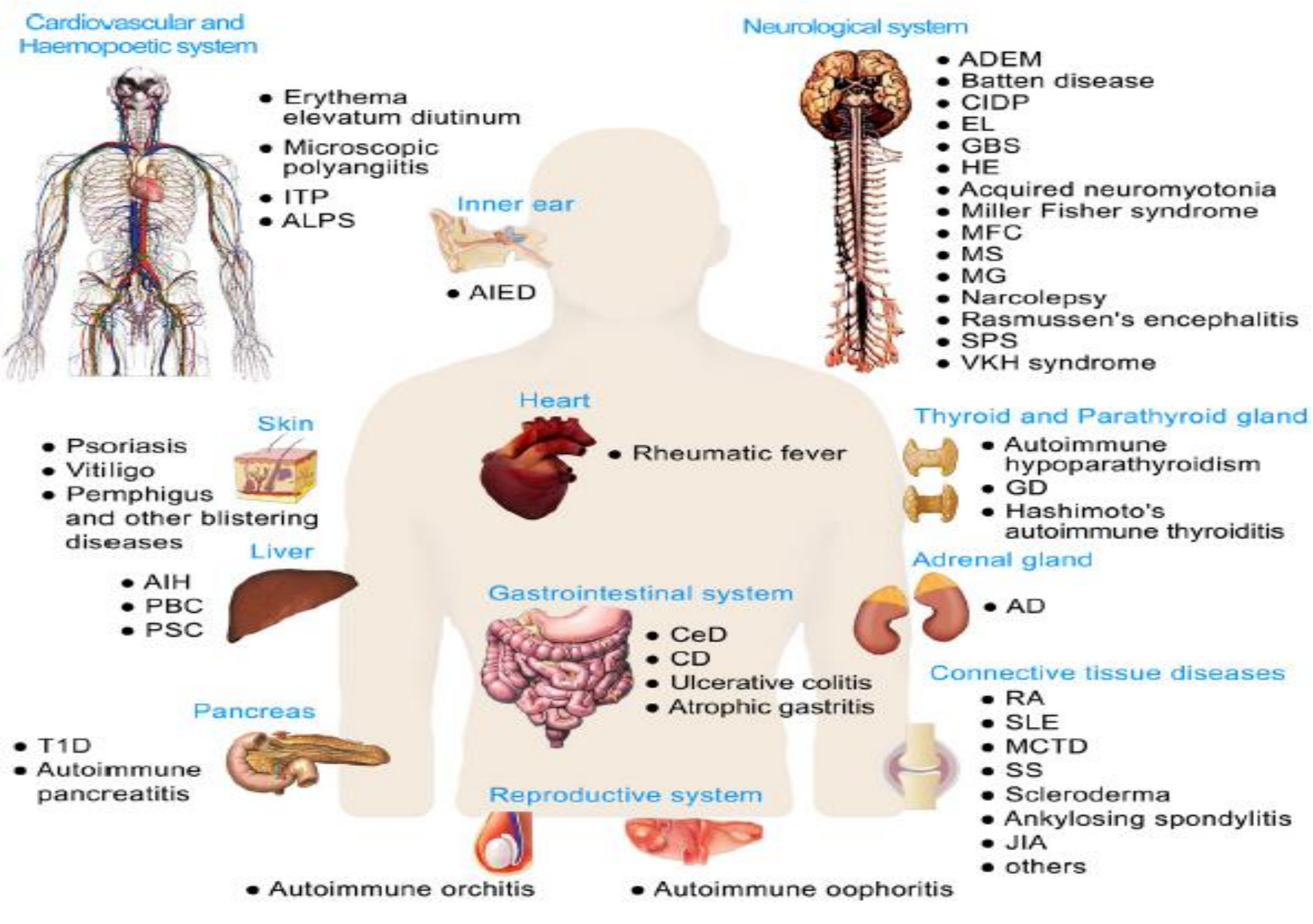
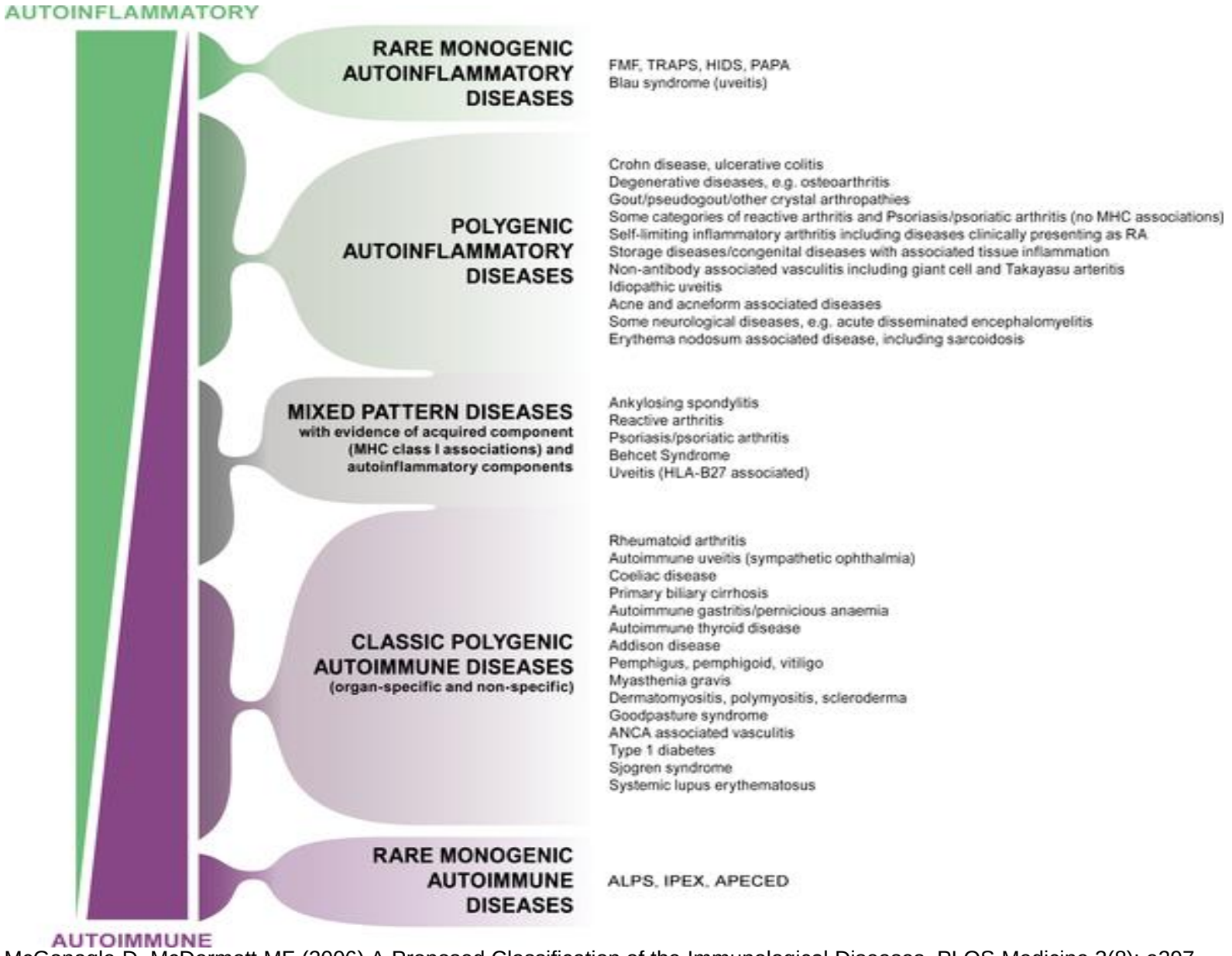


Figure 1. The Immunological Disease Continuum, with Examples



McGonagle D, McDermott MF (2006) A Proposed Classification of the Immunological Diseases. PLOS Medicine 3(8): e297. doi:10.1371/journal.pmed.0030297
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0030297

Table 2. Immunological Aspects of Pure Autoinflammation versus Pure Autoimmunity

Variable	Autoinflammatory	Autoimmune
Factors determining disease manifestations	Local tissue factors at disease-prone sites, including tissue trauma, necrosis, mechanical factors, and bacteria or their constituent molecules	Clinical disease expression determined by events taking place in primary and secondary lymphoid tissues, including bone marrow, thymus, lymph nodes, and spleen
	Innate immune activation	Adaptive immune activation
Key theory relating to disease expression	The danger signal theory of Matzinger, with tissue-specific factors determining disease localisation	The major factor determining disease is aberrant SNS discrimination, with breakdown of immunological tolerance
Immunological basis	Genetically related to perturbations of innate immune function, including pro-inflammatory cytokine signalling abnormalities/ bacterial sensing/local tissue abnormalities	Acquired immune perturbation key-to-disease expression
Cellular basis	Expression determined by cells of innate immune system, including neutrophils and macrophages or nonimmune cells	Expression mainly determined by factors affecting B and T cell activity
	Genetic mutations in HPFs, including TRAPS and FMF, affect these cells	Genetic mutations in rare autoimmune diseases affect these cells or their selection in thymus

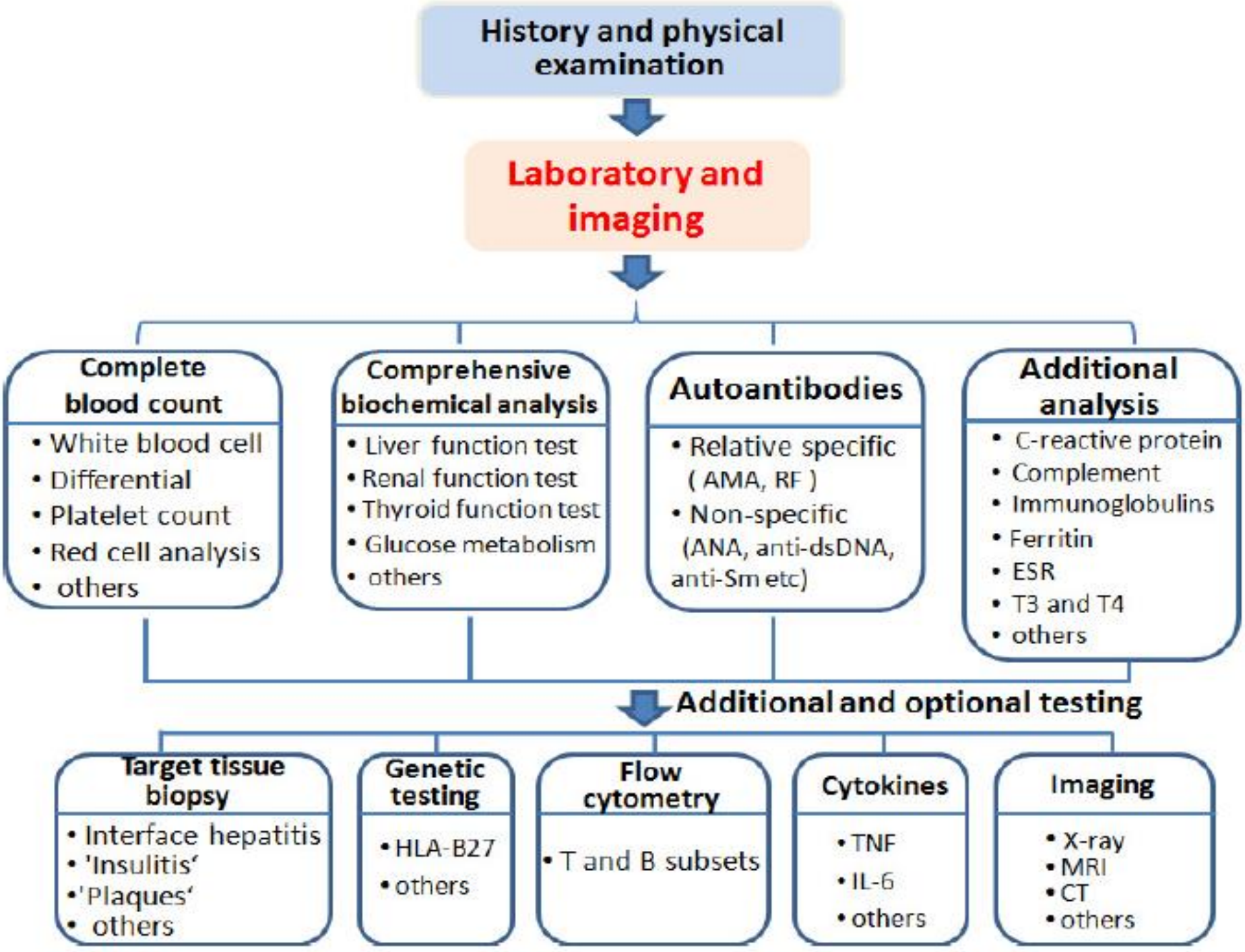
DOI: 10.1371/journal.pmed.0030297.t002

This table represents some of the key features that allow differentiation of a "pure autoinflammatory disease" from a "pure autoimmune disease." The rare monogenic HPFs are the prototypic autoinflammatory diseases, whereas the prototypes for autoimmune diseases include the polygenic MHC and autoantibody-related diseases, as well as some rare monogenic diseases. SNS, self/nonself.

McGonagle D, McDermott MF (2006) A Proposed Classification of the Immunological Diseases. PLOS Medicine 3(8): e297. doi:10.1371/journal.pmed.0030297
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0030297

Disease	Known antigen	Autoantibodies	Target organ	Pathology (or biopsy)	Diagnostic criteria
Multiple sclerosis	Myelin protein, (MBP, MOG, PLP, MAG, lipids)	Antibodies against myelin protein (lack diagnostic specificity)	Central nervous system	Freshly demyelinated 'plaques' in the brain matter	Revised 2010 McDonald diagnostic criteria [232]
Type 1 diabetes	Glutamate decarboxylase (GAD-65), insulin receptor, IA-2 (ICA512), insulin	IAA, GADA, IA-2A, ZnT8A	Pancreas β-islets	Decreased β cell mass with infiltration of mononuclear cells into the islets ('insulitis')	2010 diagnostic criteria [233]
Primary biliary cirrhosis	Mitochondrial (PDC-E2)	AMA	Small- and medium-sized intrahepatic bile ducts	Ludwig's stage I–IV	2009 diagnostic criteria [234]
Autoimmune hepatitis	Chromatin, ribonucleoproteins, asialoglycoprotein receptor, cytochrome P4502D6 (CYP2D6), F-actin	ANA, anti-LKM-1, antismooth muscle antibody, anti-actin	Liver	Interface (periportal or perseptal) hepatitis with a predominantly lymphoplasmacytic necroinflammatory infiltrate	1999 [235] and 2008 [236] criteria
Primary sclerosing cholangitis	Tubulin-β isoform 5	Antineutrophil cytoplasmic antibody, ANA, anti-SM, anti-endothelial cell antibody, anticardiolipin antibody	Bile ducts	Typical 'onion-skinning' lesions Ludwig's stage I–IV	2010 diagnostic criteria [237]
Graves' disease	TSHR, sodium iodide transporter	Anti-TSHR autoantibodies	Thyroid	Thyroid follicles	2010 diagnostic criteria [238]
Crohn's disease	Desmin, *saccharomyces cerevisiae*, Tubulin-β isoform 5?	Anti-TG2, antigliadin	Gastrointestinal tract	Focal (discontinuous) chronic inflammation, focal crypt architectural irregularity, transmural inflammation, granulomas (not related to crypt injury), increased intra-epithelial lymphocytes, pyloric gland metaplasia	2010 diagnostic criteria [239]

Disease	Known antigen	Autoantibodies	Target organ	Pathology (or biopsy)	Diagnostic criteria
Ulcerative colitis	Desmin, *saccharomyces cerevisiae*, tubulin-β isoform 5?	ANCA, GAB	Colon	Diffuse inflammatory cell infiltration of the mucosa with basal plasmacytosis, crypt architecture, reduction of mucus-secreting goblet cells	2008 diagnostic criteria [240]
Coeliac disease	Tissue transglutaminase	Endomysial IgA antibodies and antitissue transglutaminase antibodies	Small intestine	Intra-epithelial lymphocytosis, crypt hyperplasia, villous atrophy	1990 revised ESPGAN criteria [88, 241]
Addison's disease	21-hydroxylase (CYP21)	ACA	Adrenal glands	Widespread mononuclear cell infiltrate in adrenal glands (containing lymphocytes, plasma cells, and macrophages, during the active phase)	2014 criteria [163]
Sjogren's syndrome	La phosphoprotein (La 55-B), golgin (95, 97, 160, 180) Ro52/TRIM21, Ro60/TROVE2, La/SSB	Anti-Ro/SSA, anti-La/SSB, ANA	Several organs (e.g. lungs, liver, kidneys, central nervous system), mainly salivary and lacrimal glands	(Lymphocytic sialadenitis), lymphoepithelial lesions in salivary and lacrimal glands	2012 revised ACR/SICCA criteria [242, 243]
Systemic lupus erythematosus	Cardiolipin, carbonic anhydrase II, collagen, RNA polymerase I–III (RNP), fibronectin, golgin (95, 97, 160, 180), C1q, histone H2A-H2B-DNA	Antinuclear antibody, anti-dsDNA antibody, anti-Sm, antiphospholipid antibody	Several organs (heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system)	Nephritis compatible with lupus	2012 new SLICC classification criteria [168, 244]
Rheumatoid arthritis	Rheumatoid factor, keratin, CCP, collagen, fibronectin	Anti-CCP RF-IgG, ACPA, anti-Carp	synovium of joints	Pathological changes in synovium	2010 ACR/EULAR criteria [245]


History and physical examination
Laboratory and imaging
Complete blood count
• White blood cell
• Differential
• Platelet count
• Red cell analysis
• others
Comprehensive biochemical analysis
• Liver function test
• Renal function test
• Thyroid function test
• Glucose metabolism
• others
Autoantibodies
• Relative specific (AMA, RF)
• Non-specific (ANA, anti-dsDNA, anti-Sm etc)
Additional analysis
• C-reactive protein
• Complement
• Immunoglobulins
• Ferritin
• ESR
• T3 and T4
• others
Additional and optional testing
Target tissue biopsy
• Interface hepatitis
• 'Insulitis'
• 'Plaques'
• others
Genetic testing
• HLA-B27
• others
Flow cytometry
• T and B subsets
Cytokines
• TNF
• IL-6
• others
Imaging
• X-ray
• MRI
• CT
• others

American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE).

Table 1. American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE).*

Criterion	Definition
Malar rash	A rash on the cheeks and nose, often in the shape of a butterfly
Discoid rash	A rash that appears as red, raised, disk-shaped patches
Photosensitivity	A reaction to sunlight that causes a rash to appear or get worse
Oral ulcers	Sores in the mouth
Arthritis	Joint pain and swelling of two or more joints
Serositis	Inflammation of the lining around the lungs (pleuritis) or inflammation of the lining around the heart that causes chest pain, which is worse with deep breathing (pericarditis)
Kidney disorder	Persistent protein or cellular casts in the urine
Neurologic disorder	Seizures or psychosis
Blood disorder	Anemia (low red-cell count), leukopenia (low white-cell count), lymphopenia (low level of specific white cells), or thrombocytopenia (low platelet count)
Immunologic disorder	Positive test for anti–double-stranded DNA, anti-Sm, or antiphospholipid antibodies
Abnormal antinuclear antibodies	Positive antinuclear-antibody test

* Four of the 11 criteria are needed for the formal diagnosis of SLE.

Tsokos GC. N Engl J Med 2011;365:2110-2121.

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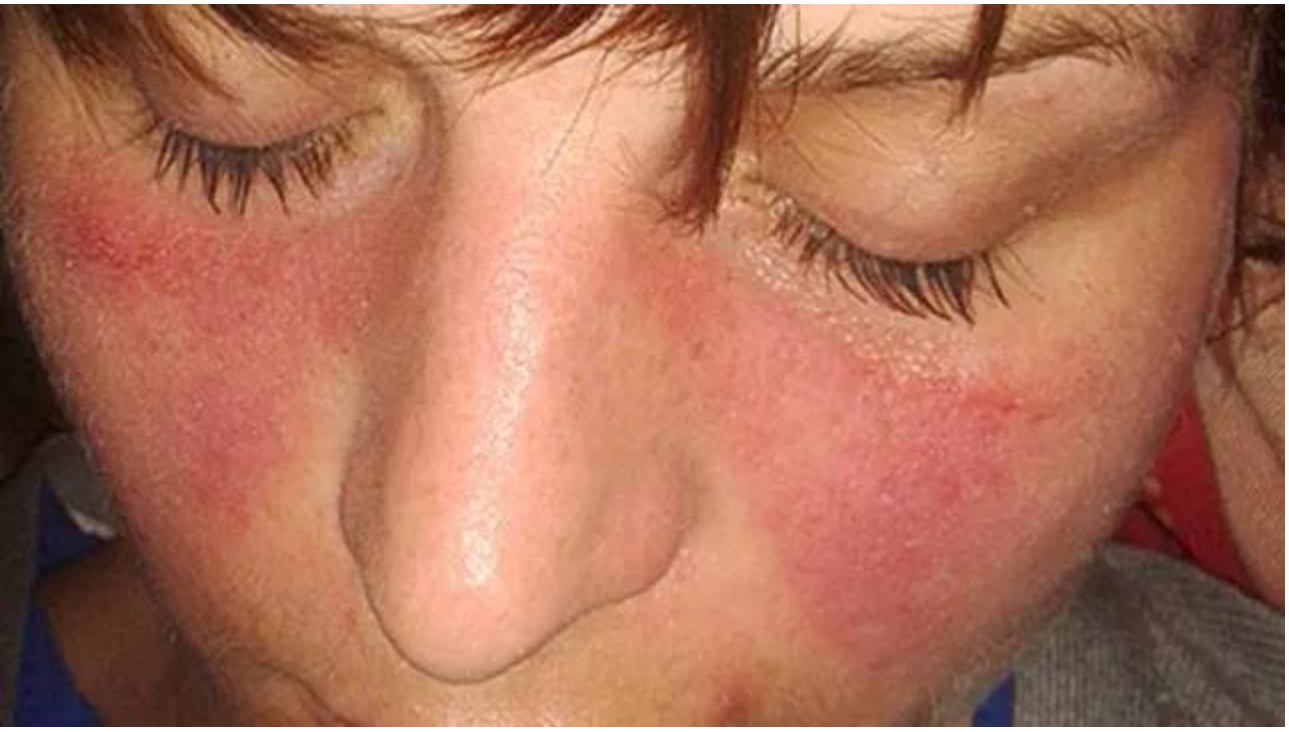
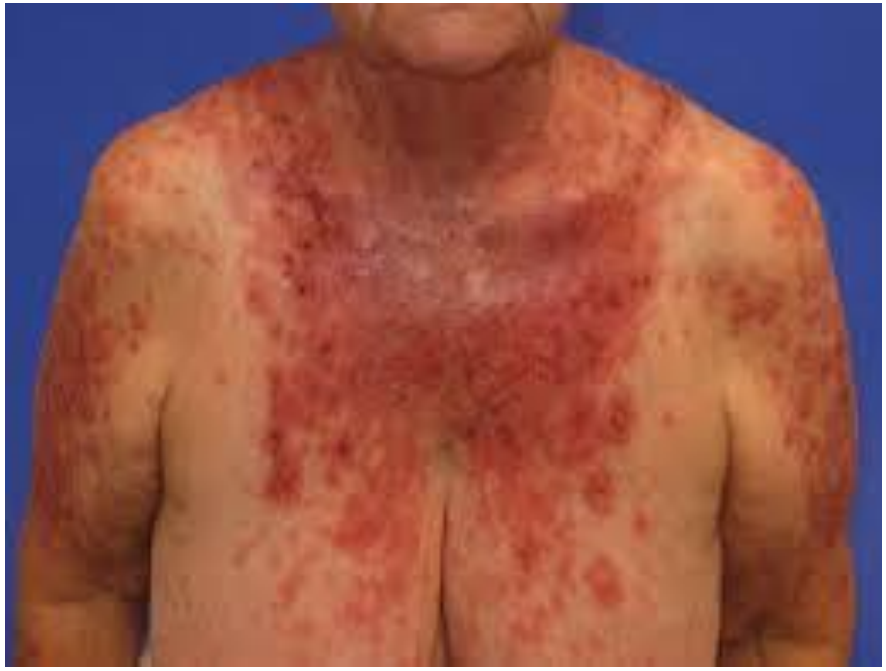
Diagnostic criteria over the years.

	1971 ACR	1982 ACR	1997 ACR	2012 SLICC
Immunologic abnormal	**2 items** • LE cells • Chronic false-positive serological test for syphilis	**2 items** • Positive lupus erythematosus preparation, anti-dsDNA and anti-Sm and false-positive for syphilis serological test • Positive ANA	**2 items** • Positive anti-dsDNA, anti-Sm or antiphospholipid antibodies • Positive ANA (by immunofluorescence or an equivalent assay)	**6 items** • Positive ANA • Positive anti-dsDNA (except ELISA) on ≥2 occasions • Anti-Sm • Antiphospholipid antibody (including lupus anticoagulant, false-positive RPR, anticardiolipin, anti-β2 glycoprotein 1) • Low complement (C3, C4 or CH50) • Direct Coombs test in the absence of hemolytic anemia
Diagnosis	**Satisfy 4 or more items**	**Satisfy 4 or more items**	**Satisfy 4 or more items**	**Satisfy 4 items** (with one having to be a clinical item and one having to be an immunologic item), e.g. lupus nephritis, in the presence of at least one of the immunologic variables

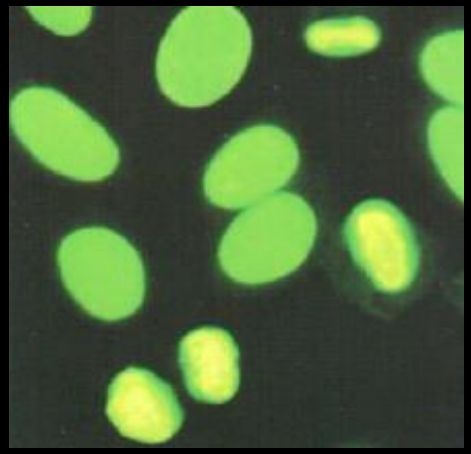


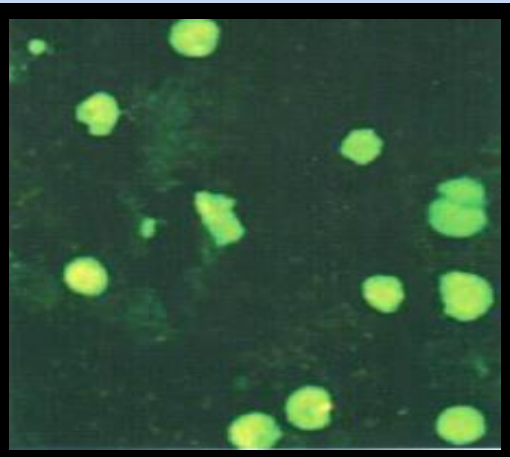
LES
BUTTERFLY RASH

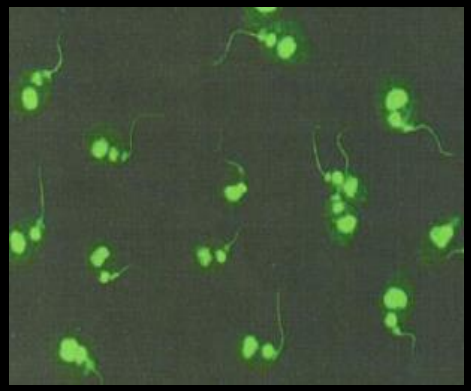


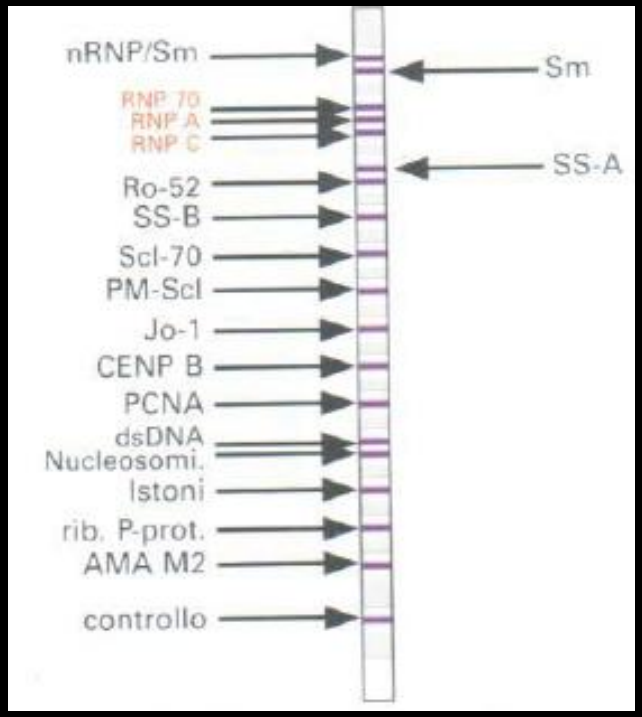
LES
RASH NELLE ZONE FOTOESPOSTE

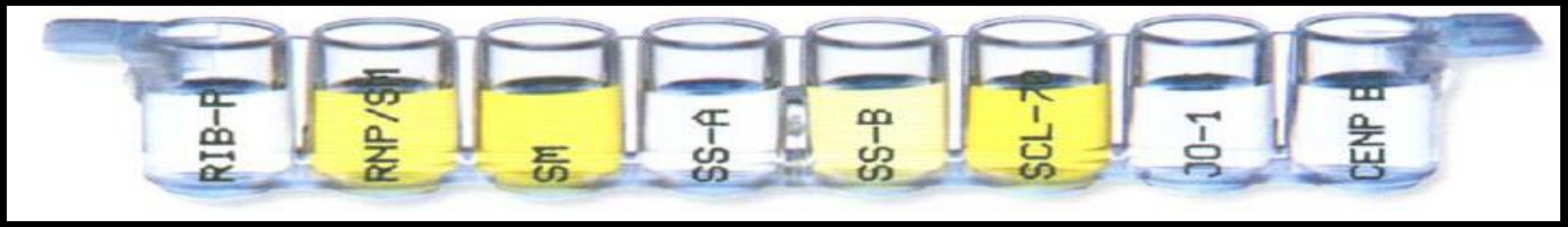
Test per ANA



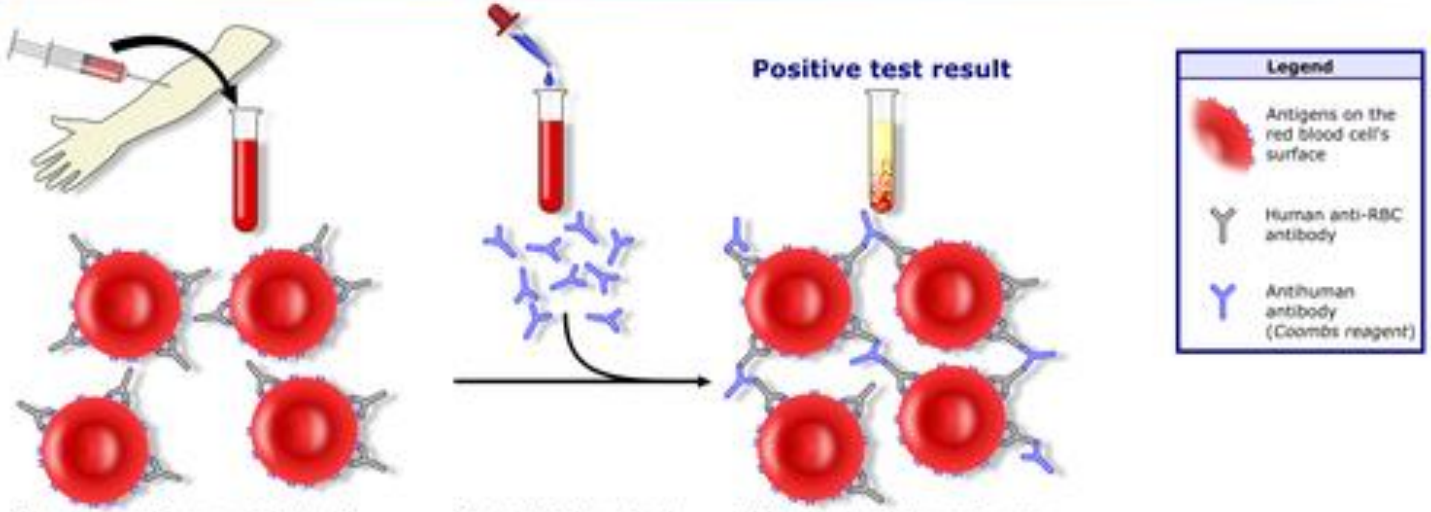





nRNP/Sm
Sm
RNP 70
RNP A
RNP C
SS-A
Ro-52
SS-B
Scl-70
PM-Scl
Jo-1
CENP B
PCNA
dsDNA
Nucleosomi.
Istoni
rib. P-prot.
AMA M2
controllo


RIB-P
RNP/SM
SM
SS-A
SS-B
SCL-7
JO-1
CENP B

Direct Coombs test / Direct antiglobulin test

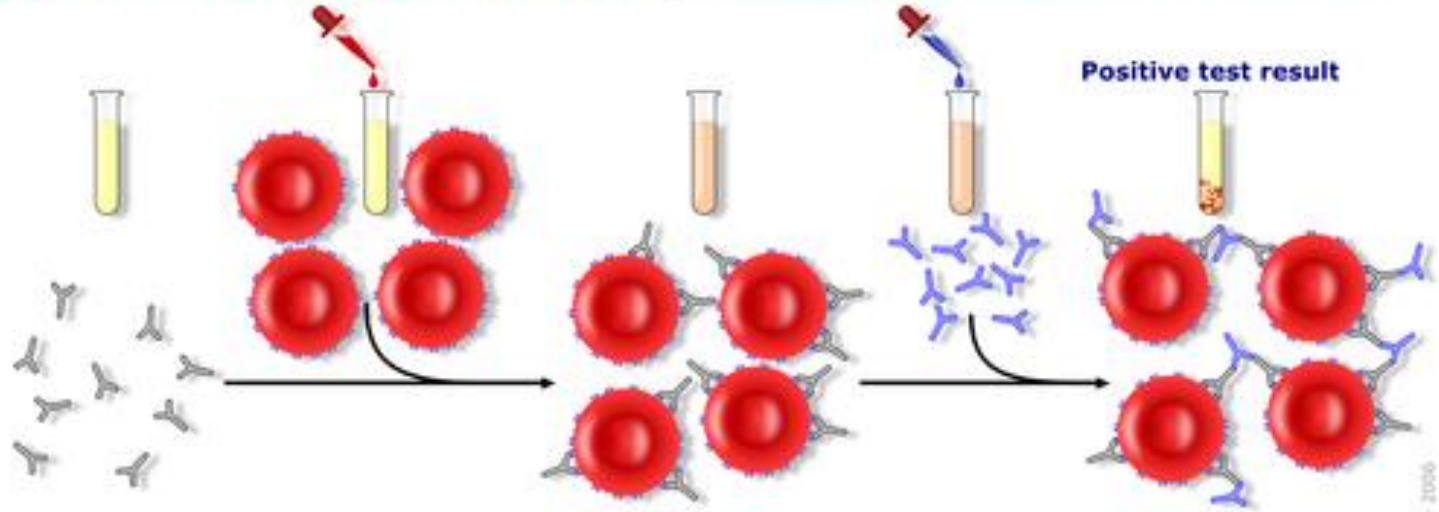


Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient's washed RBCs are incubated with antihuman antibodies (*Coombs reagent*).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Indirect Coombs test / Indirect antiglobulin test



Recipient's serum is obtained, containing antibodies (Ig's).

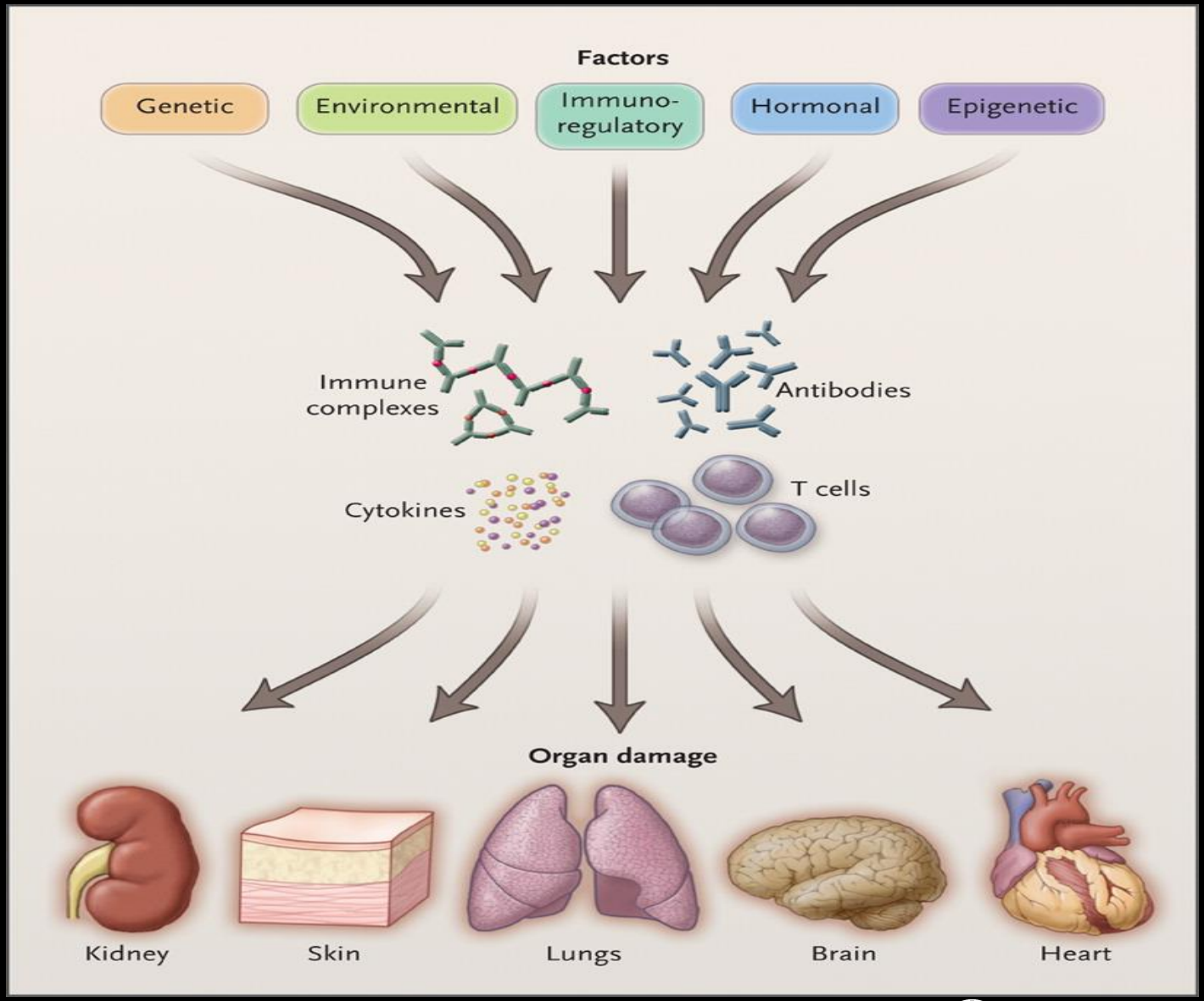
Donor's blood sample is added to the tube with serum.

Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

Anti-human Ig's (*Coombs antibodies*) are added to the solution.

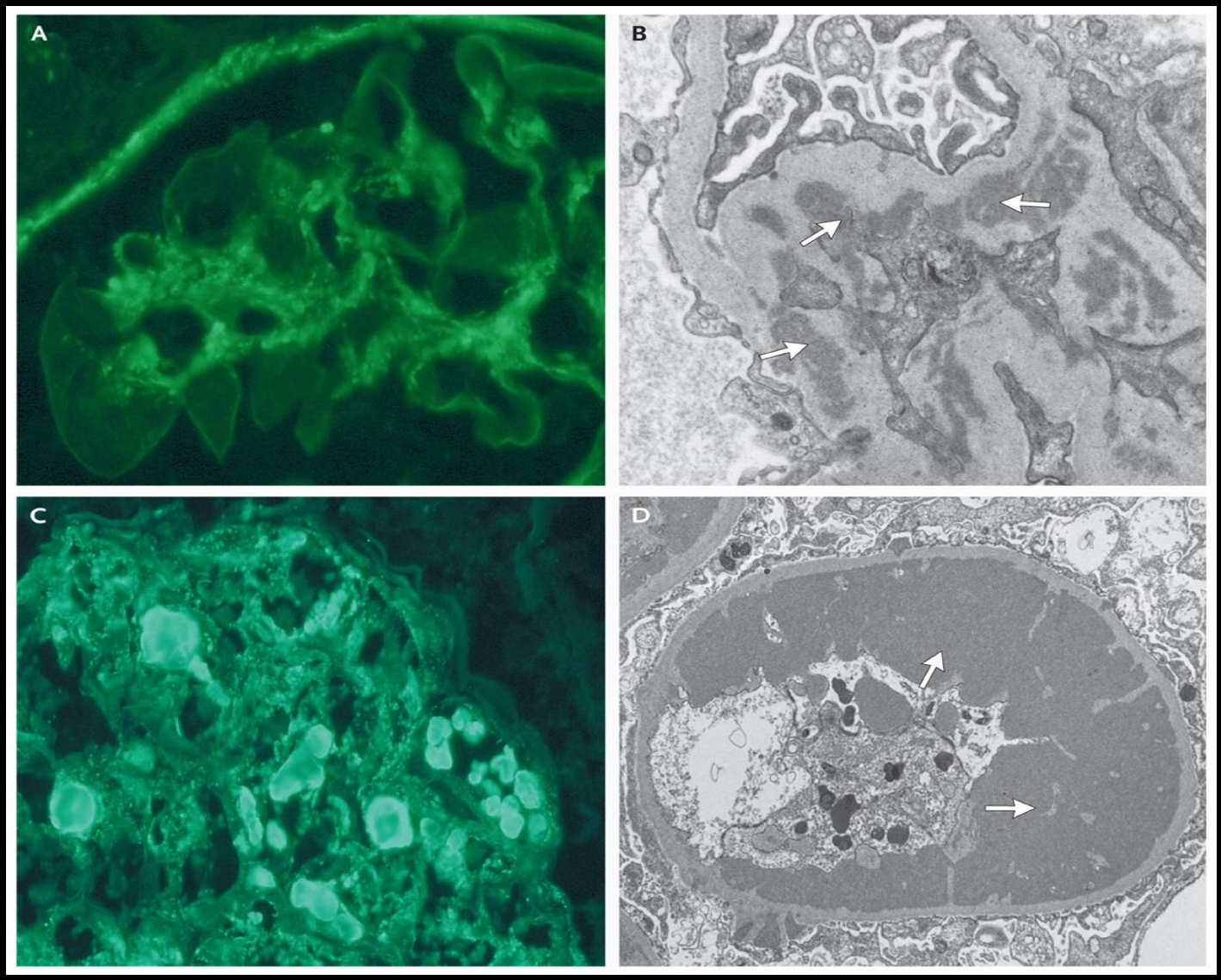
Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.

Overview of the Pathogenesis of Systemic Lupus Erythematosus.



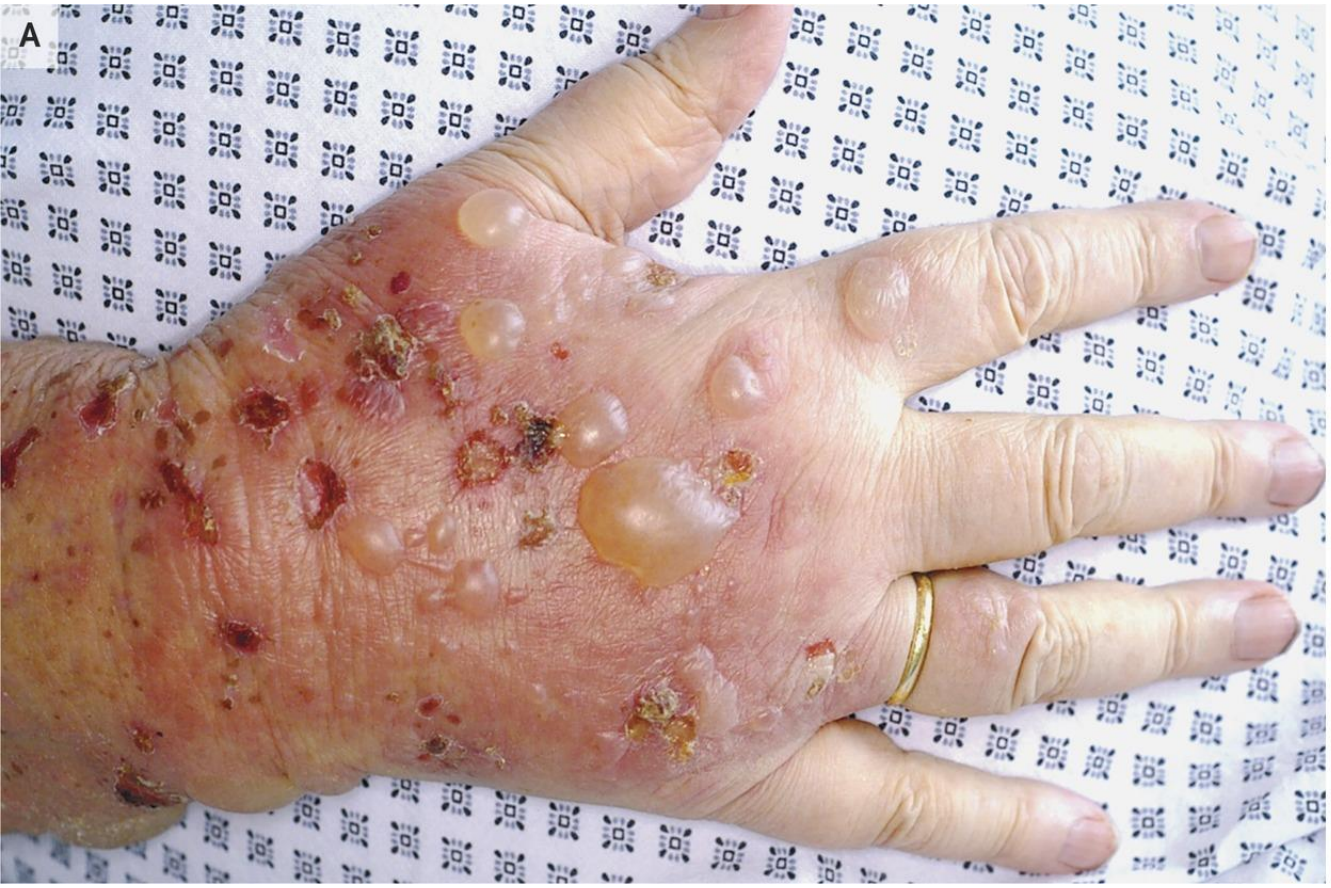
Tsokos GC. N Engl J Med 2011;365:2110-2121.

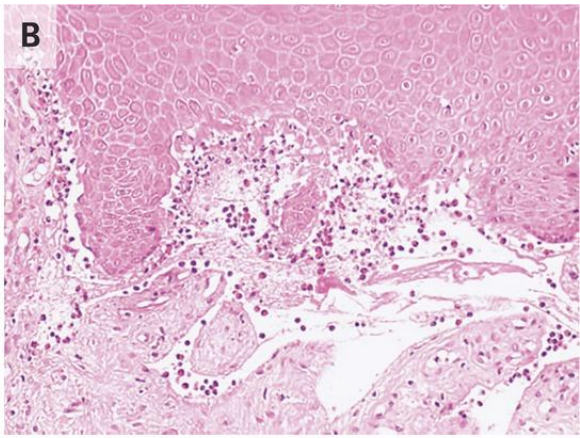
Features of Lupus Nephritis on Immunofluorescence Staining and Transmission Electron Microscopy.

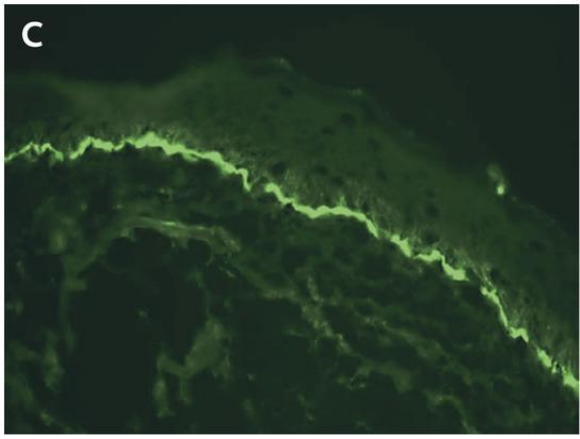


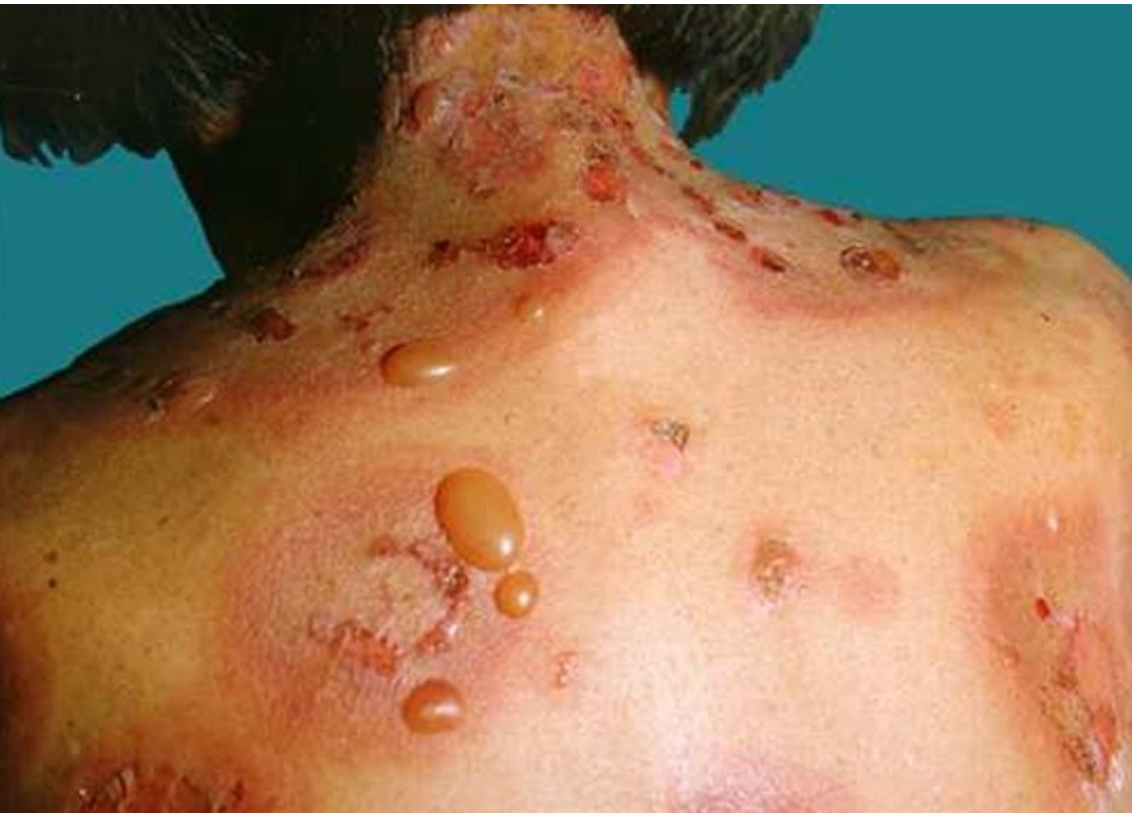
Tsokos GC. N Engl J Med 2011;365:2110-2121.

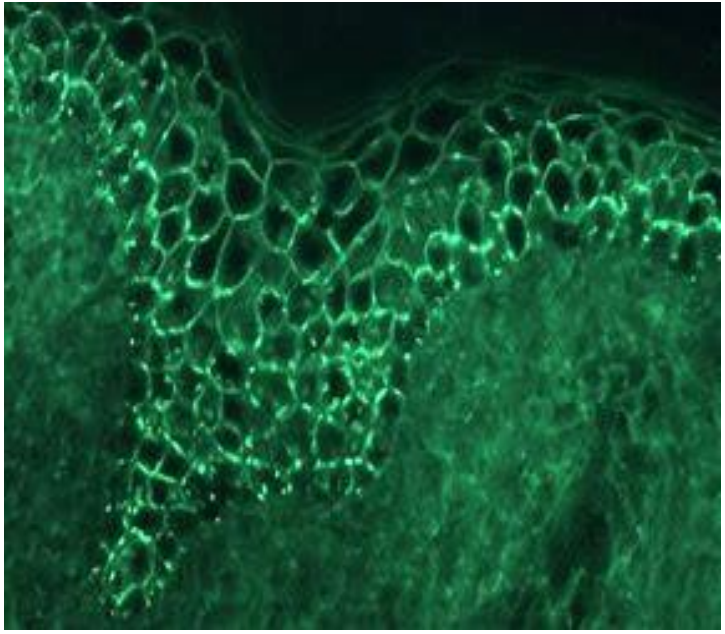
PEMFIGOIDE BOLLOSO

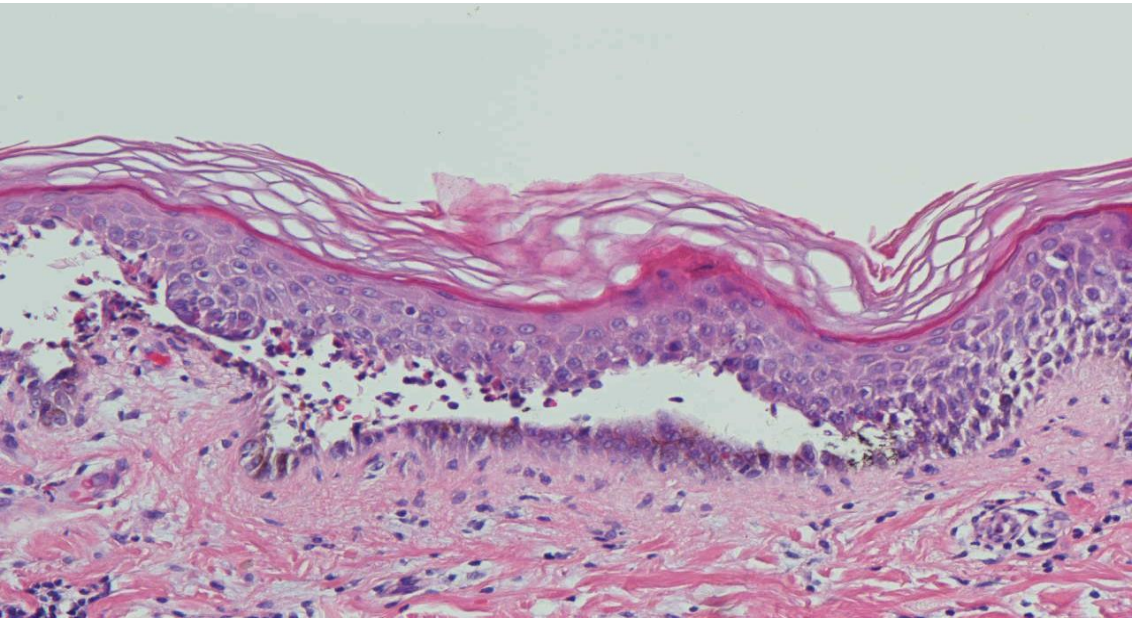


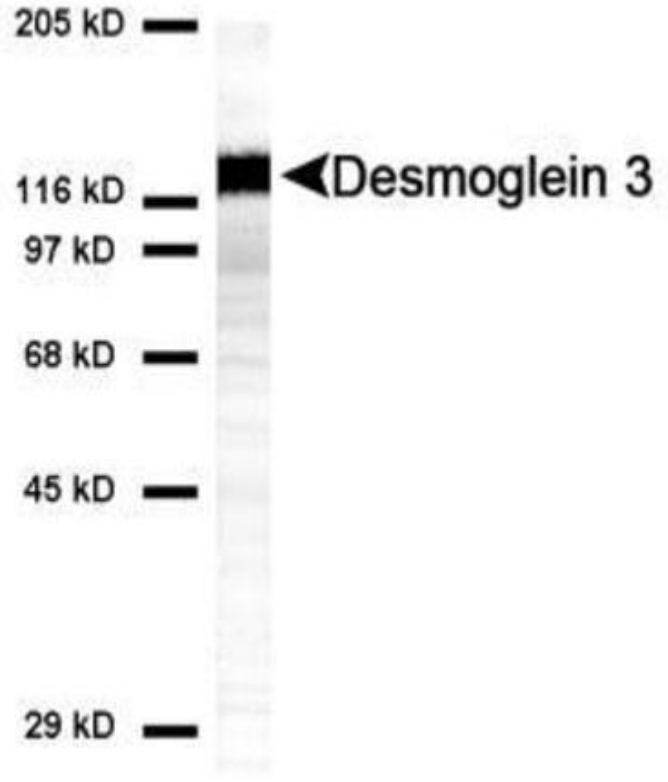




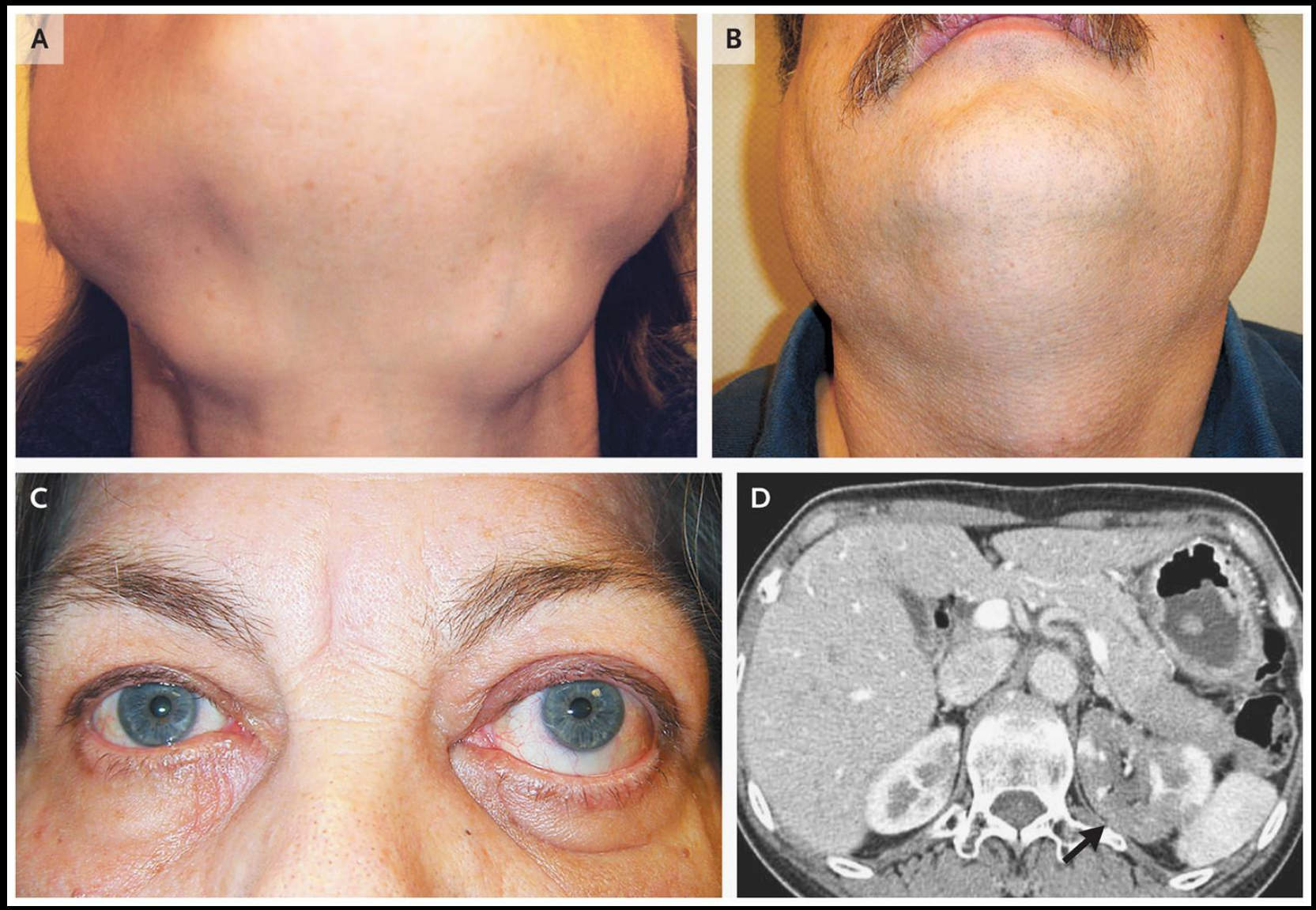







205 kD
116 kD
97 kD
68 kD
45 kD
29 kD
Desmoglein 3

Clinical and Radiologic Features of Selected Manifestations of IgG4-Related Disease.



Stone JH et al. N Engl J Med 2012;366:539-551.

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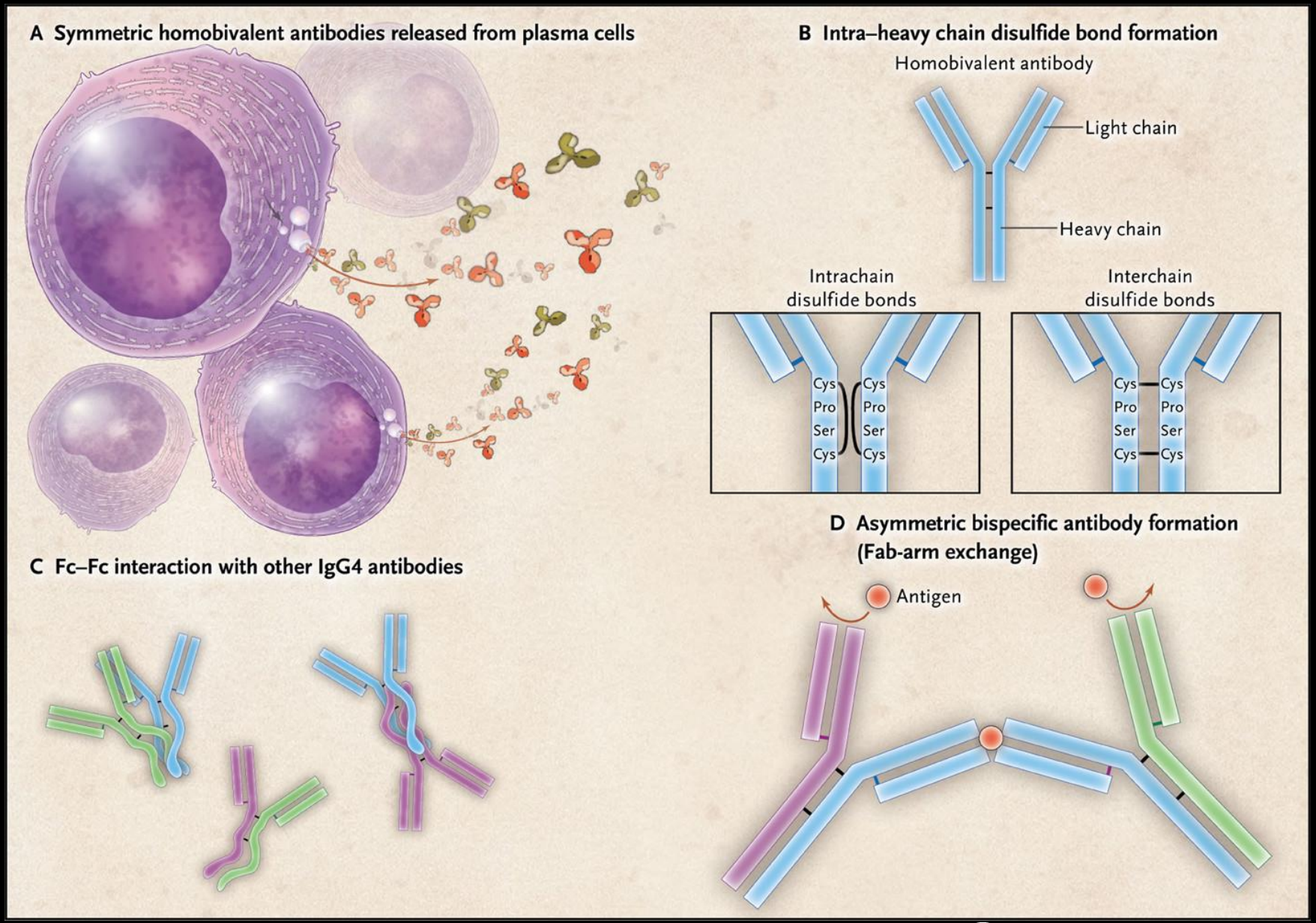
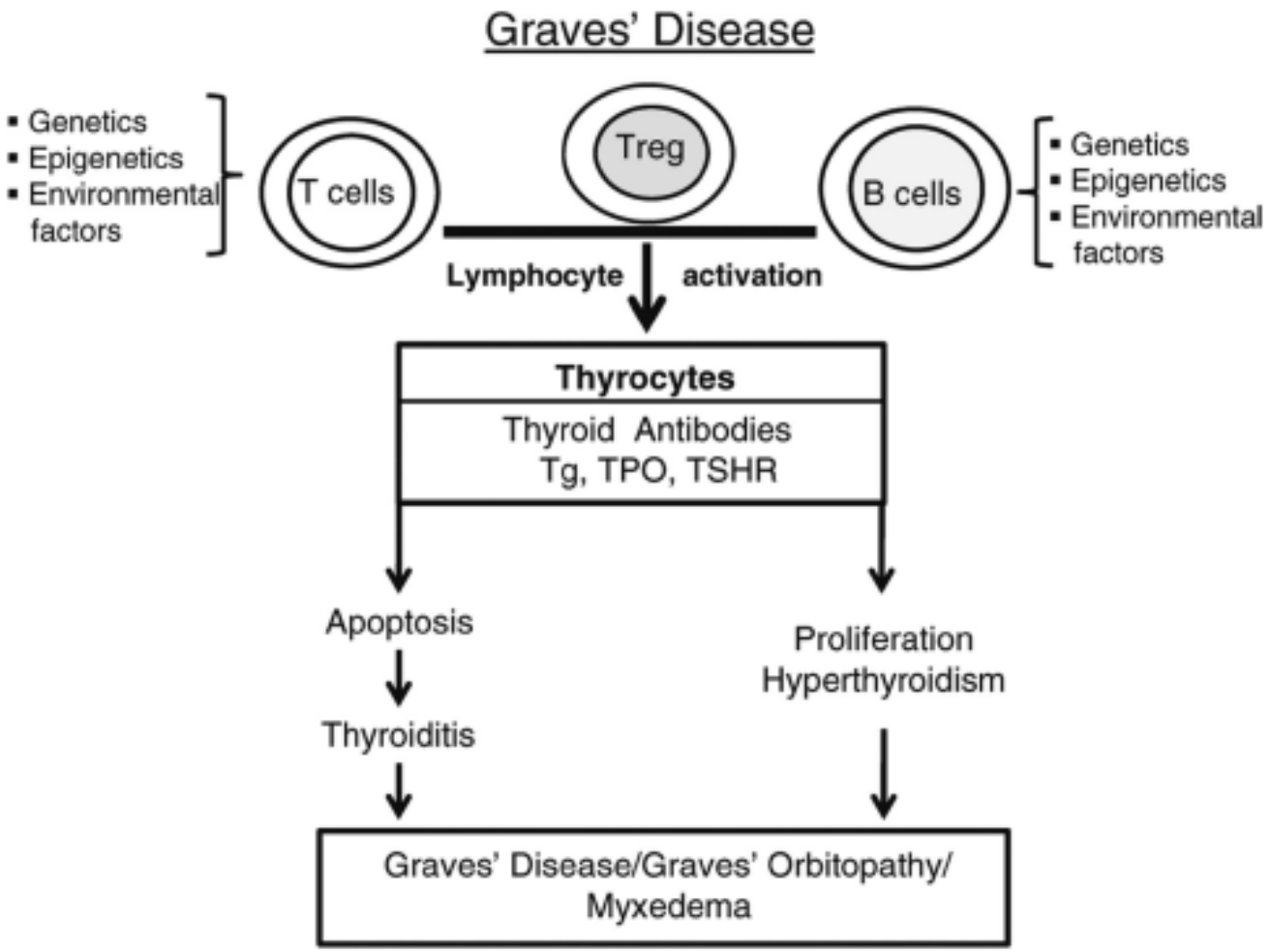
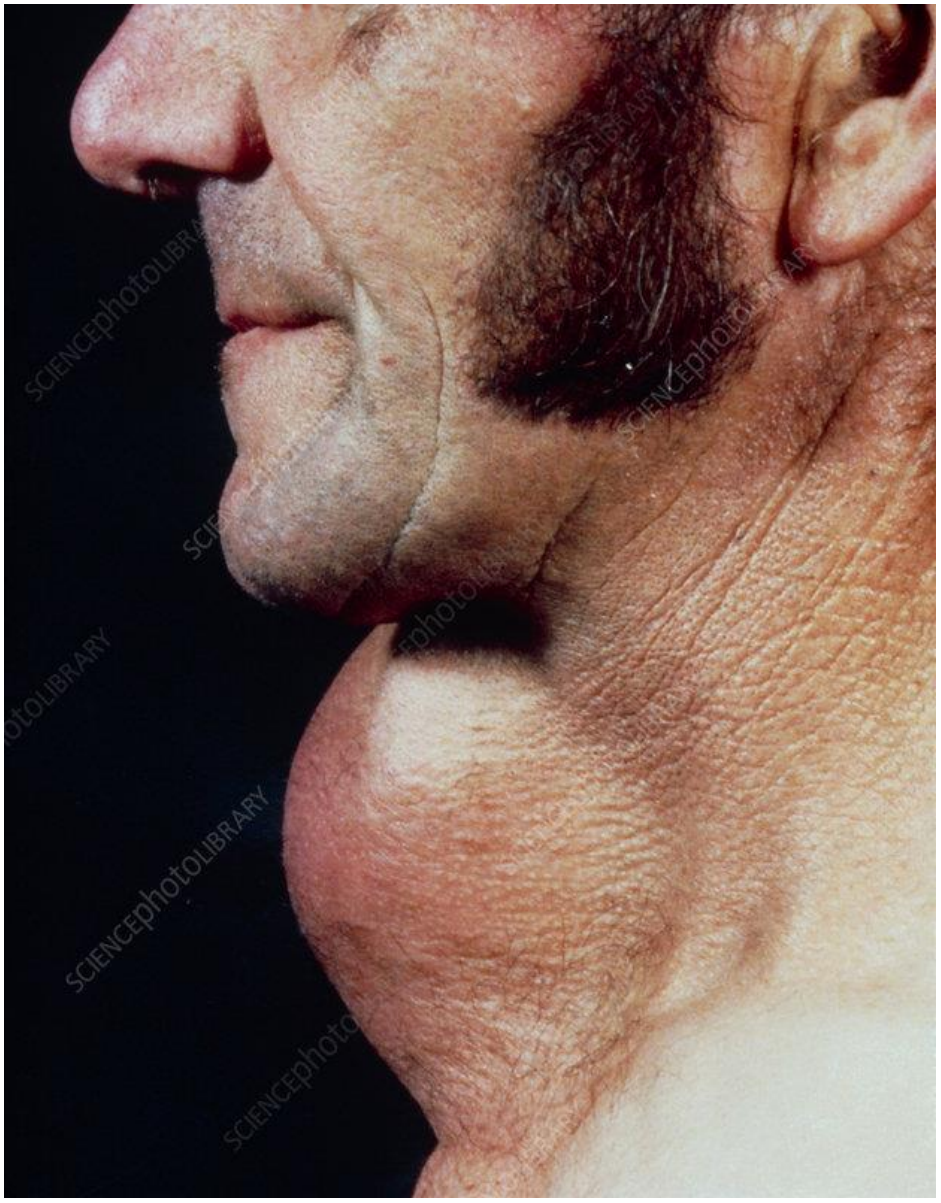
Biologic Characteristics of IgG4.



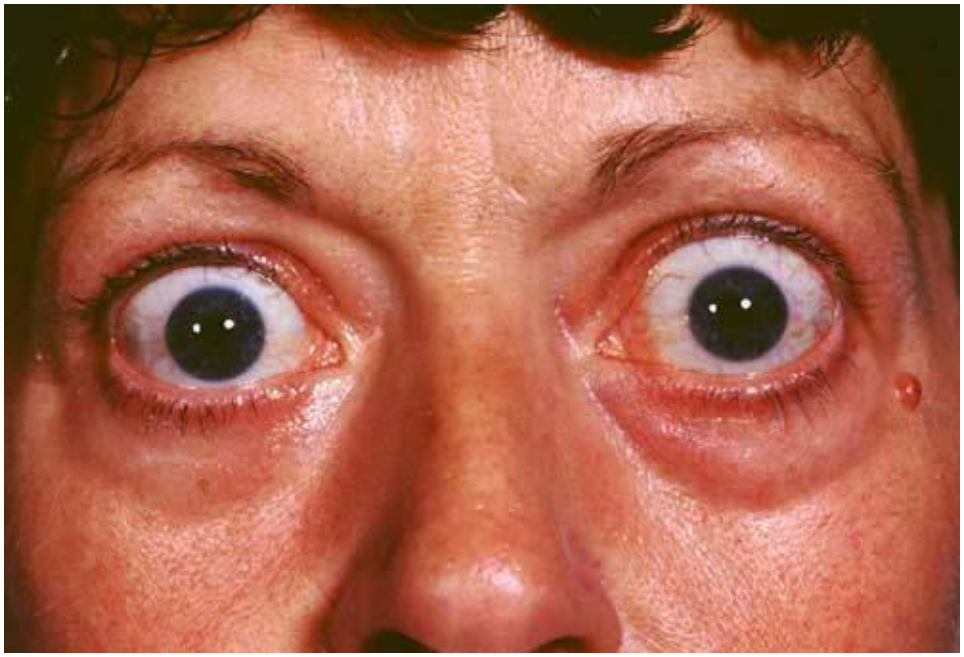
Stone JH et al. N Engl J Med 2012;366:539-551.

FATTORI CHE CONTRIBUISCONO ALLO SVILUPPO DELLA MALATTIA DI GRAVES

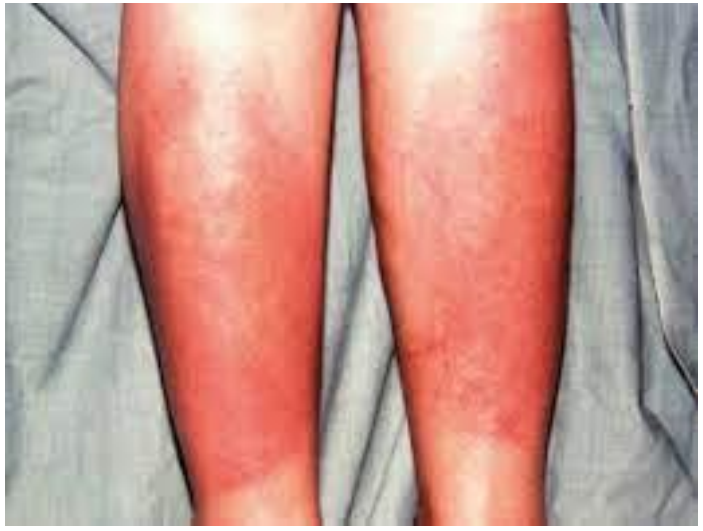




Morbo di GRAVES: GOZZO

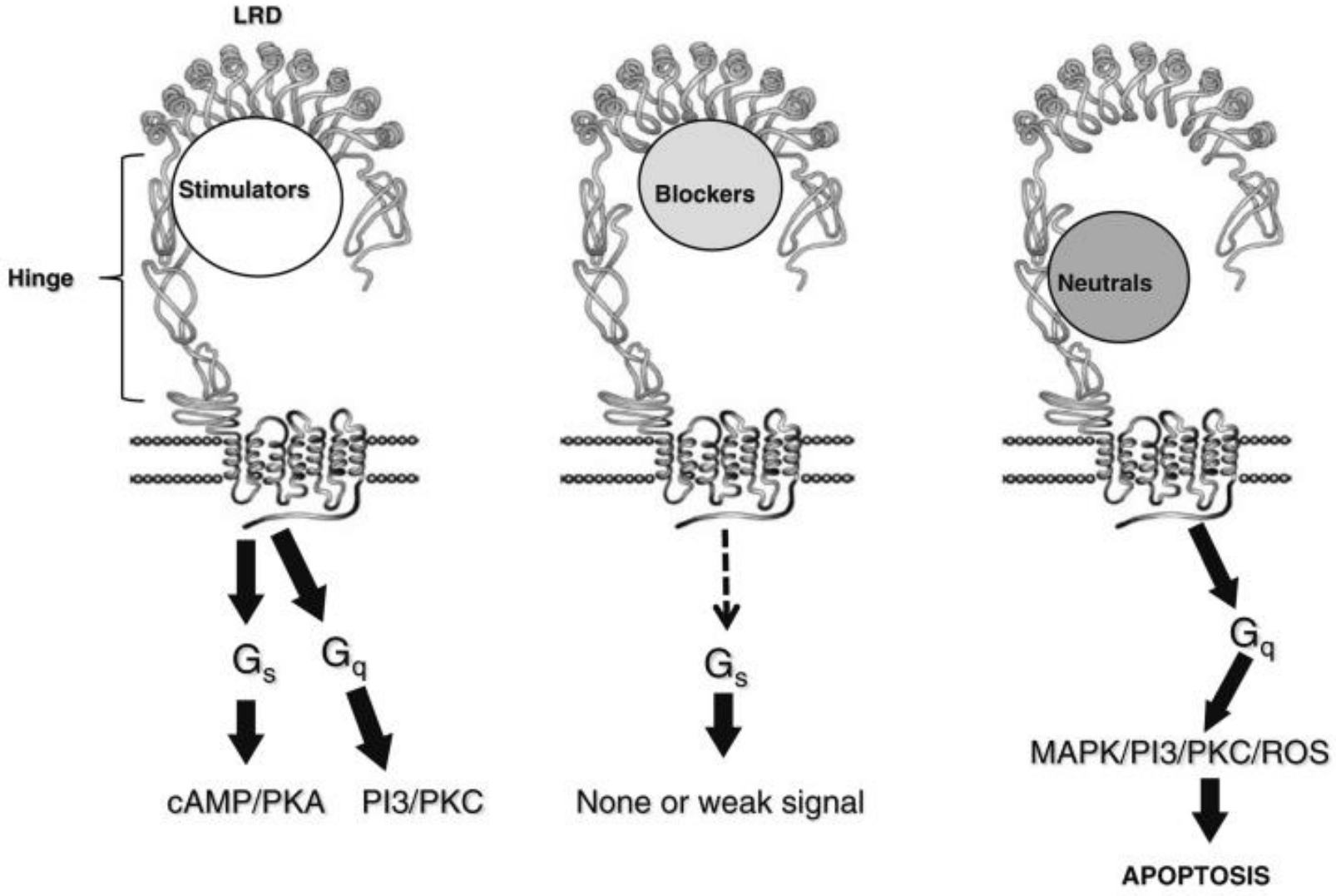


Morbo di GRAVES: ESOFTALMO

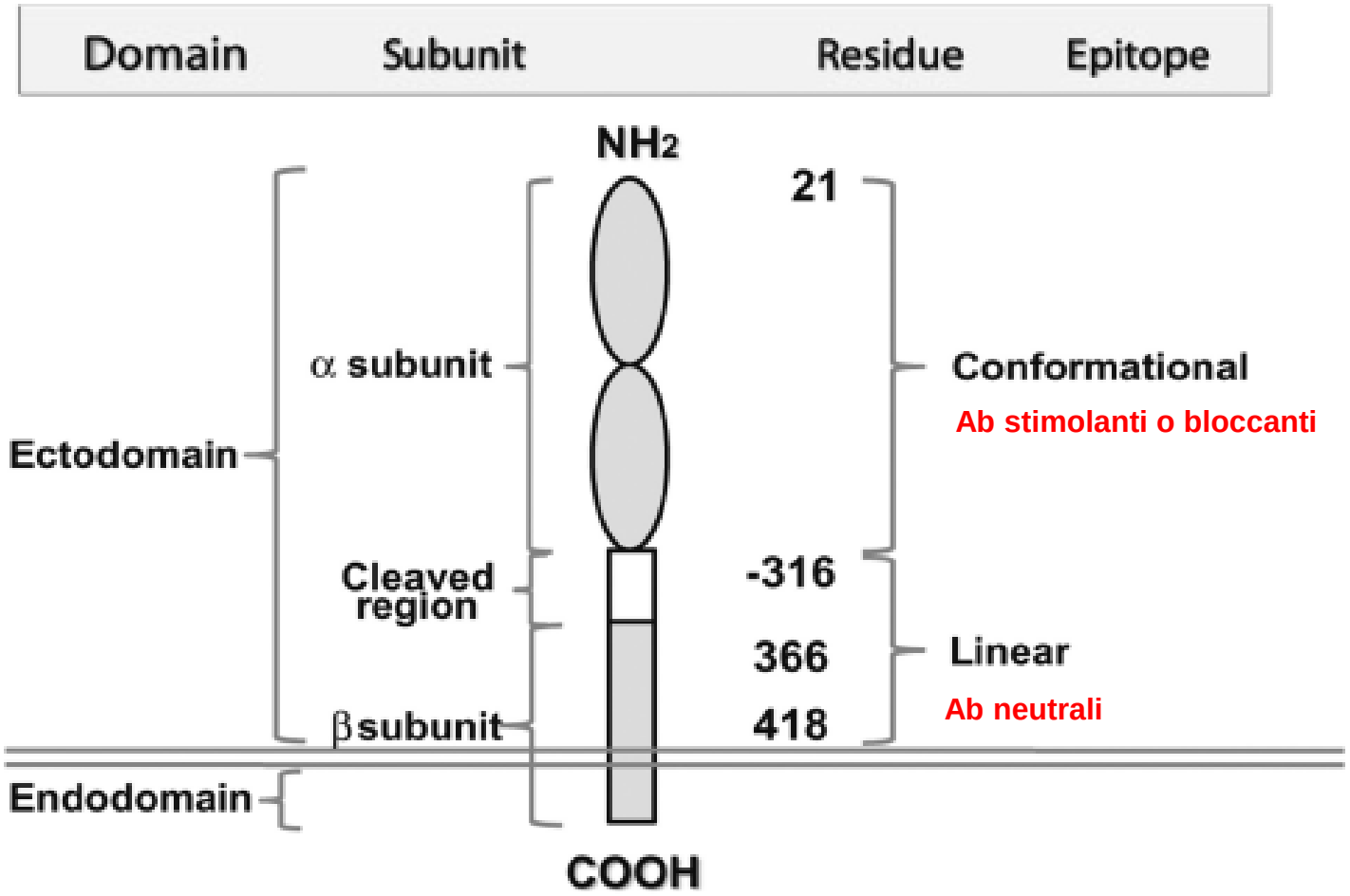


Morbo di Graves: mixedema pretibiale

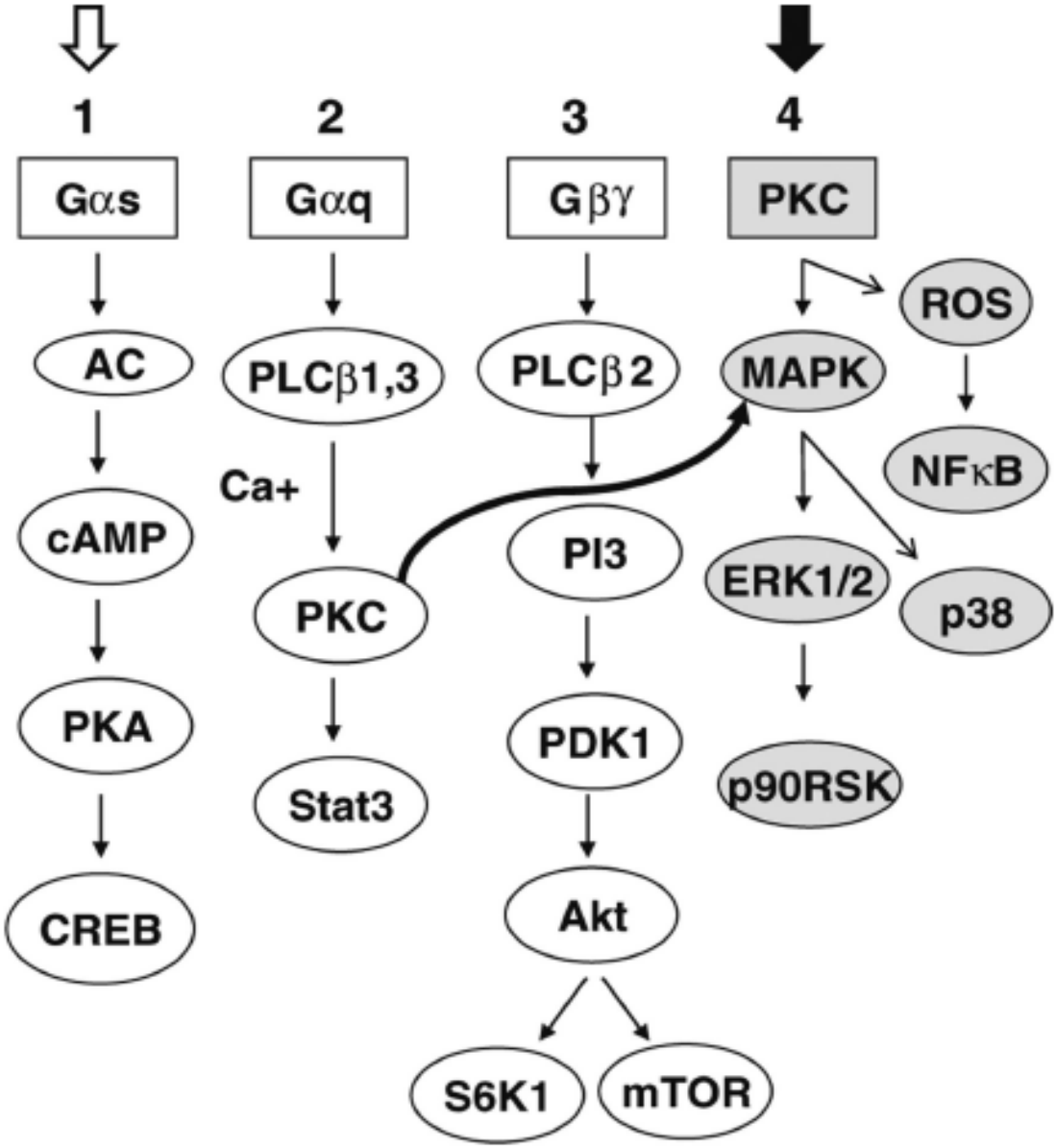
Principali TSHR-Ab e meccanismi di azione



Principali TSHR-Ab e meccanismi di azione



PATHWAYS DI SEGNALAZIONE UTILIZZATI DA TSHR Ab



Diagnosing Myasthenia Gravis with an Ice Pack

Liu WW, Chen A. N Engl J Med 2016;375:e39.

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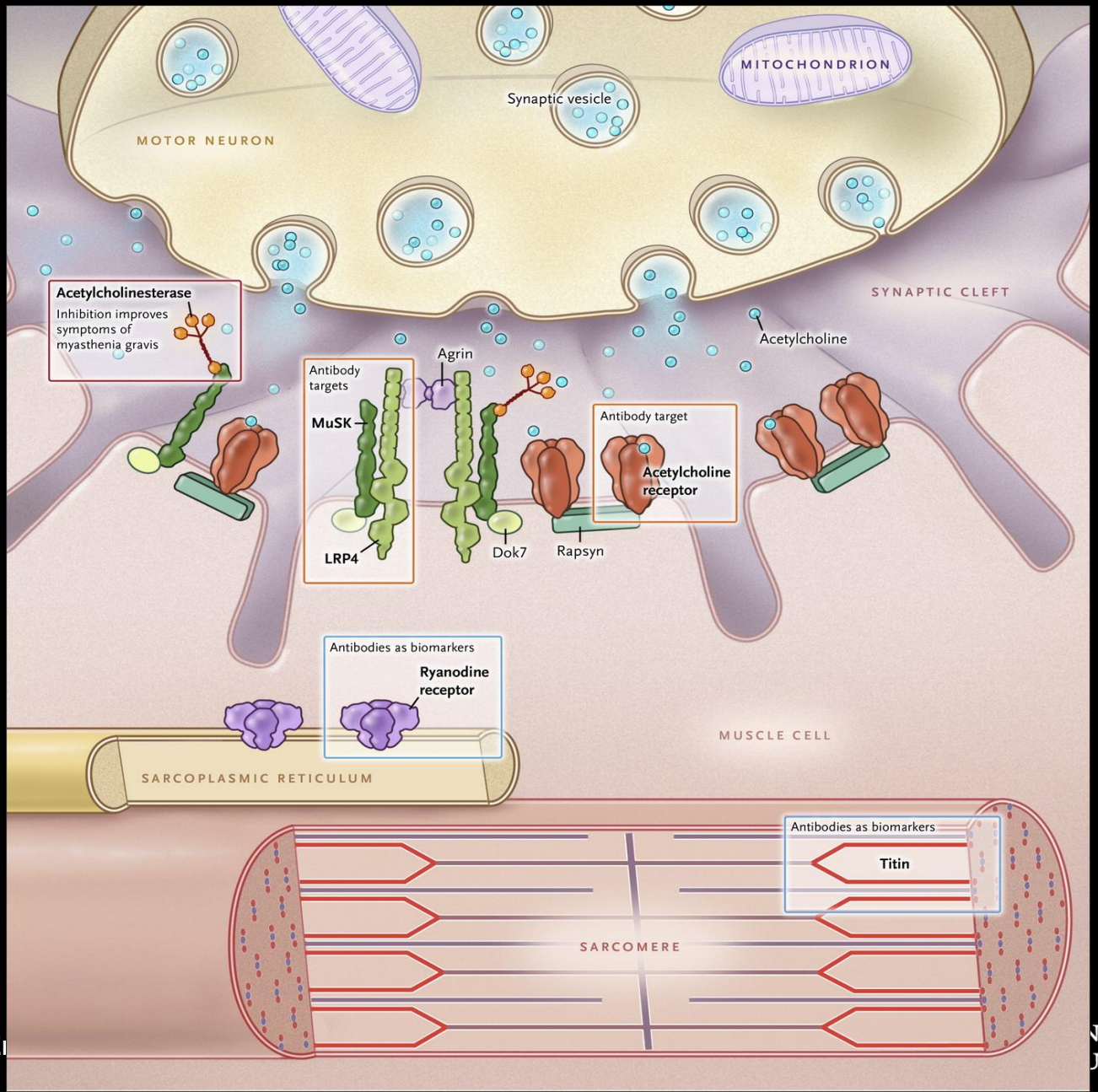
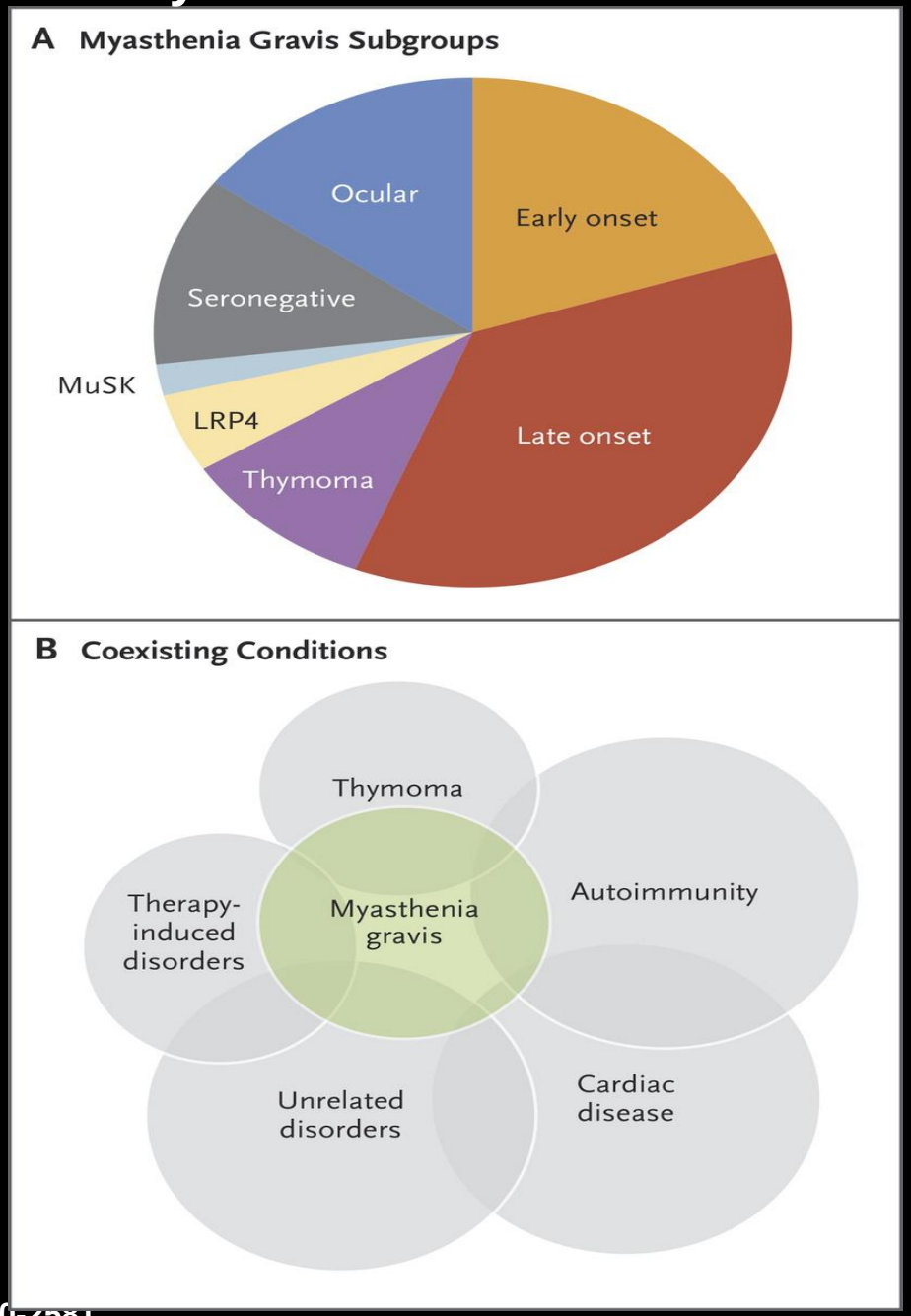
Neuromuscular Junction and Key Elements for the Pathogenesis of Myasthenia Gravis.



Gilhus NE. N E

NEW ENGLAND JOURNAL of MEDICINE

Subgroups of Myasthenia Gravis and Coexisting Conditions.



Gilhus NE.
N Engl J Med 2016;375:2570-2581.

Features of Myasthenia Gravis Subgroups.

Table 1. Features of Myasthenia Gravis Subgroups.*

Subgroup	Antibody	Age at Onset	Thymus
Early onset	Acetylcholine receptor	<50 yr	Hyperplasia common
Late onset	Acetylcholine receptor	≥50 yr	Atrophy common
Thymoma	Acetylcholine receptor	Any age	Lymphoepithelioma
Muscle-specific kinase	Muscle-specific kinase	Any age	Normal
LRP4	LRP4	Any age	Normal
Seronegative	None detected	Any age	Variable
Ocular	Variable	Any age	Variable

* LRP4 denotes lipoprotein receptor–related protein 4.

Gilhus NE. N Engl J Med 2016;375:2570-2581.

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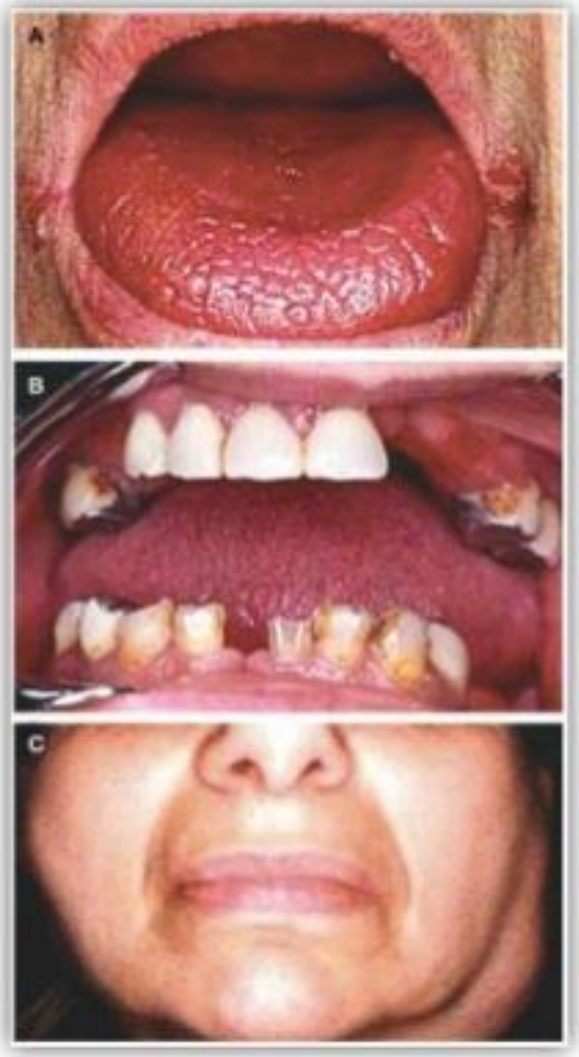
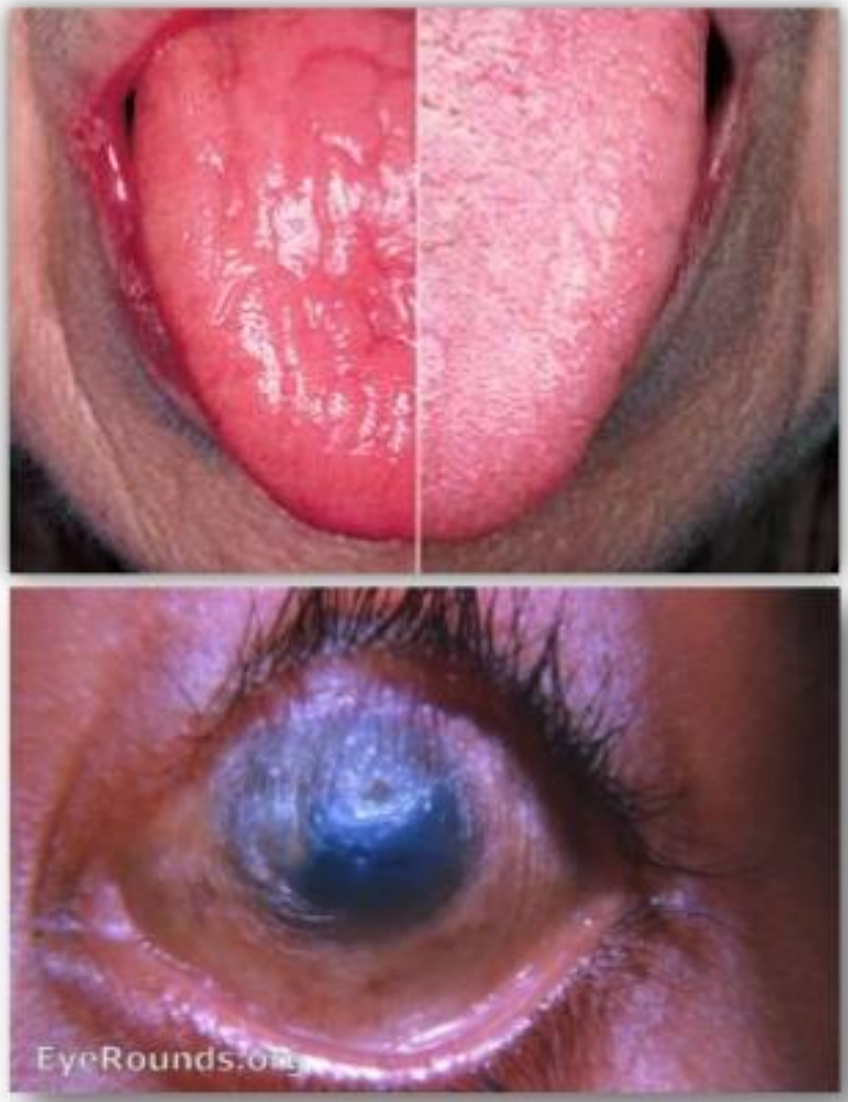
Sindrome di Sjogren





New classification criteria (modified according to [20])

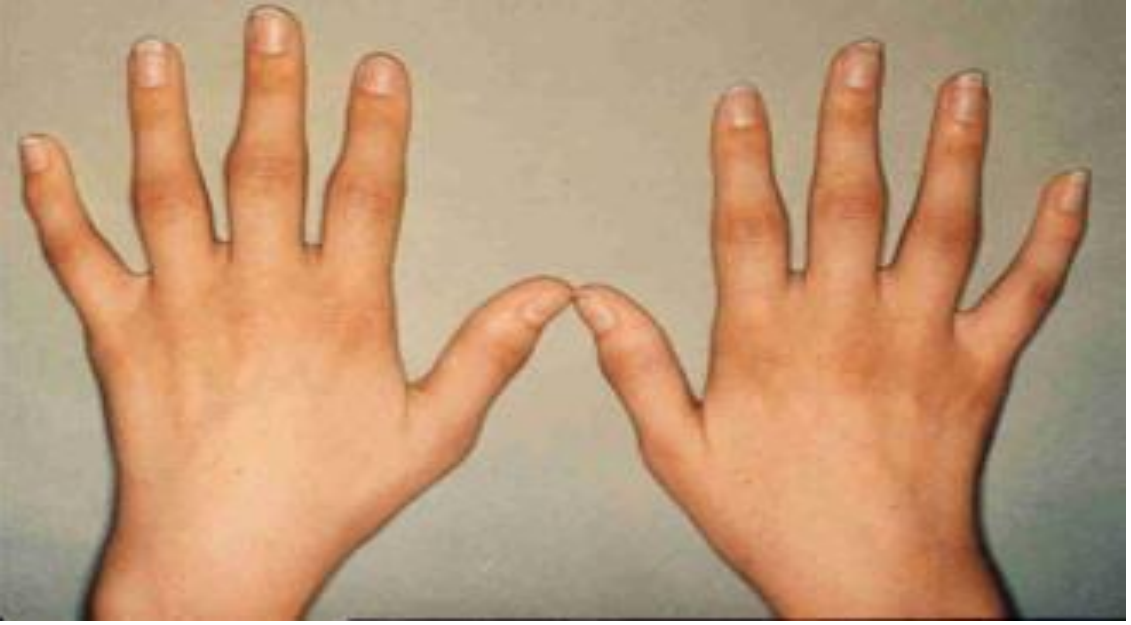
- **Current European–American consensus criteria for the classification of primary Sjögren's syndrome**
  - Unstimulated salivary flow rate*1 abnormal ≤0.1 mL/minute (1 point)
  - Abnormal Schirmer's test (<5 mm in 5 minutes) (1 point)
  - Abnormal findings with lissamine green or fluorescein staining (≥ 5 in Ocular Staining Score or ≥ 4 in Van Bijsterveld Score) (1 point)
  - Autoantibody detection: anti-Ro/SSA (3 points)
  - Histology*2 —focal lymphocytic sialadenitis, Focus score ≥ 1 focus/4 mm², 1 focus = 50 lymphocytes/4 mm² (3 points)

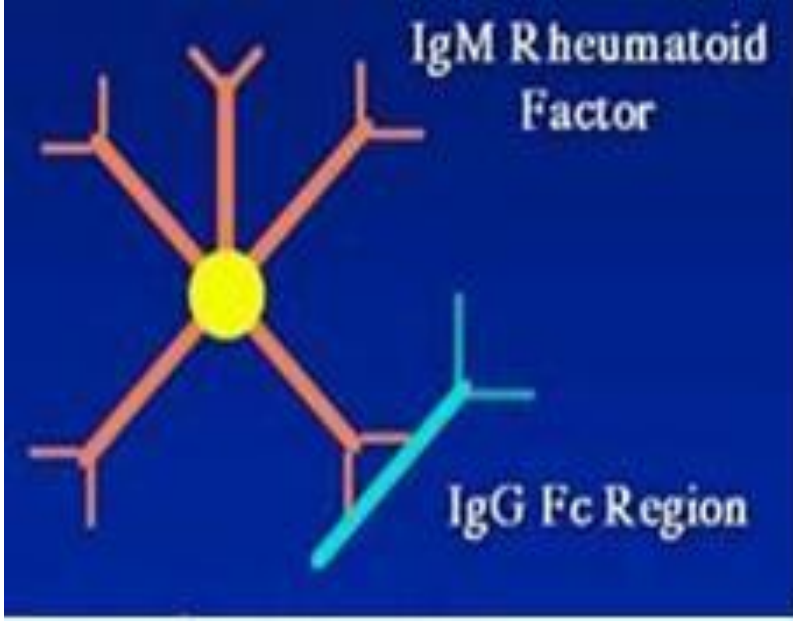
- **Diagnosis is considered established if score ≥ 4 points, after application of inclusion and exclusion criteria**
  - Inclusion criteria:
    Dryness of eyes and/or mouth for at least 3 months, not explained otherwise (e.g. medications, infection)
  - Exclusion criteria:
    Status post head/neck radiation, HIV/Aids, sarcoidosis, active infection with hepatitis C virus (PCR replication rate), amyloidosis, graft-versus-host disease, IgG4-related disease

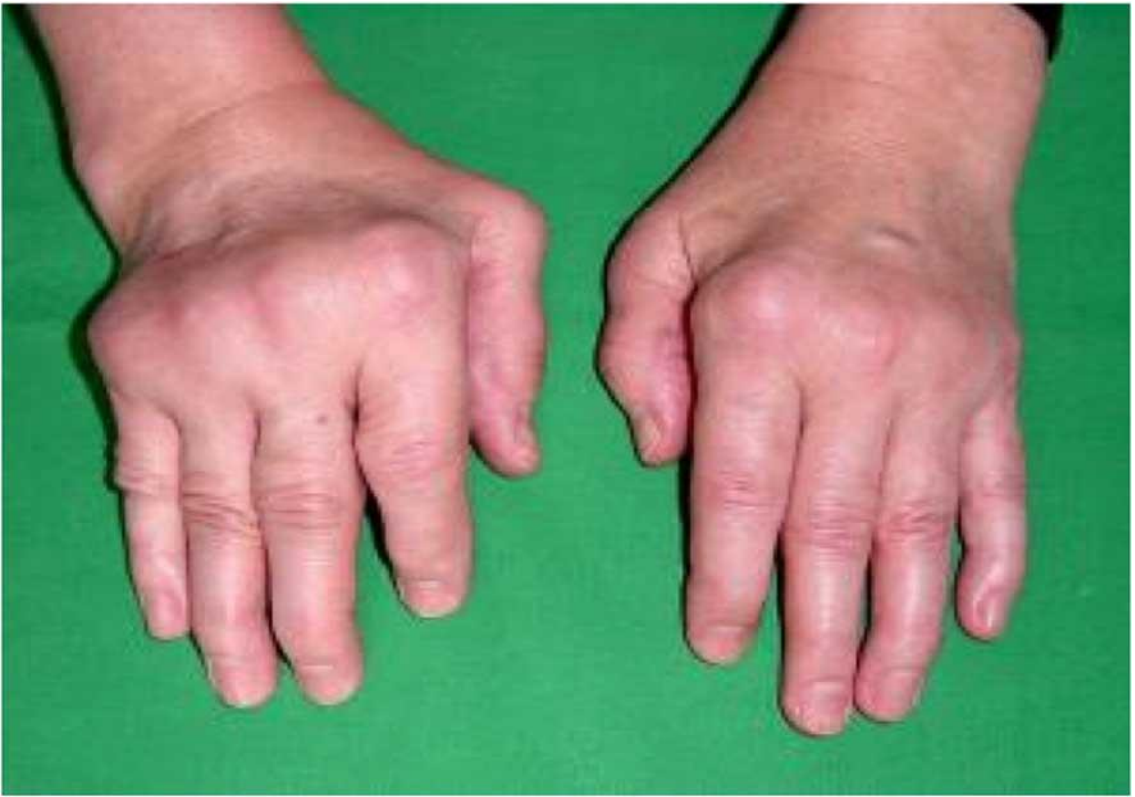
- **The lack of any other potentially associated disease is the key requirement for classification as a pSS.**

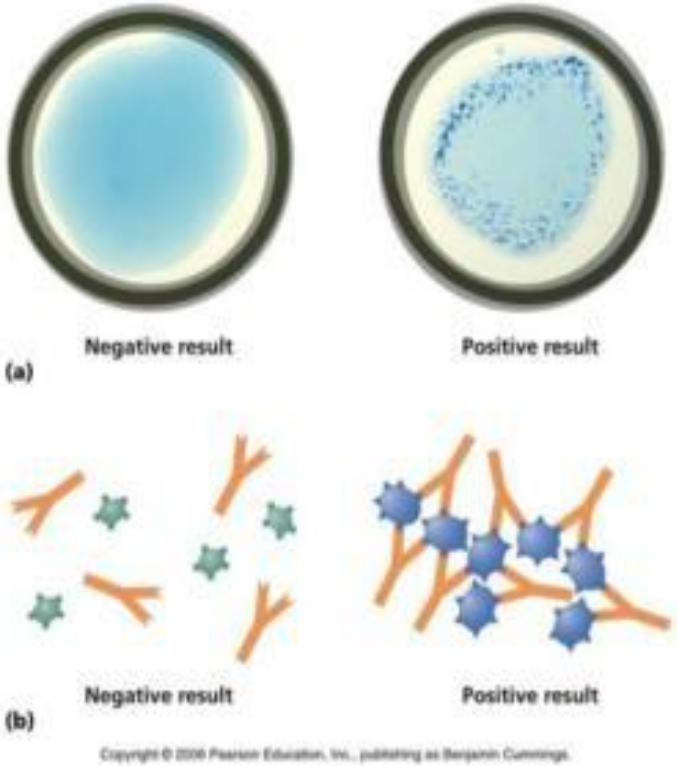
---

*1 The patient is asked to sit still, not to speak or to chew for 5 to 15 minutes; the saliva produced during this time is transferred to a test tube and weighed.
*2 Biopsy: Removal of 3 to 5 labial minor salivary glands from the lower lip under local anesthesia; fixation of biopsy material in formalin and HE staining; caution: local paresthesia after biopsy
HE, hematoxylin and eosin stain; PCR, polymerase chain reaction









2010 ACR/EULAR Classification Criteria for RA

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

Major Categories of Noninfectious Vasculitis.

TABLE 1. MAJOR CATEGORIES OF NONINFECTIOUS VASCULITIS.*

Large-vessel vasculitis

Giant-cell arteritis
Takayasu's arteritis

Medium-sized-vessel vasculitis

Polyarteritis nodosa
Kawasaki's disease
Primary granulomatous central nervous system vasculitis

Small-vessel vasculitis

ANCA-associated small-vessel vasculitis
- Microscopic polyangiitis
- Wegener's granulomatosis
- Churg–Strauss syndrome
- Drug-induced ANCA-associated vasculitis

Immune-complex small-vessel vasculitis
- Henoch–Schönlein purpura
- Cryoglobulinemic vasculitis
- Lupus vasculitis
- Rheumatoid vasculitis
- Sjögren's syndrome vasculitis
- Hypocomplementemic urticarial vasculitis
- Behçet's disease
- Goodpasture's syndrome
- Serum-sickness vasculitis
- Drug-induced immune-complex vasculitis
- Infection-induced immune-complex vasculitis

Paraneoplastic small-vessel vasculitis
- Lymphoproliferative neoplasm-induced vasculitis
- Myeloproliferative neoplasm-induced vasculitis
- Carcinoma-induced vasculitis

Inflammatory bowel disease vasculitis

*Vascular inflammation is categorized as either infectious vasculitis, which is caused by the direct invasion of vessel walls by pathogens (e.g., rickettsial organisms in Rocky Mountain spotted fever), or noninfectious vasculitis, which is not caused by the direct invasion of vessel walls by pathogens (although infections can indirectly induce noninfectious vasculitis — e.g., by generating pathogenic immune complexes). ANCA denotes antineutrophil cytoplasmic autoantibodies.

Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.

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Names and Definitions of Vasculitis Adopted by the Chapel Hill Consensus Conference on the Nomenclature of Syst

TABLE 2. NAMES AND DEFINITIONS OF VASCULITIS ADOPTED BY THE CHAPEL HILL CONSENSUS CONFERENCE ON THE NOMENCLATURE OF SYSTEMIC VASCULITIS.*

LARGE-VESSEL VASCULITIS	
Giant-cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. *Often involves the temporal artery. Usually occurs in patients more than 50 years old and is often associated with polymyalgia rheumatica.*
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. *Usually occurs in patients younger than 50.*
MEDIUM-SIZED-VESSEL VASCULITIS	
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki's disease	Arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome. *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.*
SMALL-VESSEL VASCULITIS	
Wegener's granulomatosis†	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). *Necrotizing glomerulonephritis is common.*
Churg–Strauss syndrome†	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels and associated with asthma and eosinophilia.
Microscopic polyangiitis†	Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules, or arterioles). *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs*
Henoch–Schönlein purpura	Vasculitis with IgA-dominant immune deposits affecting small vessels (capillaries, venules, or arterioles). *Typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis*
Essential cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (capillaries, venules, or arterioles) and associated with cryoglobulins in serum. *Skin and glomeruli are often involved.*
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

*This table is adapted with modifications from Jennette et al.,[1] with the permission of the publisher. "Large vessel" refers to the aorta and the largest arterial branches directed toward major body regions (e.g., to the extremities and the head and neck). "Medium-sized vessel" refers to the main visceral arteries and their branches. "Small vessel" refers to arterioles, venules, and capillaries, although arteries, especially small arteries, may be included in this category of vasculitis. Note that all three categories affect arteries, but only small-vessel vasculitis has a predilection for vessels smaller than arteries.

†These vasculitides are associated with antineutrophil cytoplasmic autoantibodies (ANCA).

Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.

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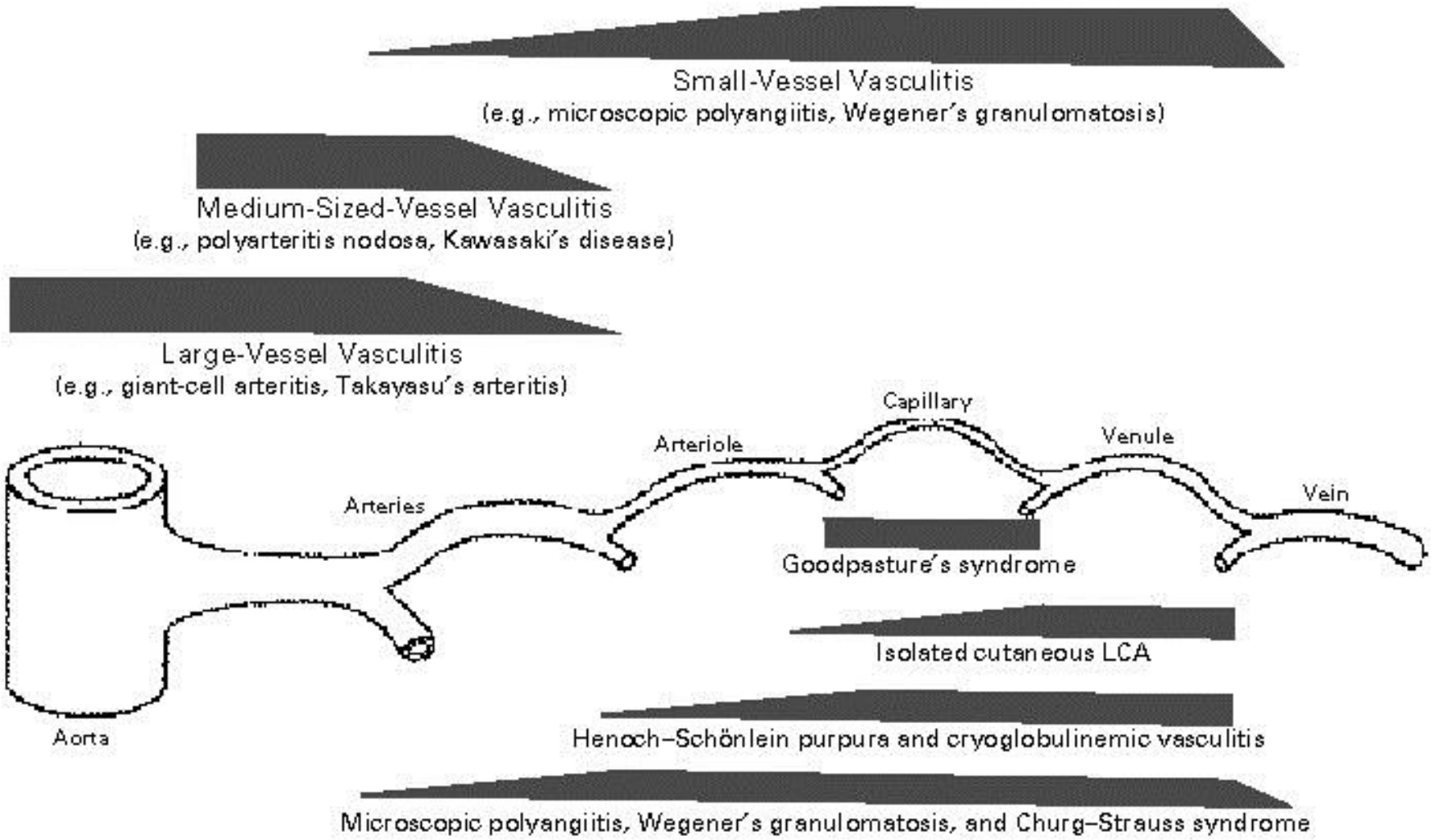
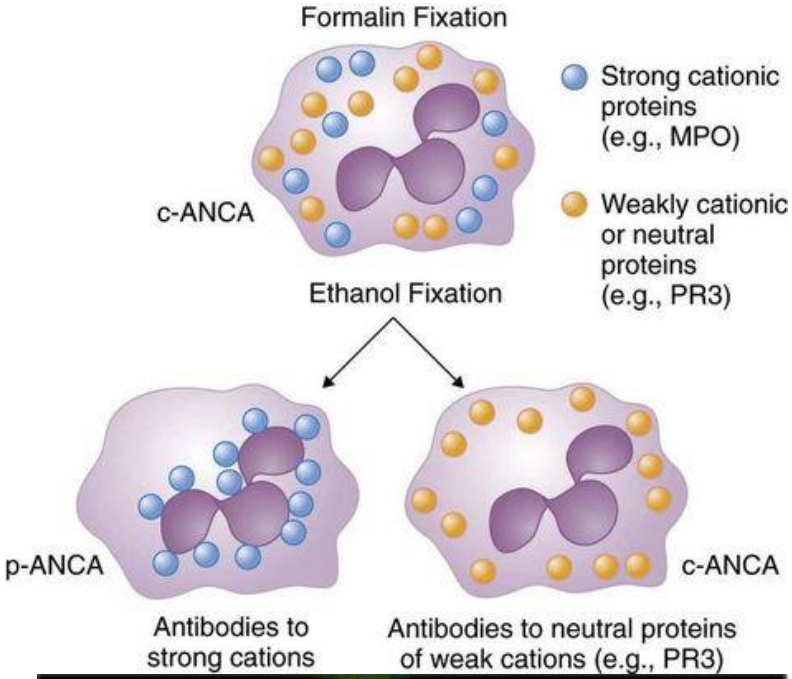
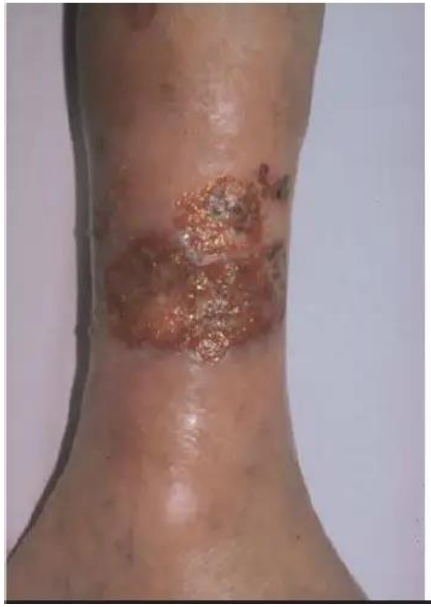
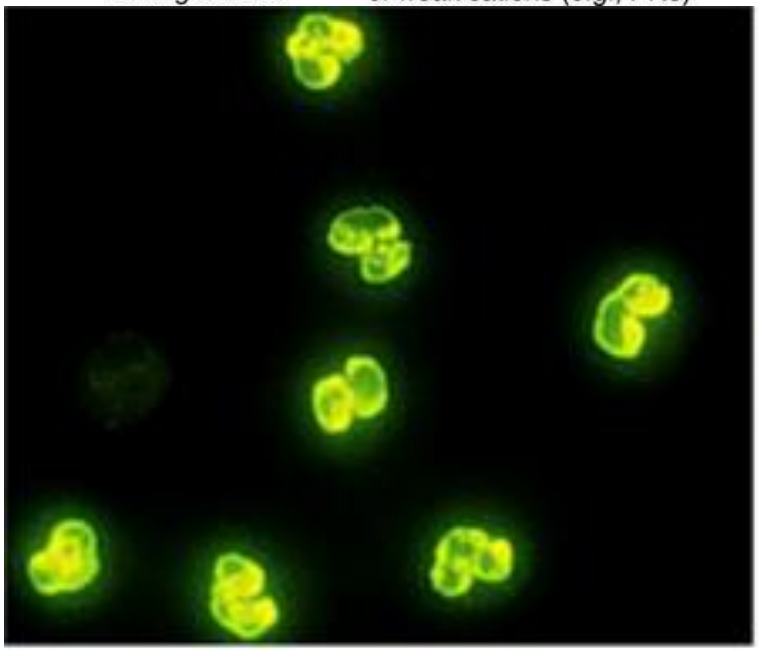
Preferred Sites of Vascular Involvement by Selected Vasculitides.



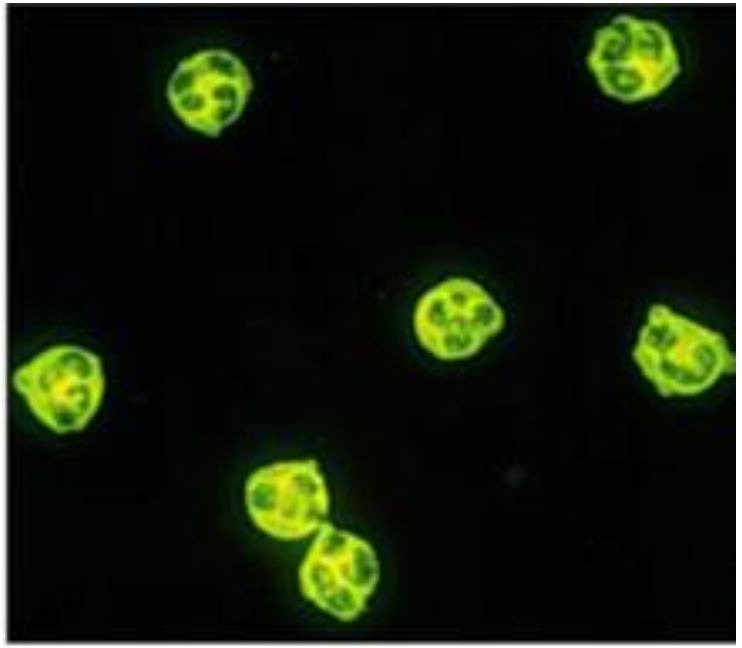
Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.





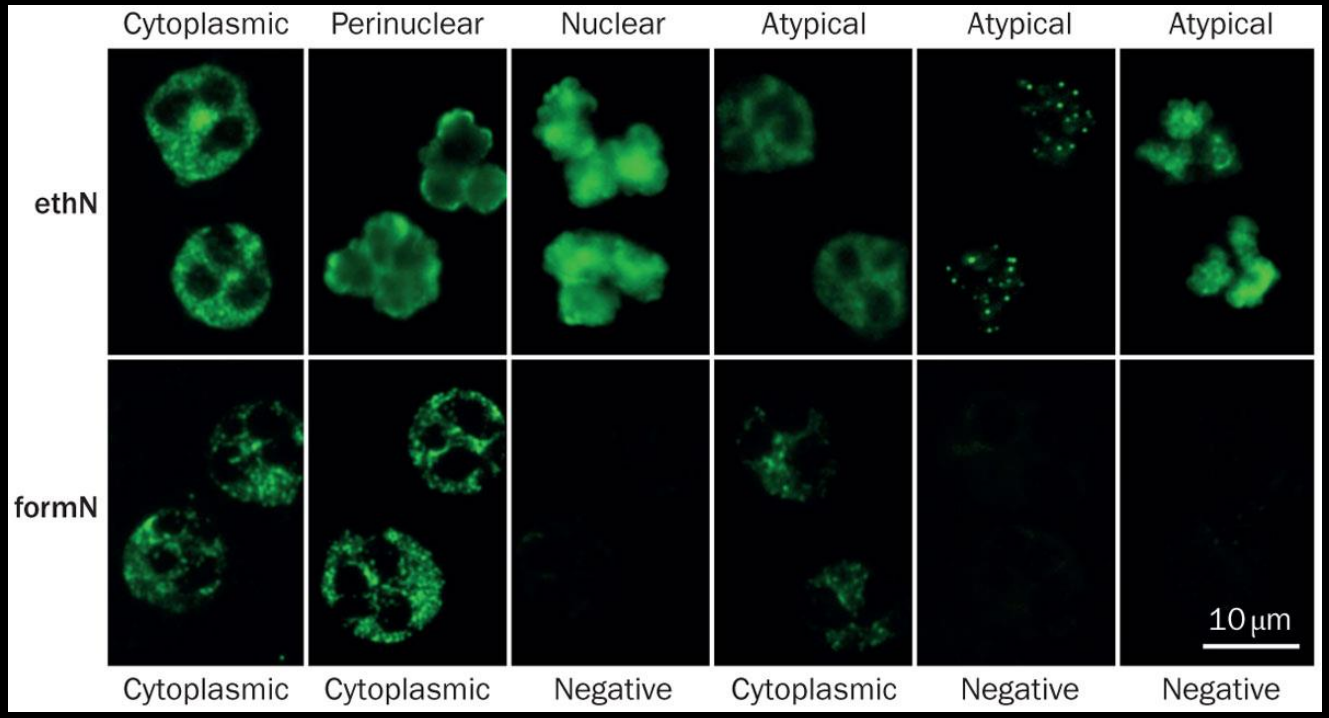


P-ANCA Pattern



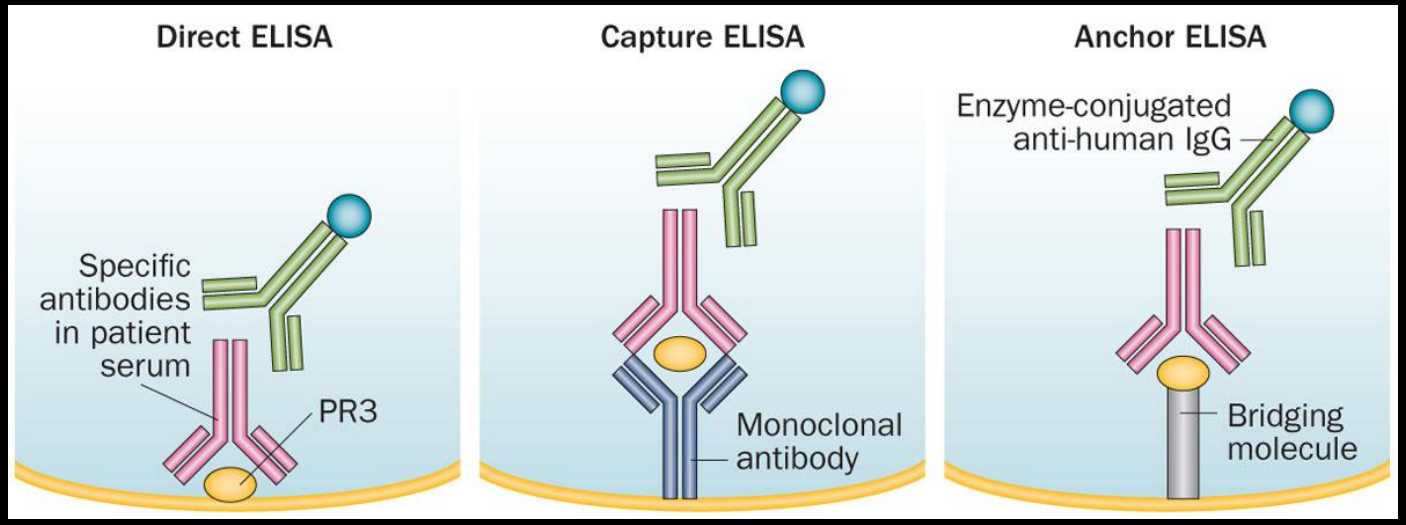
C-ANCA Pattern

Characterization of neutrophils by automated pattern-recognition image analysis



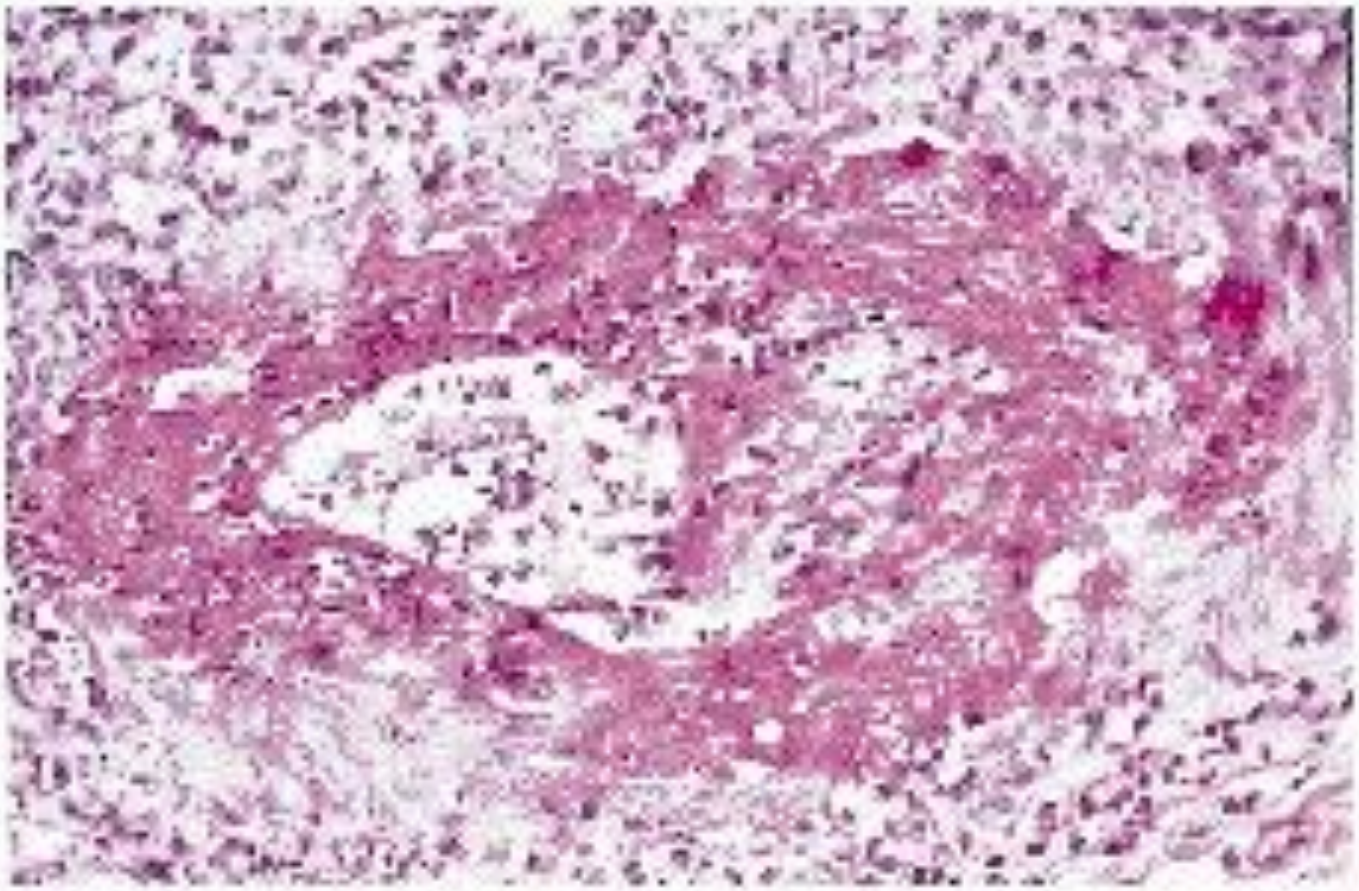
nature REVIEWS RHEUMATOLOGY

Overview of ELISA procedures for ANCA detection



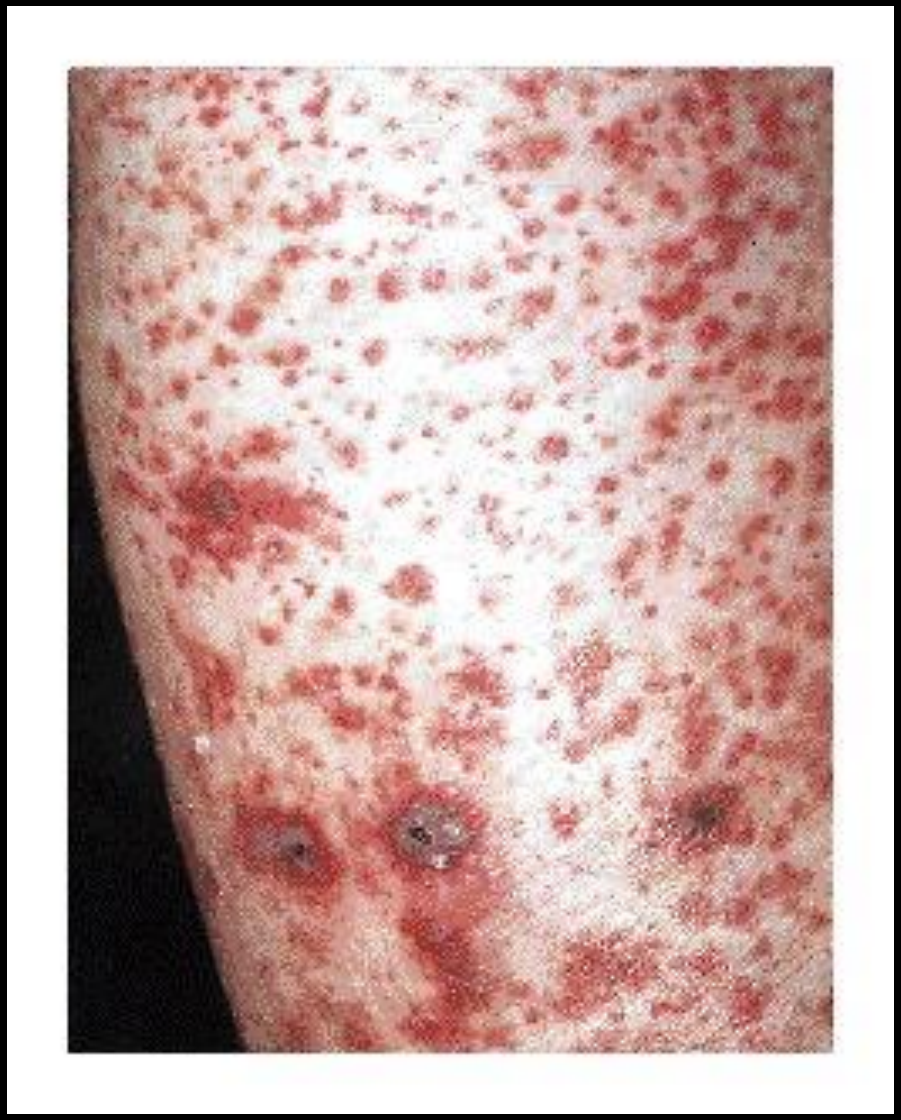
nature REVIEWS RHEUMATOLOGY

Necrotizing Arteritis in a Small Epineural Artery in a Nerve-Biopsy Specimen from a Patient with Microscopic Polyangiitis.



Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.

Purpura on the Lower Leg of a Patient Found to Have Leukocytoclastic Angiitis in a Skin-Biopsy Specimen.



Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.

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Differential Diagnostic Features of Several Forms of Small-Vessel Vasculitis.

TABLE 3. DIFFERENTIAL DIAGNOSTIC FEATURES OF SEVERAL FORMS OF SMALL-VESSEL VASCULITIS.

FEATURE	HENOCH–SCHÖNLEIN PURPURA	CRYOGLOBULINEMIC VASCULITIS	MICROSCOPIC POLYANGIITIS	WEGENER'S GRANULOMATOSIS	CHURG–STRAUSS SYNDROME
Signs and symptoms of small-vessel vasculitis*	+	+	+	+	+
IgA-dominant immune deposits	+	–	–	–	–
Cryoglobulins in blood and vessels	–	+	–	–	–
ANCA in blood	–	–	+	+	+
Necrotizing granulomas	–	–	–	+	+
Asthma and eosinophilia	–	–	–	–	+

*All of these small-vessel vasculitides can manifest any or all of the shared features of small-vessel vasculitides, such as purpura, nephritis, abdominal pain, peripheral neuropathy, myalgias, and arthralgias. Each is distinguished by the presence and, just as important, the absence of certain specific features. ANCA denotes antineutrophil cytoplasmic autoantibodies.

Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.

Approximate Frequency of Organ-System Manifestations in Several Forms of Small-Vessel Vasculitis.

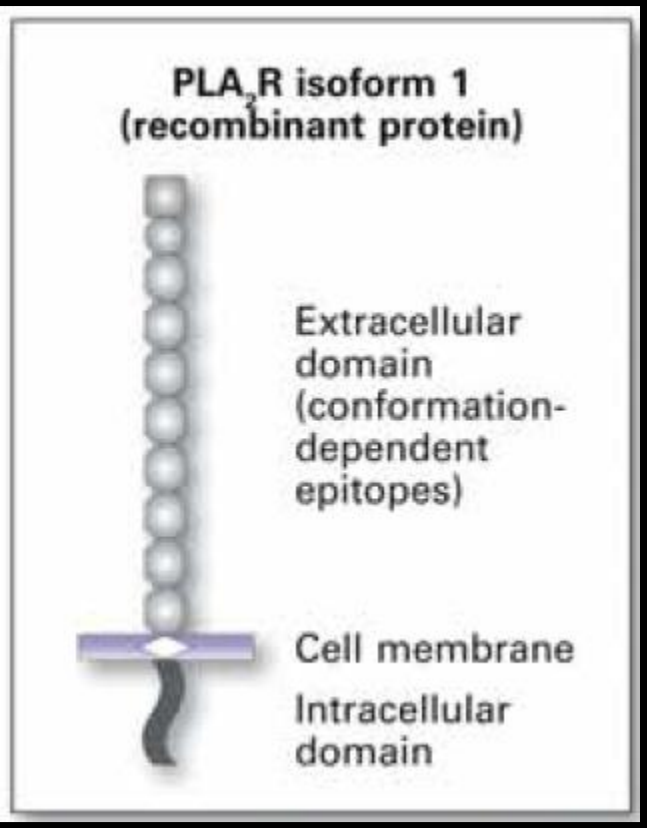
TABLE 4. APPROXIMATE FREQUENCY OF ORGAN-SYSTEM MANIFESTATIONS IN SEVERAL FORMS OF SMALL-VESSEL VASCULITIS.*

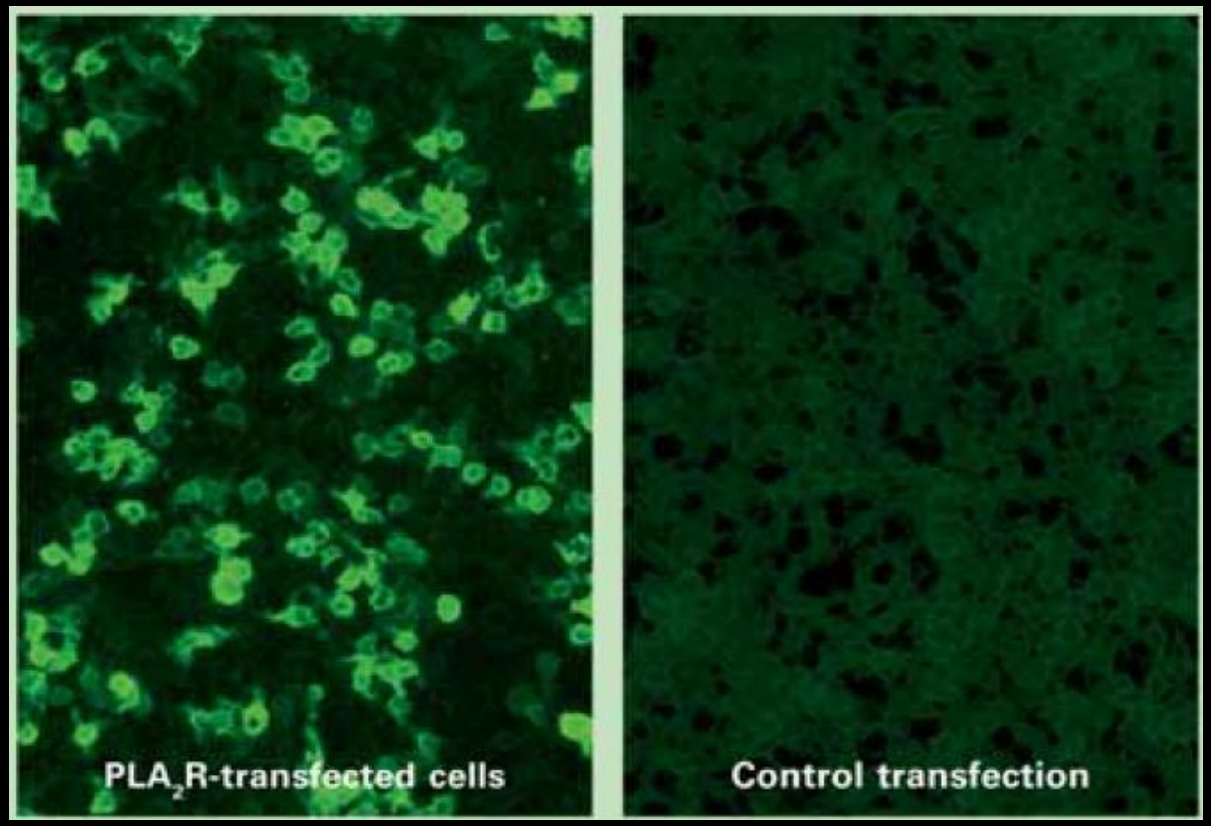
ORGAN SYSTEM	HENOCH–SCHÖNLEIN PURPURA	CRYOGLOBULINEMIC VASCULITIS	MICROSCOPIC POLYANGIITIS	WEGENER'S GRANULOMATOSIS	CHURG–STRAUSS SYNDROME
			percent		
Cutaneous	90	90	40	40	60
Renal	50	55	90	80	45
Pulmonary	<5	<5	50	90	70
Ear, nose, and throat	<5	<5	35	90	50
Musculoskeletal	75	70	60	60	50
Neurologic	10	40	30	50	70
Gastrointestinal	60	30	50	50	50

*Approximate frequencies are estimated from data in previous reports.[49-65]

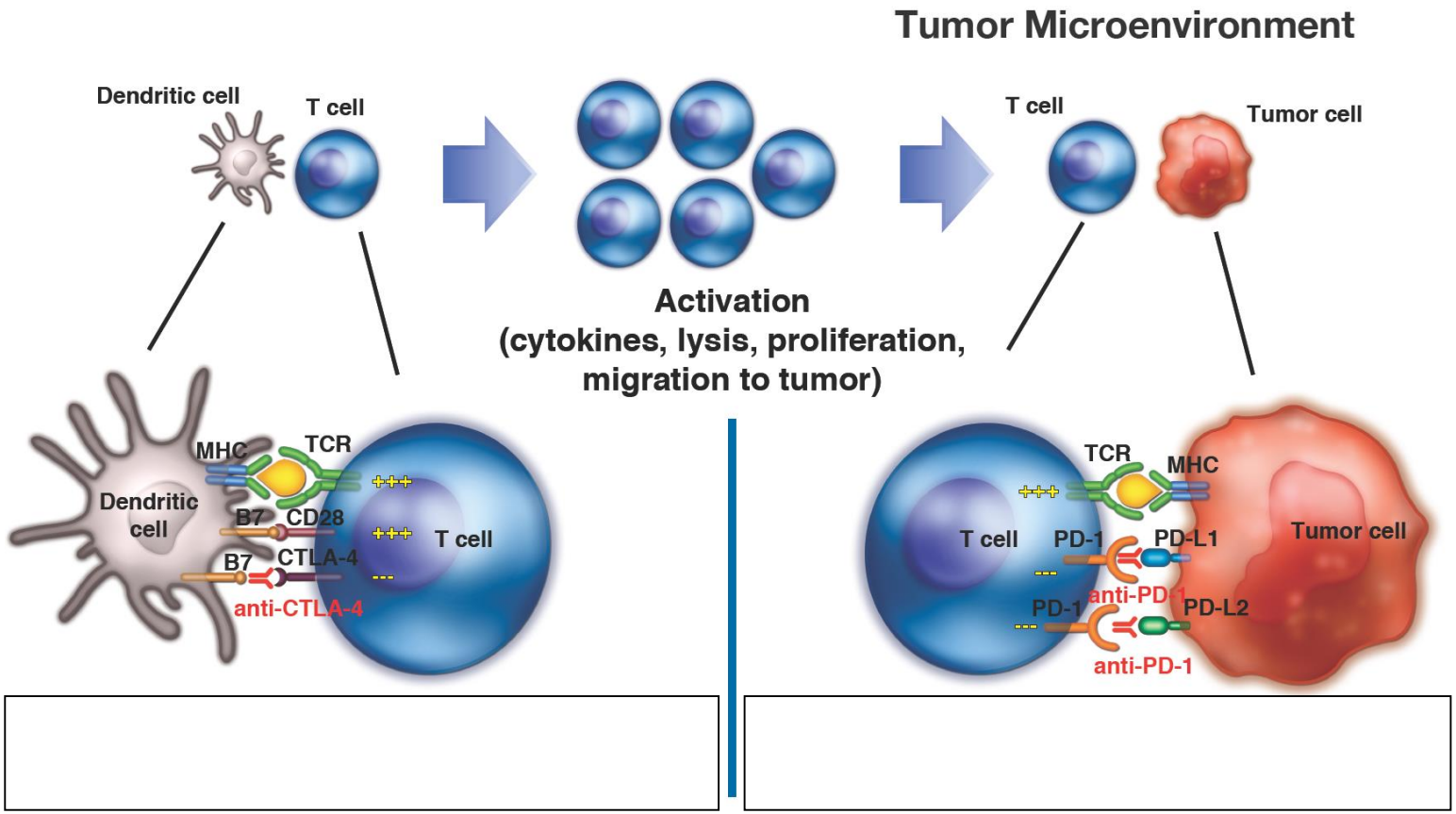
Jennette JC, Falk RJ. N Engl J Med 1997;337:1512-1523.

Glomerulonefrite membranosa (GM):
Test per la ricerca di PLA2R-Ab





Immune Checkpoint Pathways



Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Postow MA et al. N Engl J Med 2018;378:158-168.

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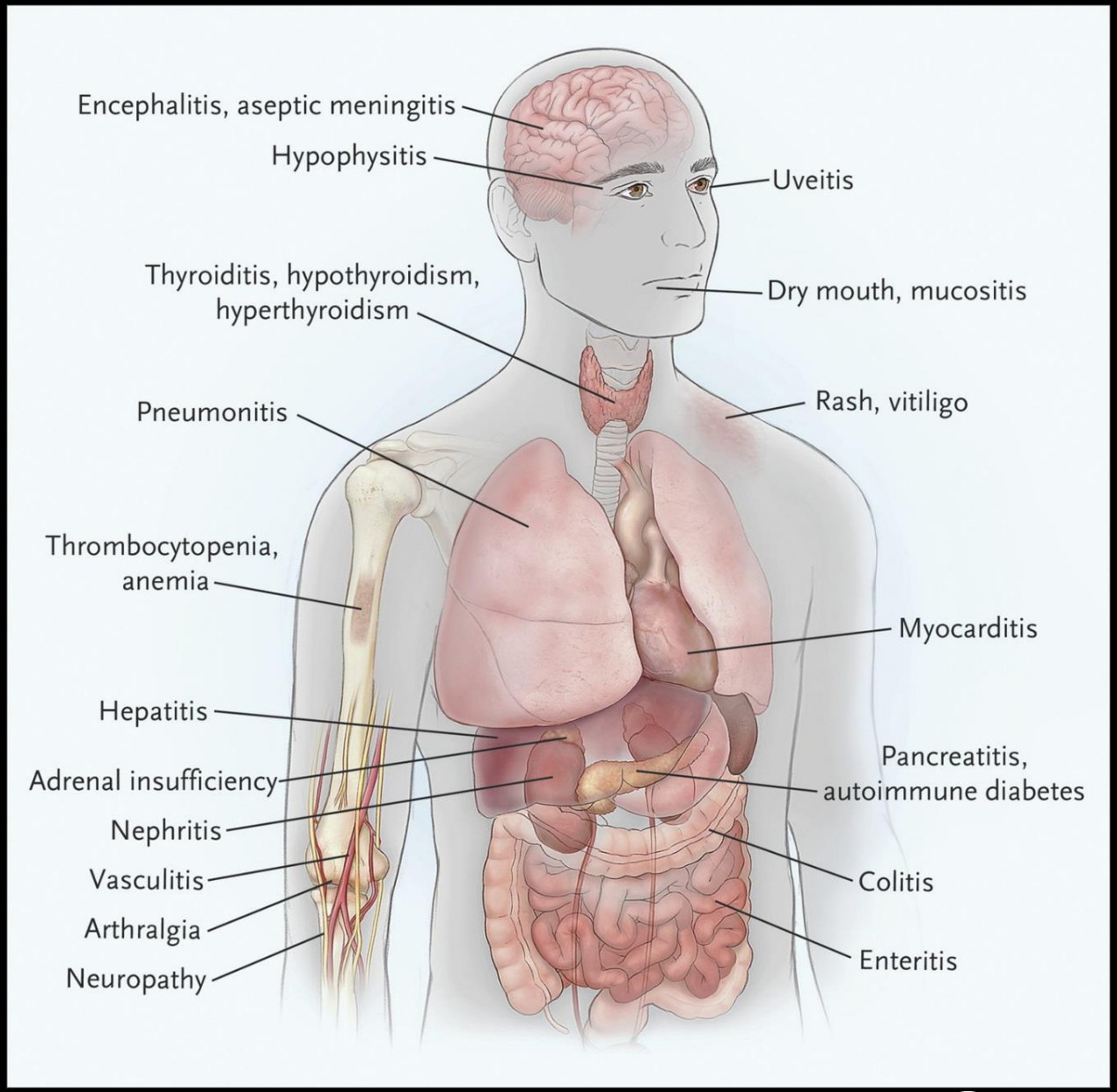
Organs Affected by Immune Checkpoint Blockade.



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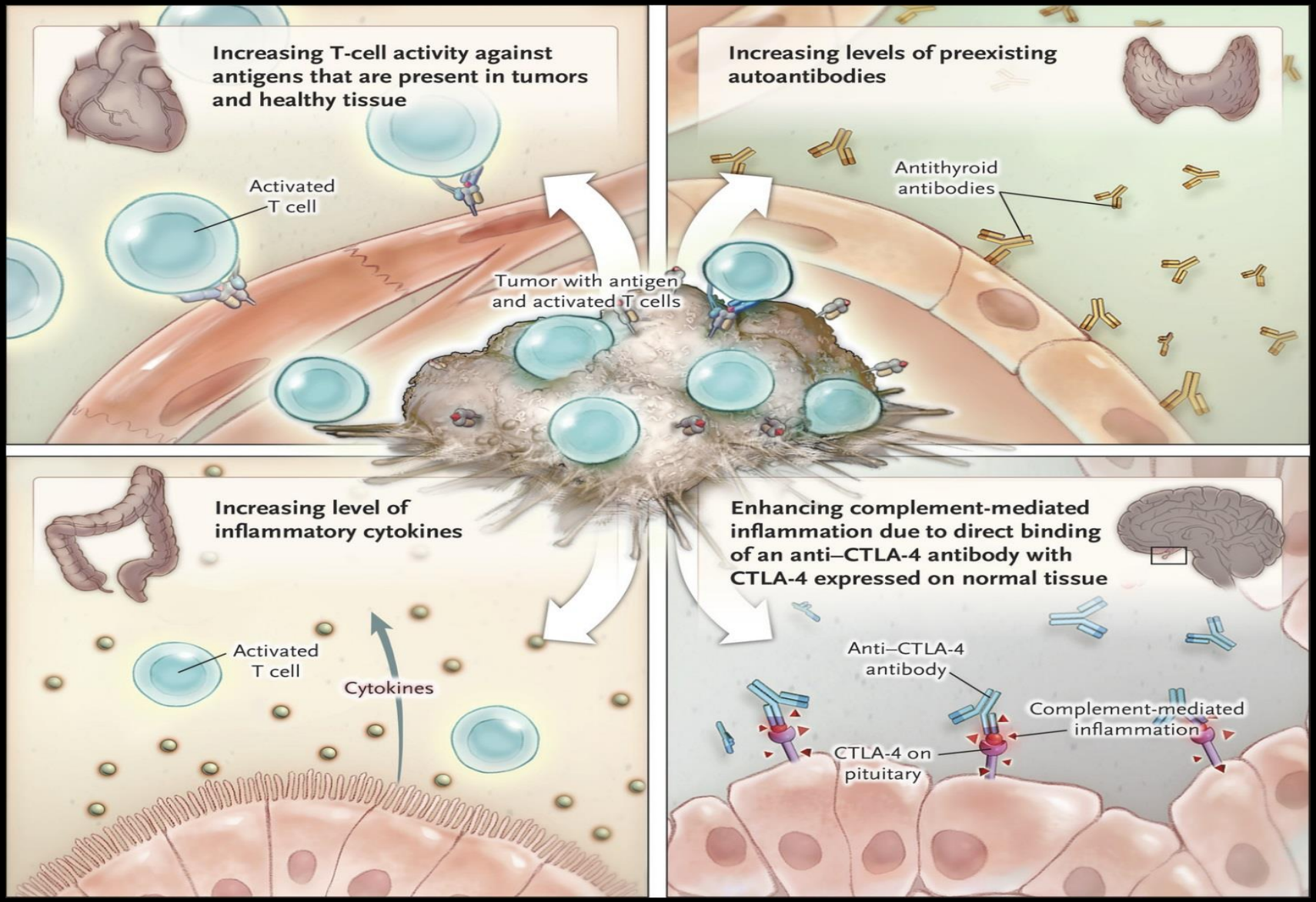
Possible Mechanisms Underlying Immune-Related Adverse Events.



Postow MA et al. N Engl J Med 2018;378:158-168.

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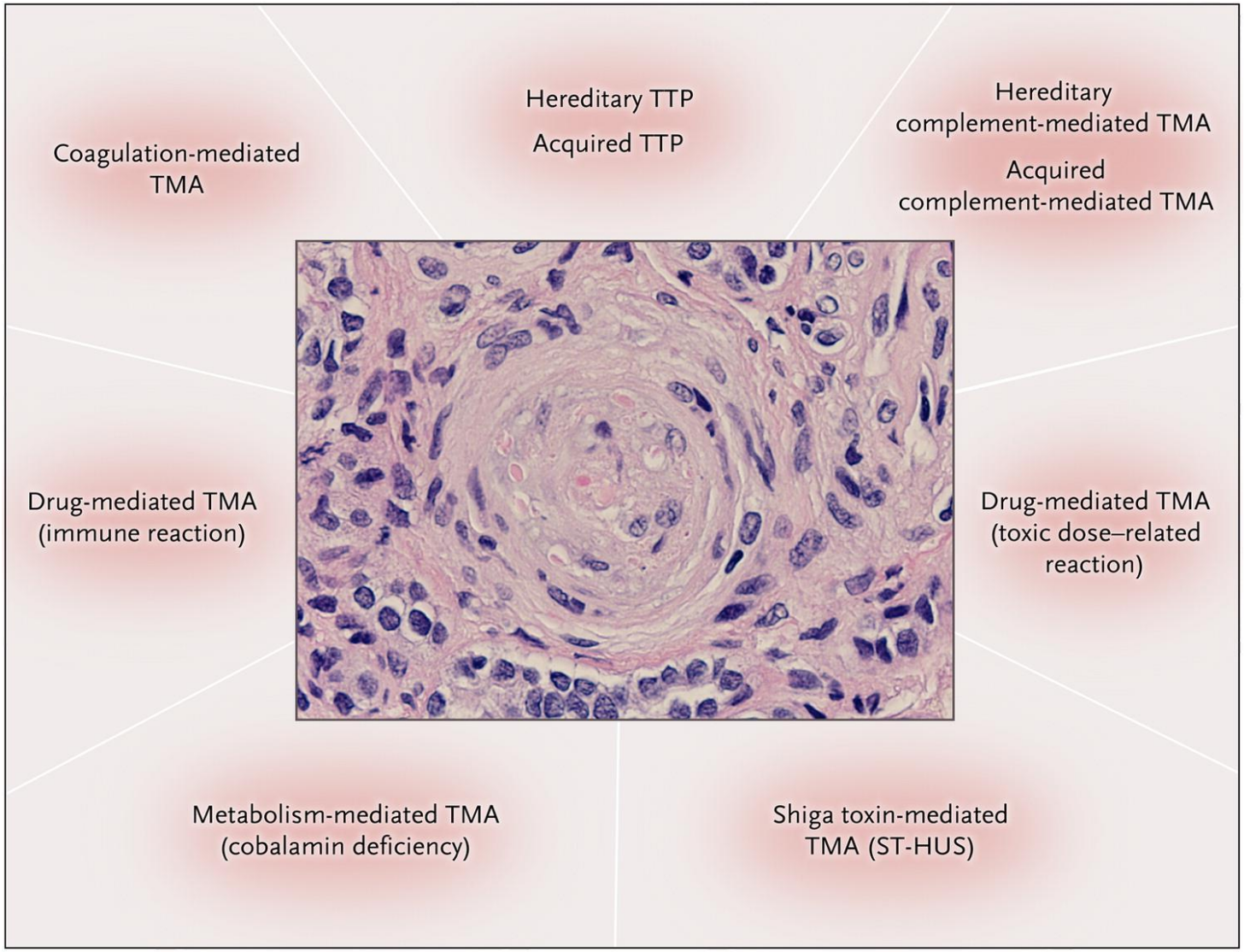

Hereditary TTP
Acquired TTP
Coagulation-mediated TMA
Hereditary complement-mediated TMA
Acquired complement-mediated TMA
Drug-mediated TMA (immune reaction)
Drug-mediated TMA (toxic dose–related reaction)
Metabolism-mediated TMA (cobalamin deficiency)
Shiga toxin-mediated TMA (ST-HUS)

Diagnosi differenziale delle TMA: SEUa, PTT e STEC-SEU

Trombocitopenia[1]

Conta piastrinica
<150.000

+

Emolisi microangiopatica[1,2]

Aumento dell'LDH[1]
e/o
riduzione dell'aptoglobina[1]
e/o **presenza di schistociti**[1,2]

Più uno o più dei seguenti

Segni neurologici[3-7]

Confusione[6,8]
e/o
Convulsioni[3,5]
e/o
Altri sintomi neurologici[8]

Insufficienza renale[1,9,10]

Alterazione della creatinina/eGFR[1,9]
e/o
Ipertensione[11]
e/o
Alterazioni analisi urine[10]

Sintomi gastrointestinali[1,5,12]

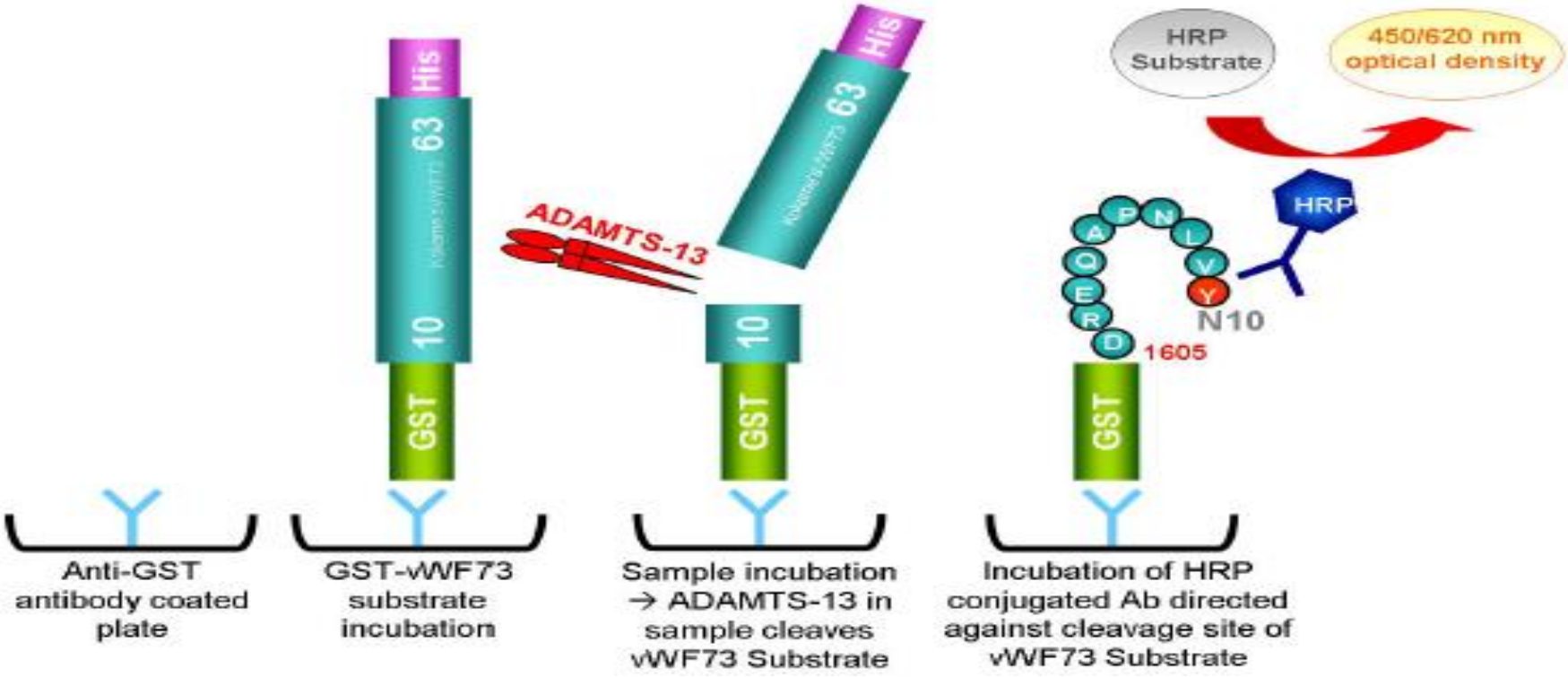
Diarrea ± sangue[12]
e/o **Nausea/vomito**[5]
e/o **Dolore addominale**[5]
e/o **Gastroenterite**[1,12]

Valutare l'attività dell'ADAMTS13 e la presenza di Shiga-tossina/EHEC* (± sintomi gastrointestinali)[7,13,14]

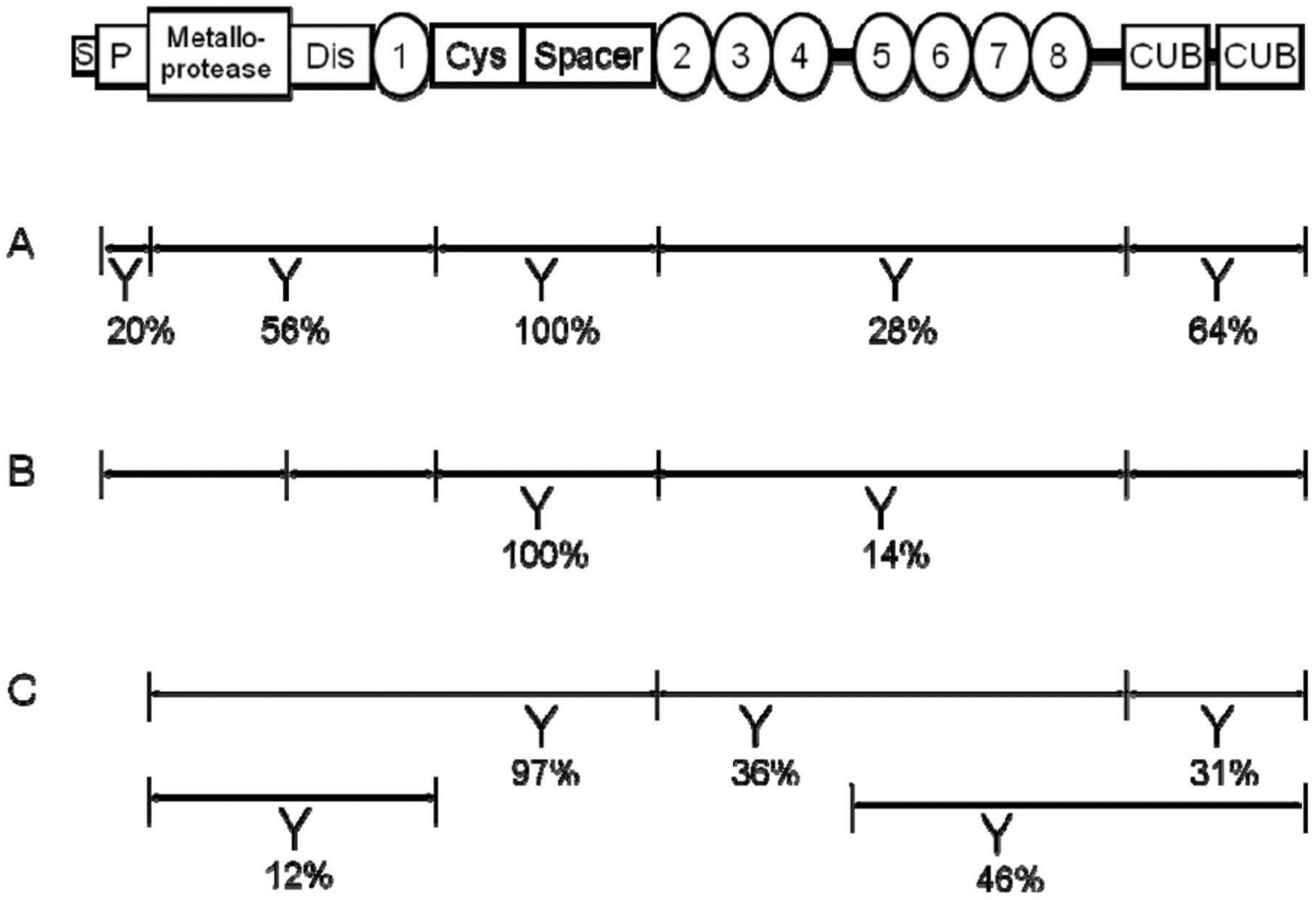
Mentre si attendono i risultati del test dell'ADAMTS13, una conta piastrinica di >30.000/mm^3 o un livello di creatinina serica di >150-200 µmol/l rende estremamente improbabile il riscontro di grave deficit di ADAMTS13[15]

Attività ADAMTS13 ≤5%[7,13,14]	Attività ADAMTS13 >5%[7] Negatività Shiga-tossina***	Positività Shiga-tossina/EHEC[16]
PTT	**SEUa**	**STEC-SEU****

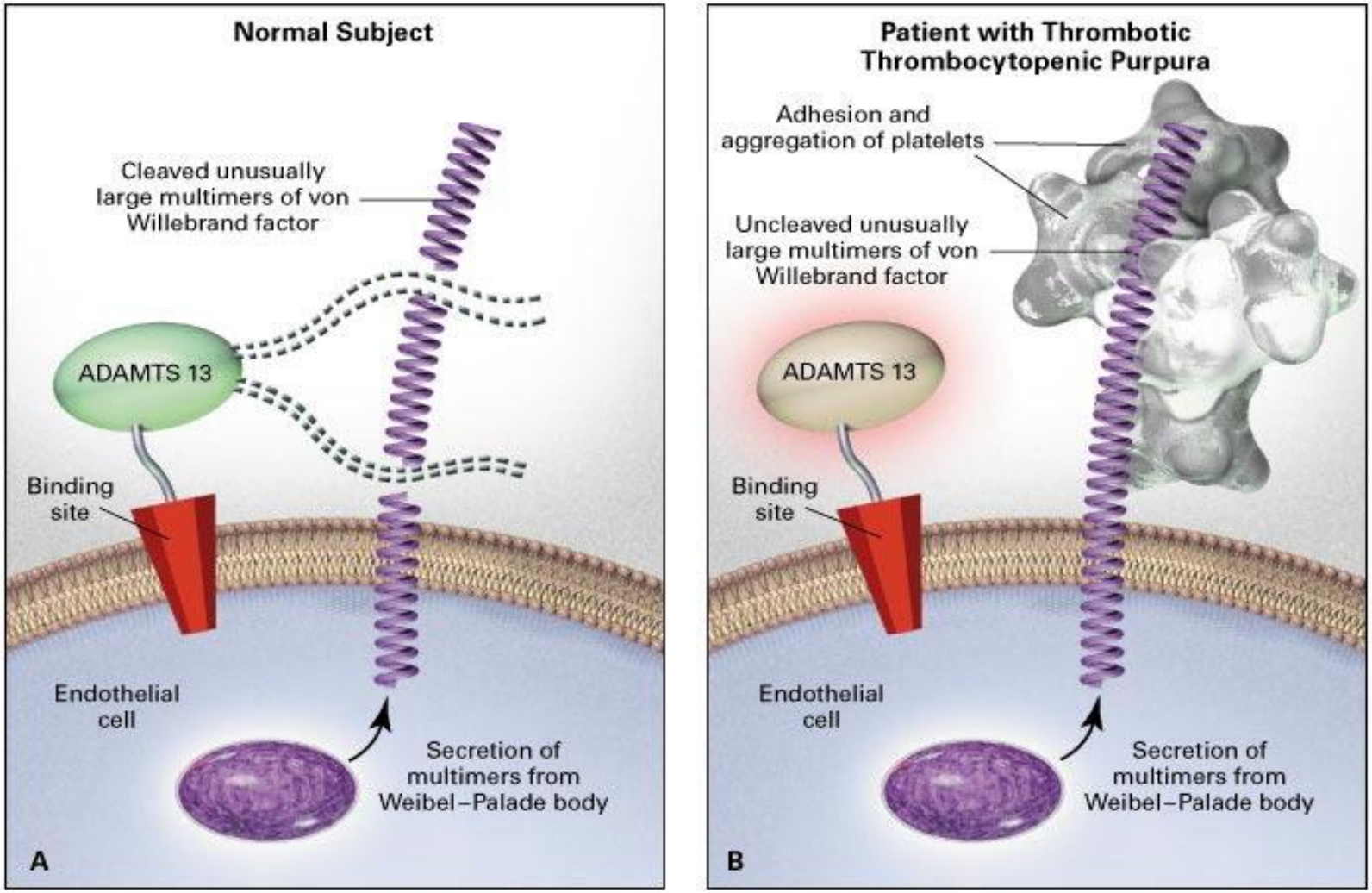
TMA: dosaggio attività anti ADAMTS13



Schematic protein domain structure of ADAMTS13 and localization of anti-ADAMTS13 autoantibody epitopes.



Johanna A. Kremer Hovinga, and Bernhard Lämmle
Hematology 2012;2012:610-616


Normal Subject
Cleaved unusually large multimers of von Willebrand factor
ADAMTS 13
Binding site
Endothelial cell
Secretion of multimers from Weibel–Palade body
A
Patient with Thrombotic Thrombocytopenic Purpura
Adhesion and aggregation of platelets
Uncleaved unusually large multimers of von Willebrand factor
ADAMTS 13
Binding site
Endothelial cell
Secretion of multimers from Weibel–Palade body
B