SAPIENZA
UNIVERSITÀ DI ROMA

la Scienza a portata di mano

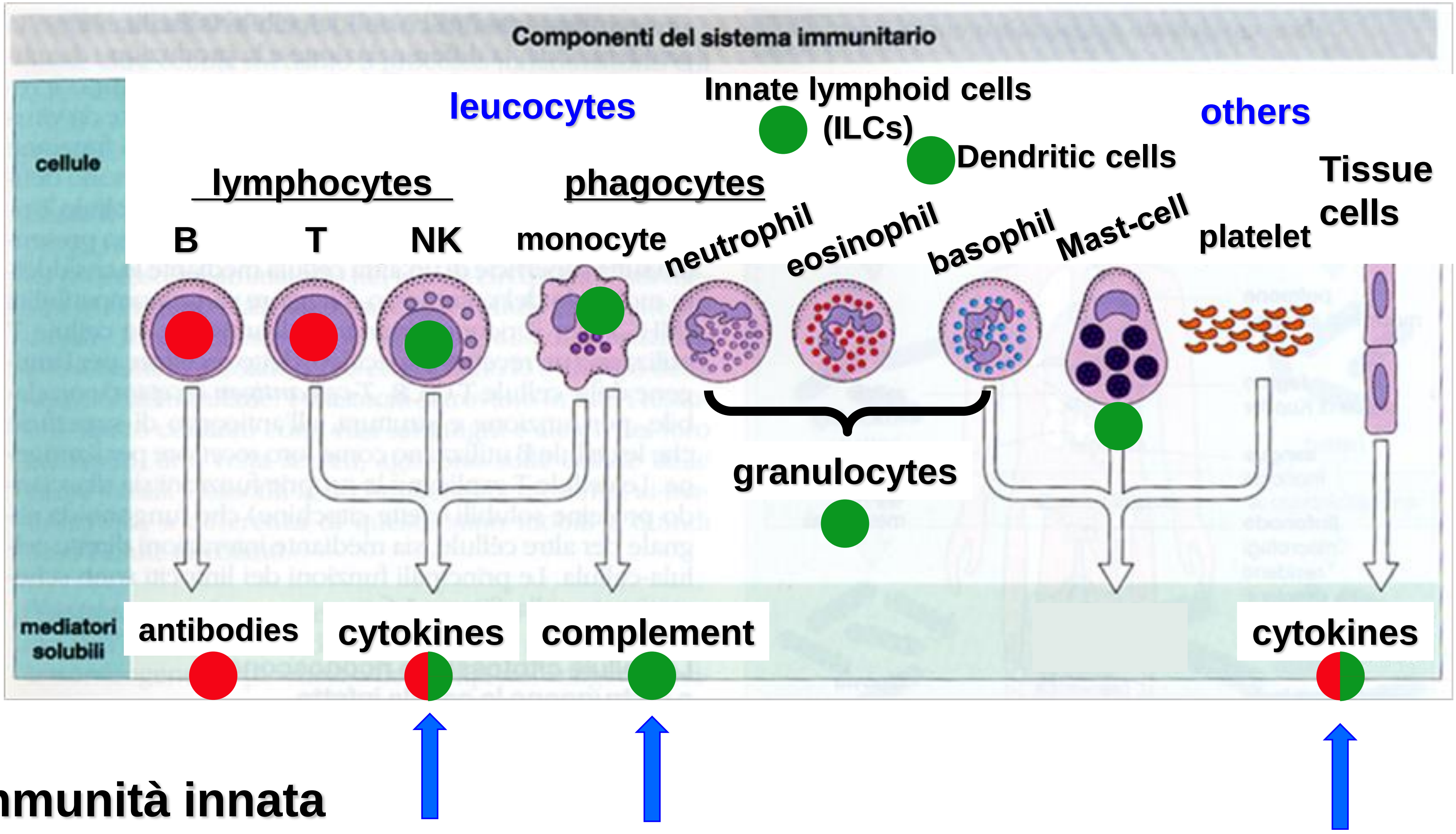
Comunicazione delle Scienze Biomediche

Prof.ssa Cristina Cerboni

L'immunità innata:
mediatori solubili (citochine e complemento)
(parte III)

Anno Accademico 2025-2026

Componenti cellulari e solubili del sistema immunitario



Immunità innata
Immunità adattativa

I MEDIATORI SOLUBILI DELL'IMMUNITA' INNATA

- LE CITOCHINE INFIAMMATORIE
- IL COMPLEMENTO
- LE COLLECTINE
- LA PROTEINA C-REATTIVA, LE PENTRAXINE
- I FATTORI DELLA COAGULAZIONE

Invasione microbica: cosa fanno le cellule dell'immunità innata che se ne accorgono?

- FAGOCITANO
- UCCIDONO
- **CHIEDONO AIUTO** ---------->

-----------> - Chiedono aiuto: come?
Mediante la produzione e la secrezione di
messaggeri molecolari: le **citochine**

Cito-china: metto in moto la cellula

Inter-leu-china: nome storico (IL-1, IL-2, IL-3…, IFN-α, β, γ…

Chemio-china: citochina con prevalente attività chemiotattica (CC, CXC)

CSF (colony-stimulating factor): citochine che agiscono prevalentemente sul midollo osseo

LE CITOCHINE

- Regolano tutti gli aspetti e tutte le fasi della risposta immunitaria.

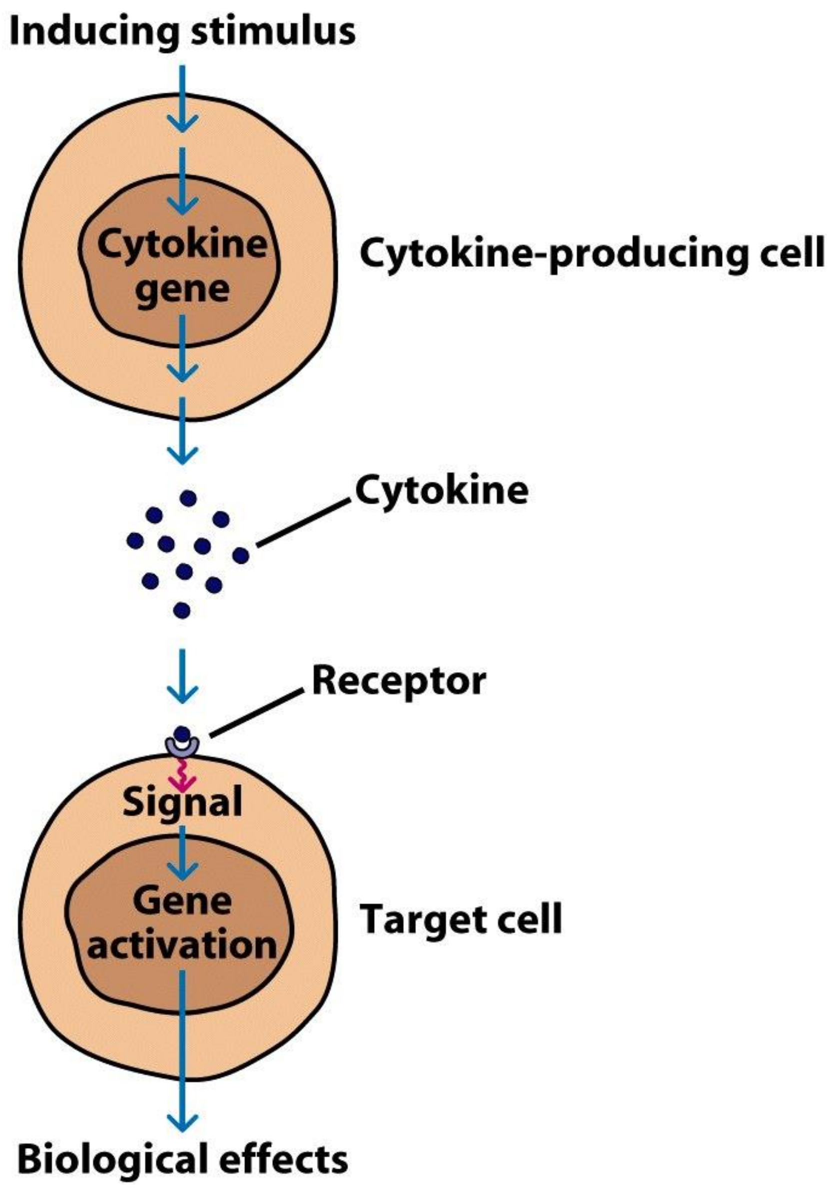
- Sono secrete non solo dai leucociti, ma da un ampio spettro di tipi cellulari diversi in risposta ad uno stimolo specifico.

- Le citochine hanno numerosi effetti biologici che esplicano legando recettori specifici espressi sulla membrana della cellula bersaglio.

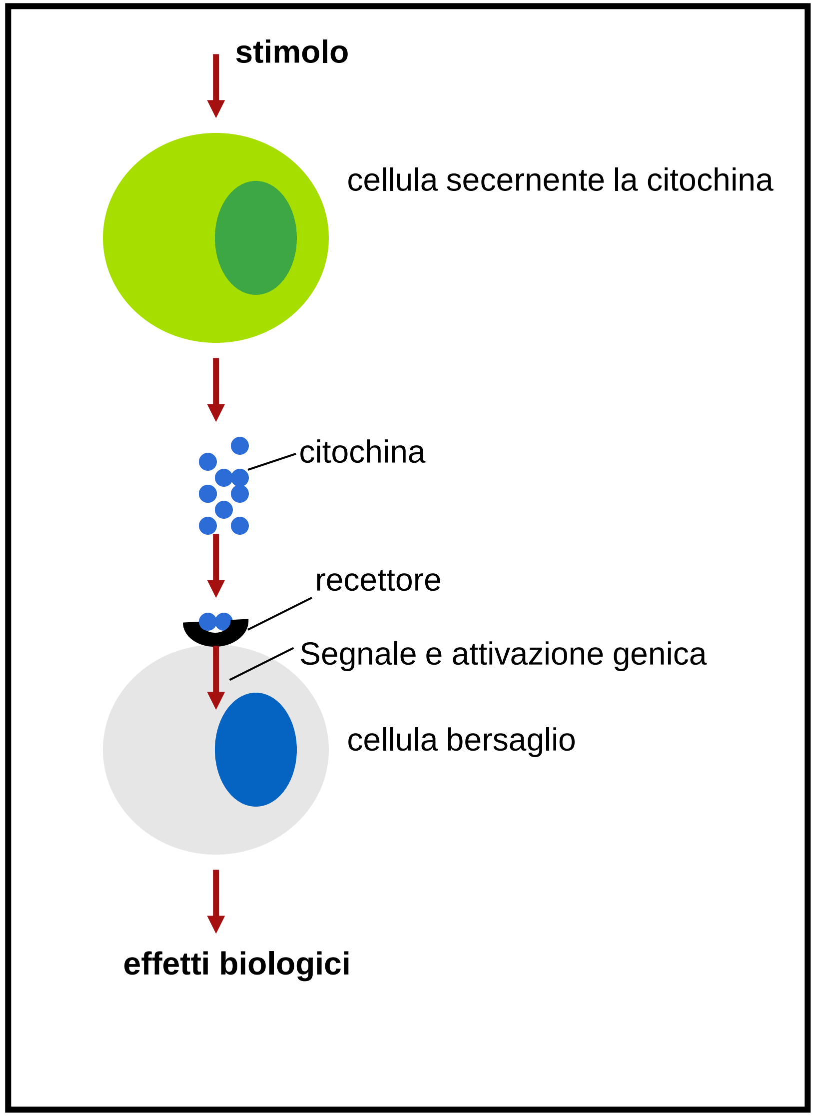
- Le citochine funzionano da messaggeri intercellulari che mettono in comunicazione regolando la durata e l'intensità della risposta immunitaria.

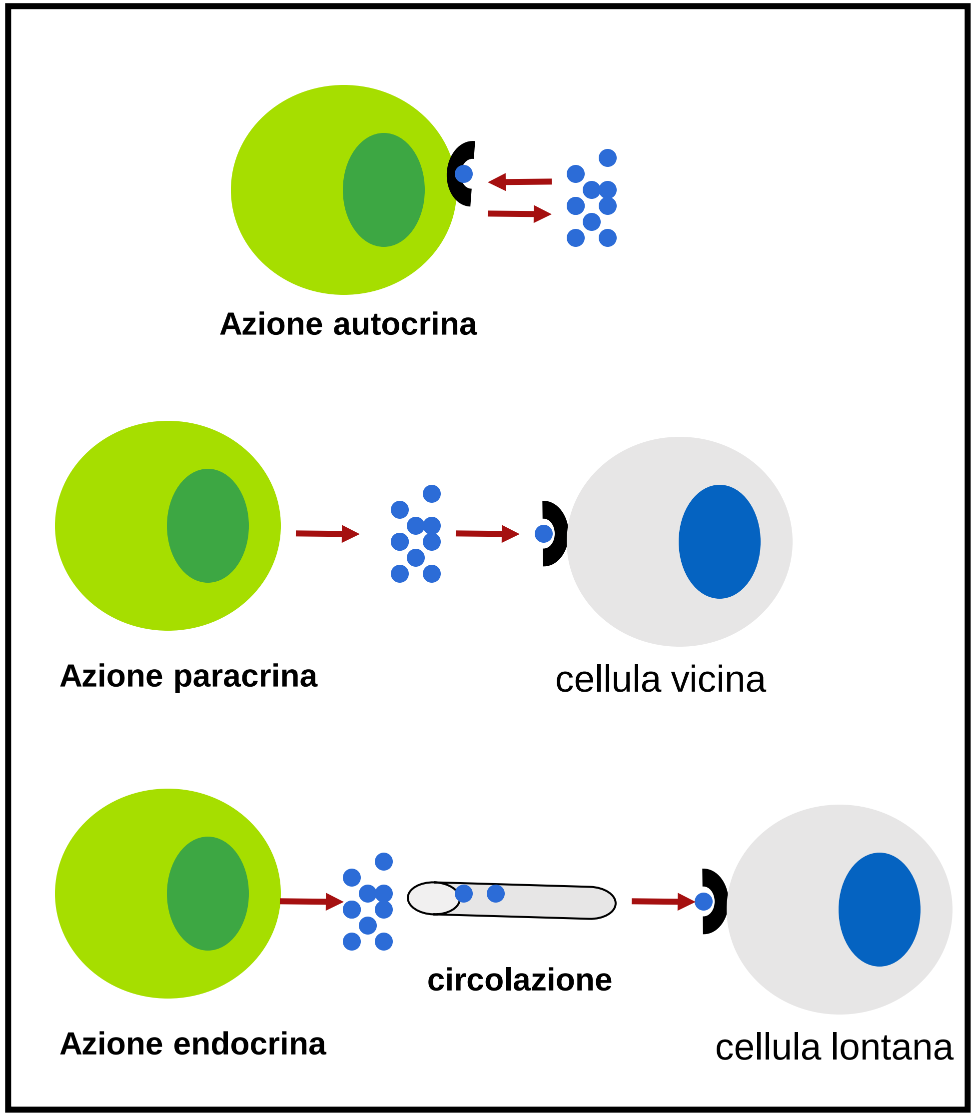
- Mettono in comunicazione le cellule del sistema immunitario TRA loro e CON diversi altri tipi cellulari.

- La loro sintesi, secrezione ed emivita sono finemente regolate, a diversi livelli.



Produzione e funzione delle citochine





Esempi di citochine (interleuchine=IL)

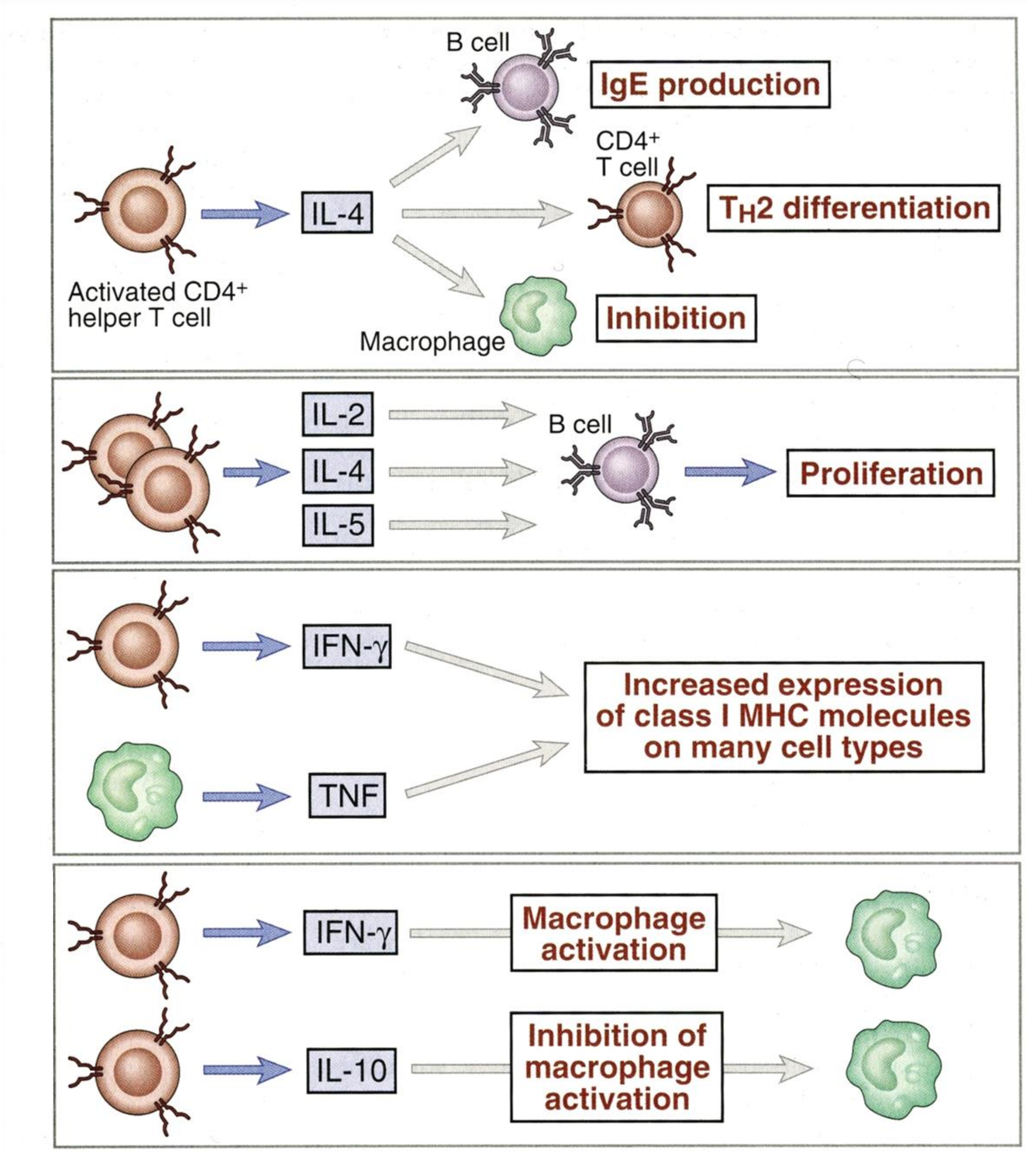
LE CARATTERISTICHE PRINCIPALI DELLE CITOCHINE

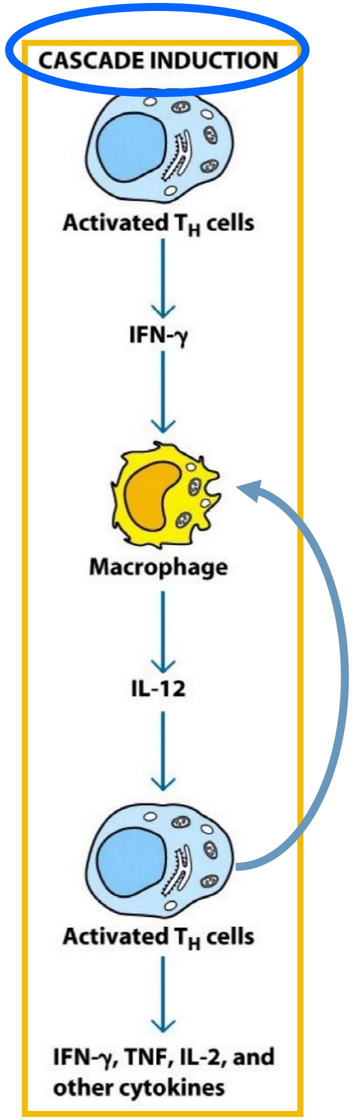
Pleiotropismo

Ridondanza

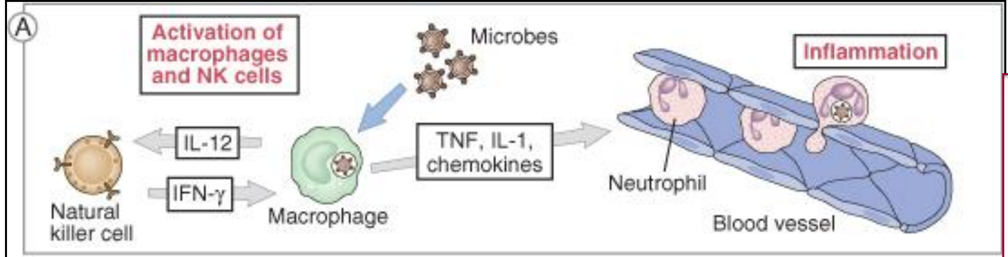
Sinergia

Antagonismo

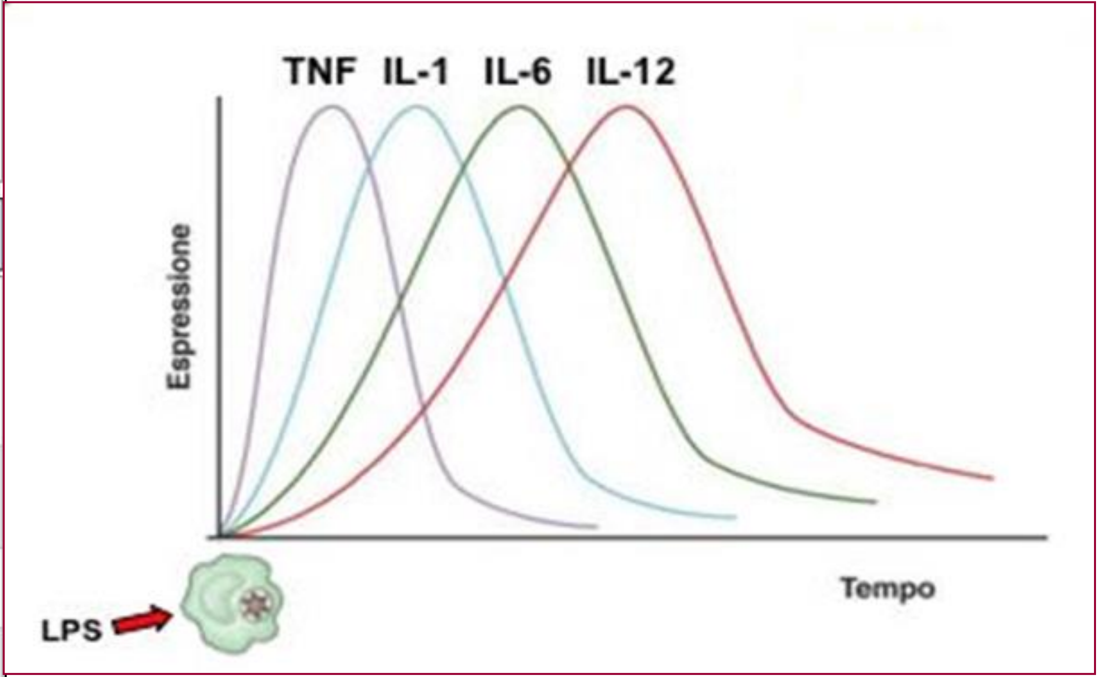




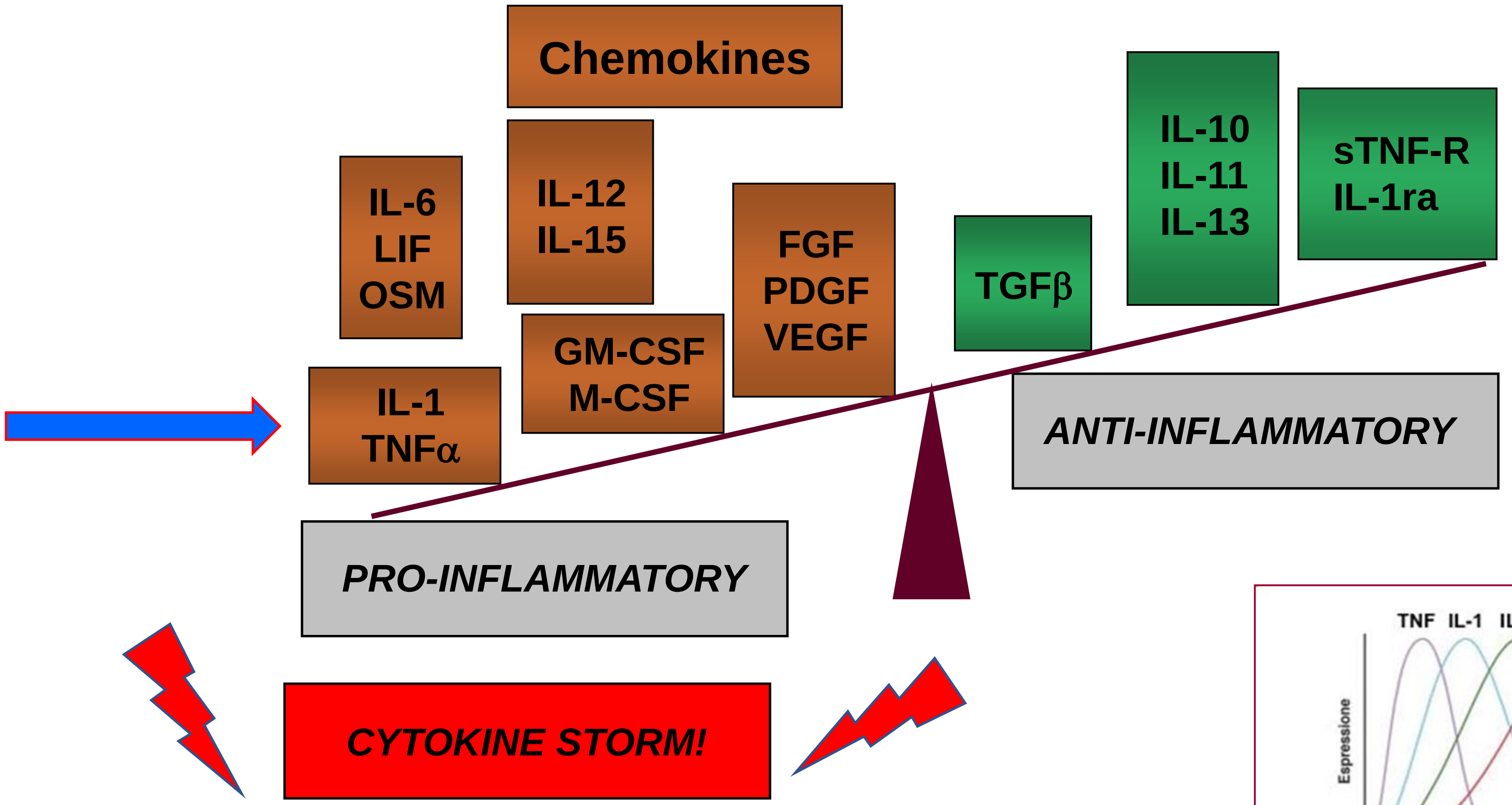
LE CITOCHINE INFIAMMATORIE

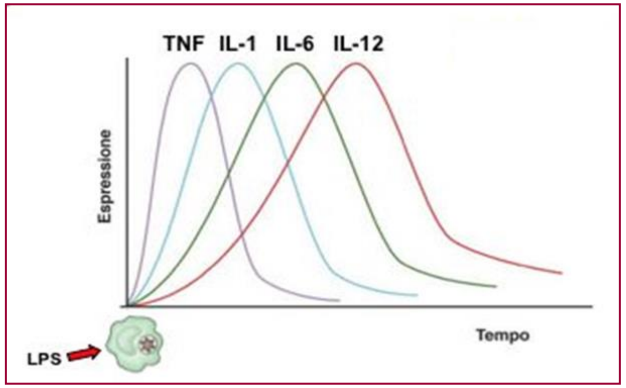


B Cytokine	Principal cell source(s)	Principal cellular targets and biologic effects
Tumor necrosis factor (TNF)	Macrophages, T cells	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Liver: synthesis of acute phase proteins Muscle, fat: catabolism (cachexia) Many cell types: apoptosis
Interleukin (IL-1)	Macrophages, endothelial cells, some epithelial cells	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever Liver: synthesis of acute phase proteins
Chemokines	Macrophages, endothelial cells, T lymphocytes, fibroblasts, platelets	Leukocytes: chemotaxis, activation
Interleukin-12 (IL-12)	Macrophages, dendritic cells	NK cells and T cells: IFN-γ synthesis, increased cytolytic activity T cells: T_H1 differentiation
Interferon-γ (IFN-γ)	NK cells, T lymphocytes	Activation of macrophages Stimulation of some antibody responses
Type I IFNs (IFN-α, IFN-β)	IFN-α: Macrophages IFN-β: Fibroblasts	All cells: antiviral state, increased class I MHC expression NK cells: activation
Interleukin-10 (IL-10)	Macrophages, T cells (mainly T_H2)	Macrophages: inhibition of IL-12 production, reduced expression of costimulators and class II MHC molecules
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T cells	Liver: synthesis of acute phase proteins B cells: proliferation of antibody-producing cells
Interleukin-15 (IL-15)	Macrophages, others	NK cells: proliferation T cells: proliferation
Interleukin-18 (IL-18)	Macrophages	NK cells and T cells: IFN-γ synthesis

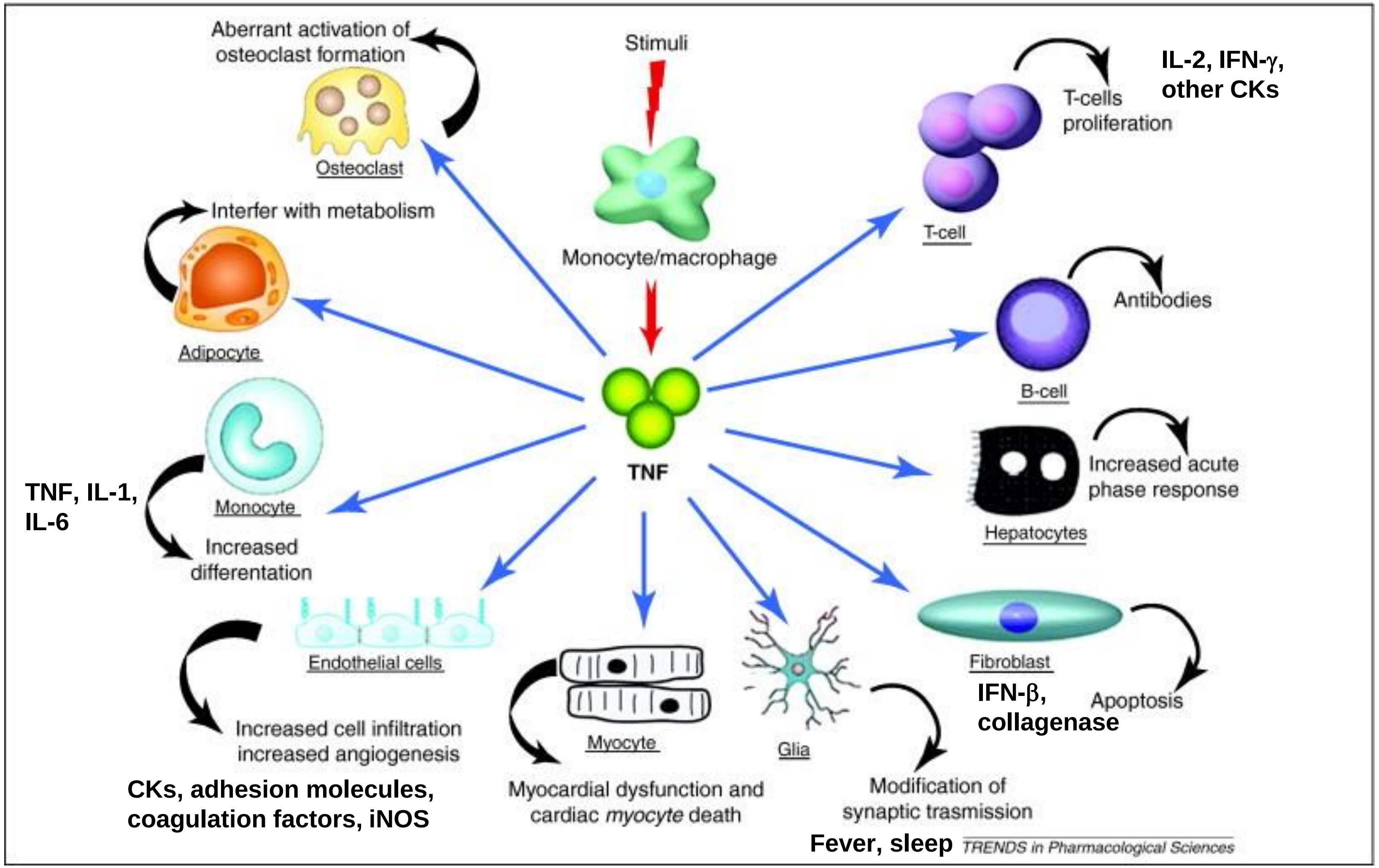


Lo squilibrio nella produzione di citochine durante l'infiammazione

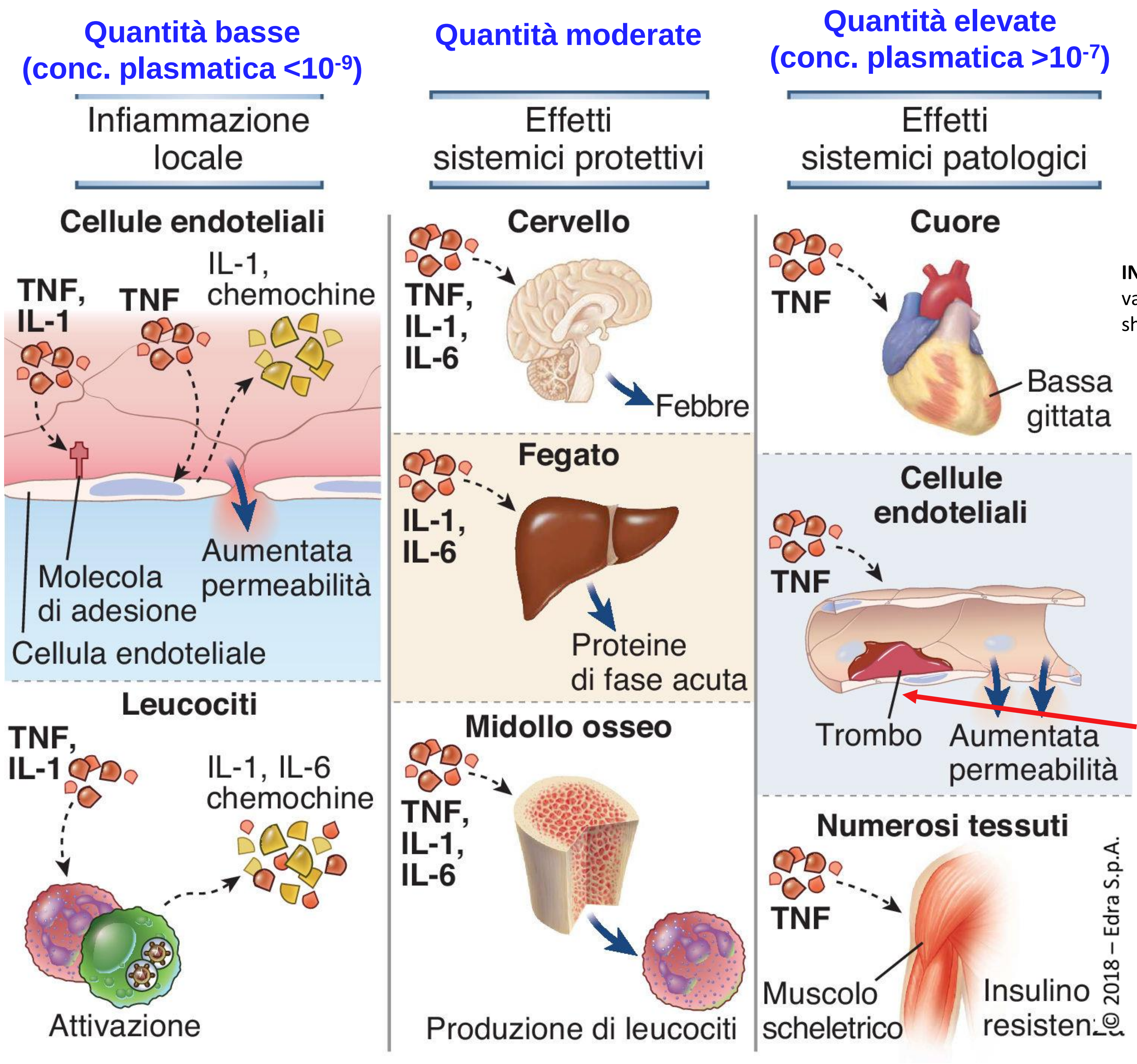




Many cells = many functions



Le funzioni principali del TNF



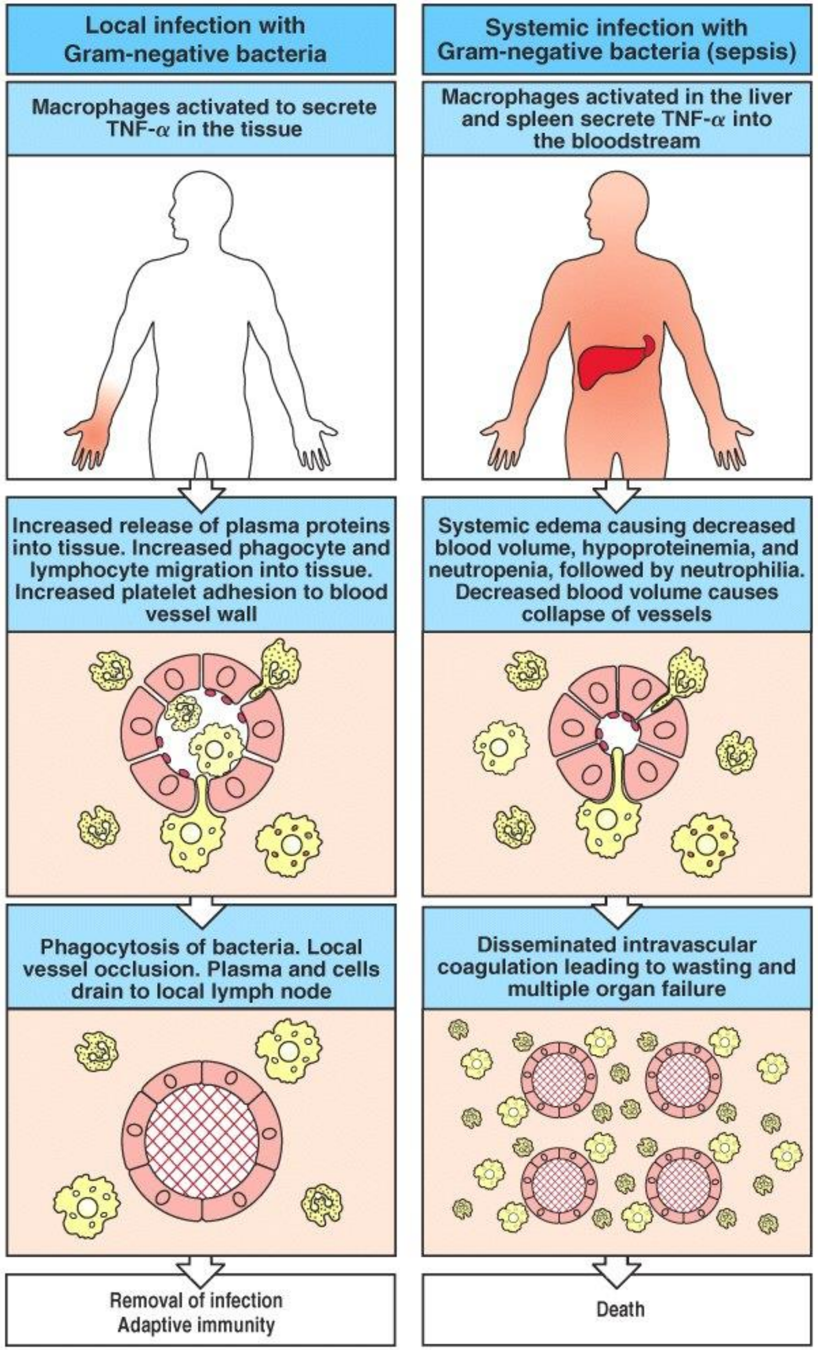
INIBIZIONE CONTRAZIONE CELLULE DEL MIOCARDIO, vasodilatazione, caduta della pressione arteriosa, shock.

TROMBOSI INTRAVASCOLARE: TNF favorisce la coagulazione (stimola la sintesi del fattore tissutale da parte dell'endotelio -che induce la formazione della trombina a partire da pro-trombina- e inibisce la coagulazione stimolando trombomodulina. Trombi favoriti anche dall'accumulo e attivazione dei neutrofili.

Da qui il nome!

IPOGLICEMIA: gravi disturbi metabolici (es., eccessivo uso di glucosio da parte del tessuto muscolare e incapacità di ripristinare i normali livelli).
CACHESSIA: perdita pronunciata di peso, dovuta a perdita dell'appetito indotta da TNF e da inibizione di enzimi che mobilizzano gli acidi grassi, e che quindi non possono essere utilizzati dai tessuti.

Locally, TNF-α can cause inflammation (most TNF is from macrophages)



Chronic systemic TNF (sometimes associated with cancer, AIDS and other diseases) can lead to cachexia

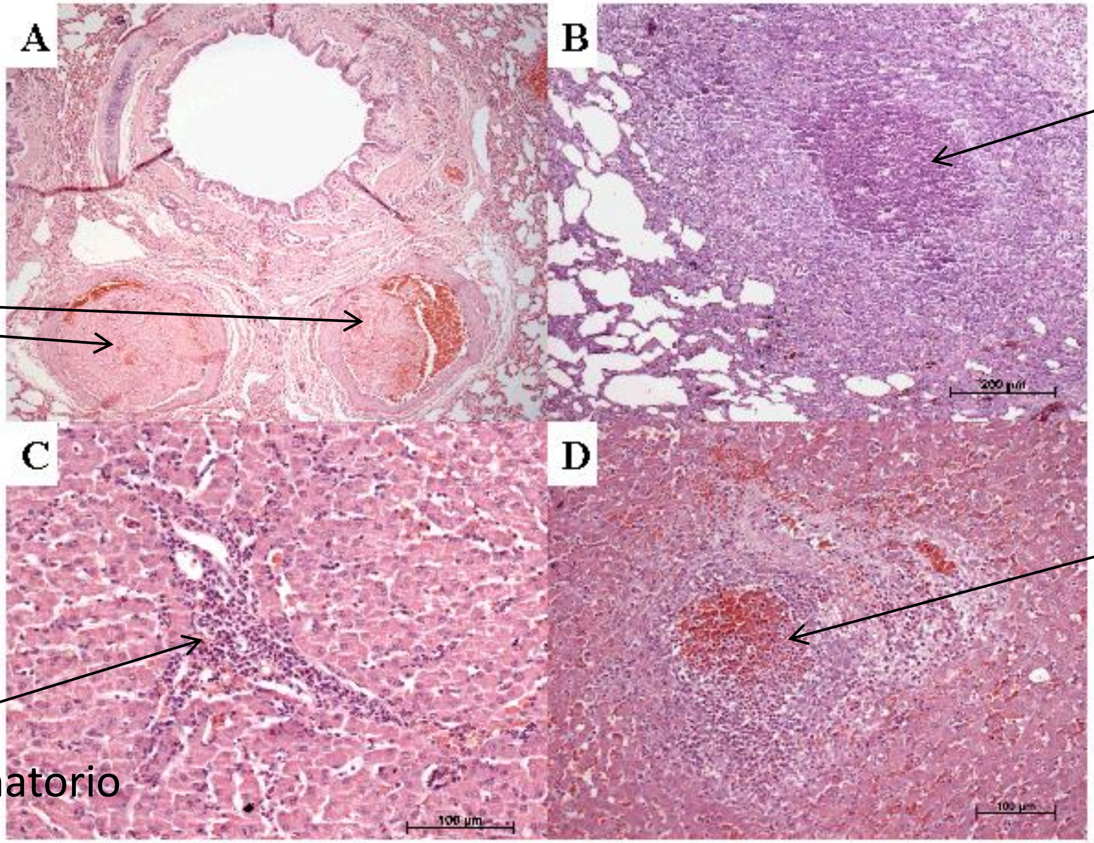
Systemically, high doses of TNF-α can cause septic shock and death

Lo shock settico: istologia

POLMONE

infiltrato infiammatorio

trombosi

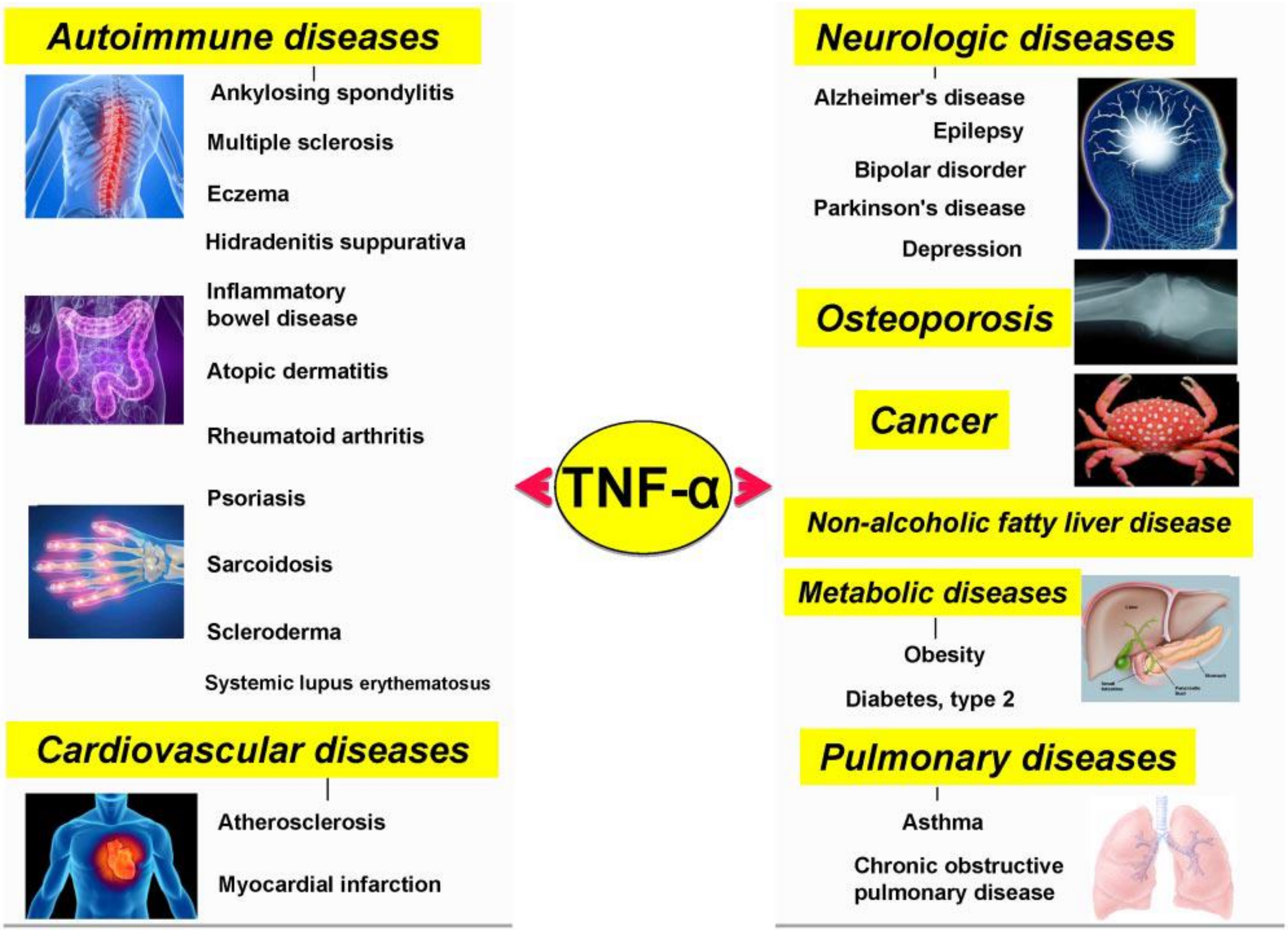


FEGATO

microascesso

infiltrato infiammatorio

Ruolo del TNF-α nelle malattie



Aggarwal B.B., Blood 2012

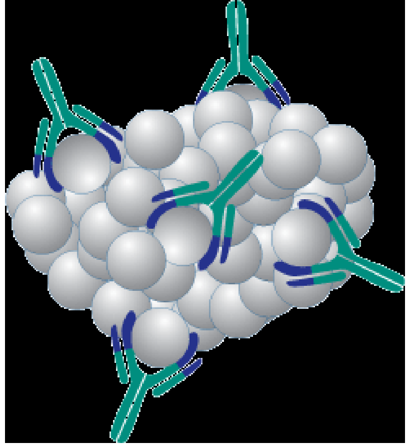
Gli antagonisti del TNF nella clinica

Immune-Mediated Inflammatory Disease (cont'd)

- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Crohn's Disease
- Psoriasis
- Psoriatic Arthritis
- Uveitis etc

→

Mediated in part by common cellular and molecular pathways

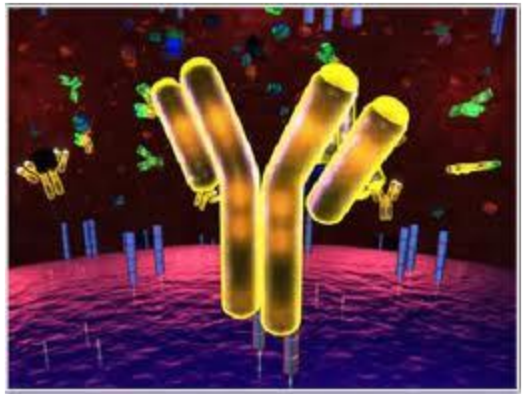


Gli anticorpi monoclonali:

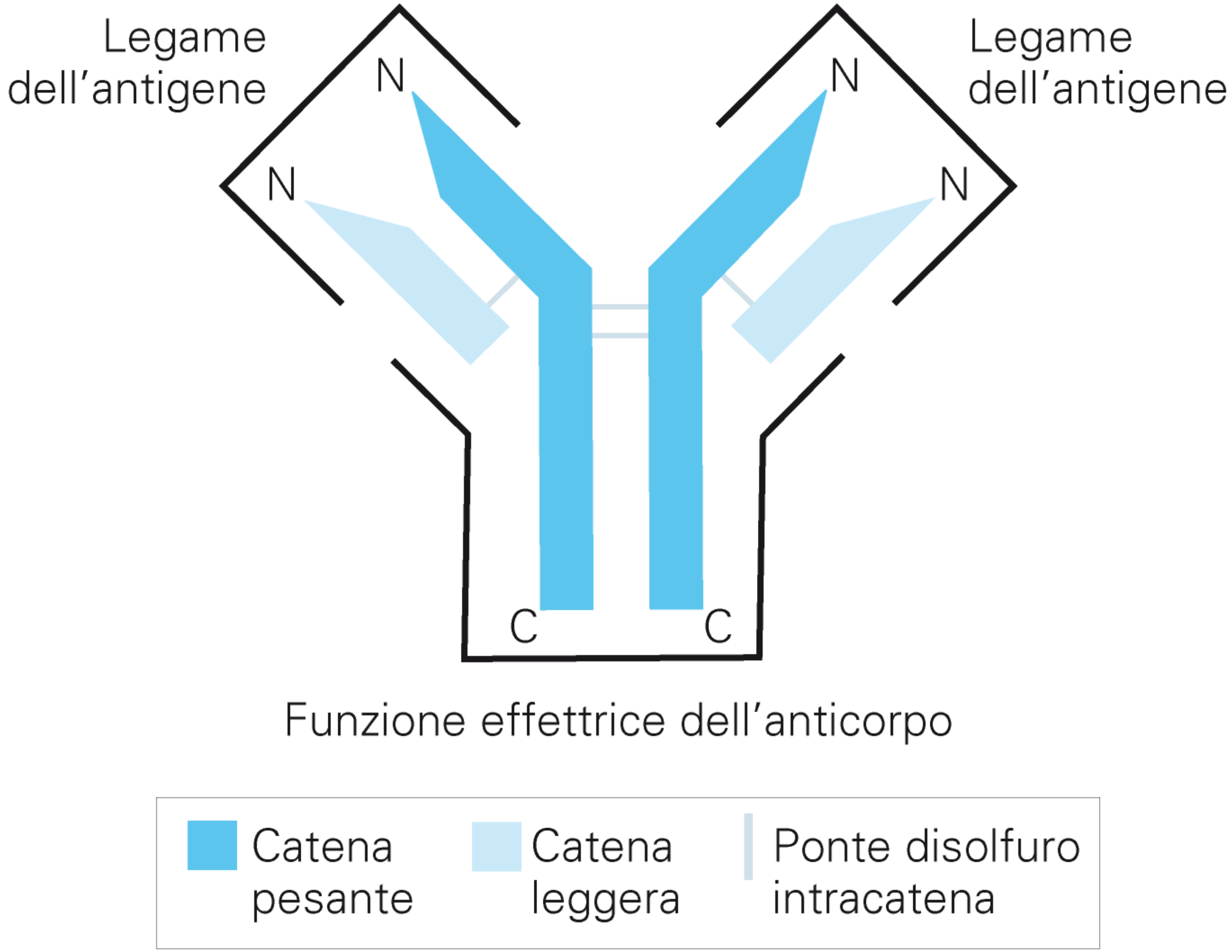
come sfruttare un prodotto del sistema immunitario

contro una molecola di superficie

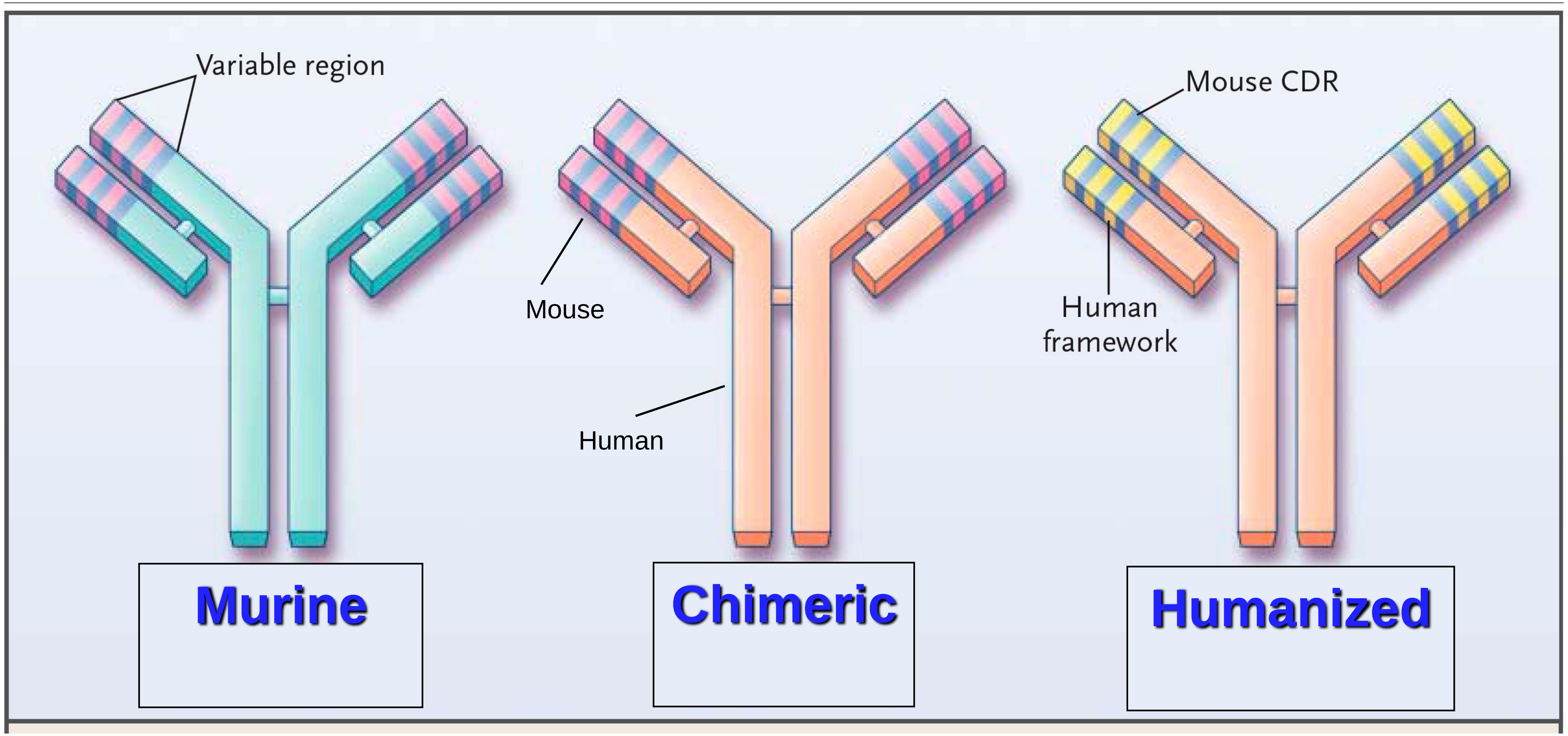
contro una molecola solubile

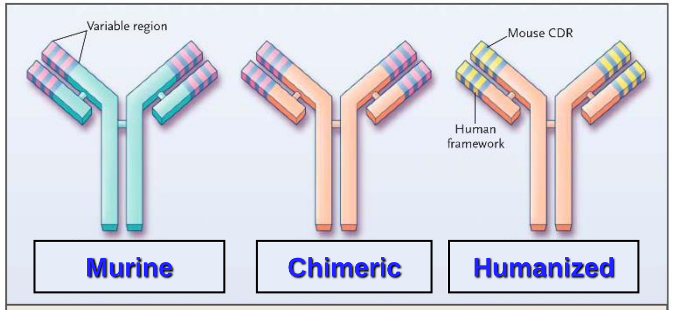


Gli anticorpi monoclonali



Three types of monoclonal antibodies now in use in the clinic





...I SUFFISSI

...mab: anticorpo monoclonale (Monoclonal AntiBody)

....ximab: anticorpo chimerico (uomo+topo)

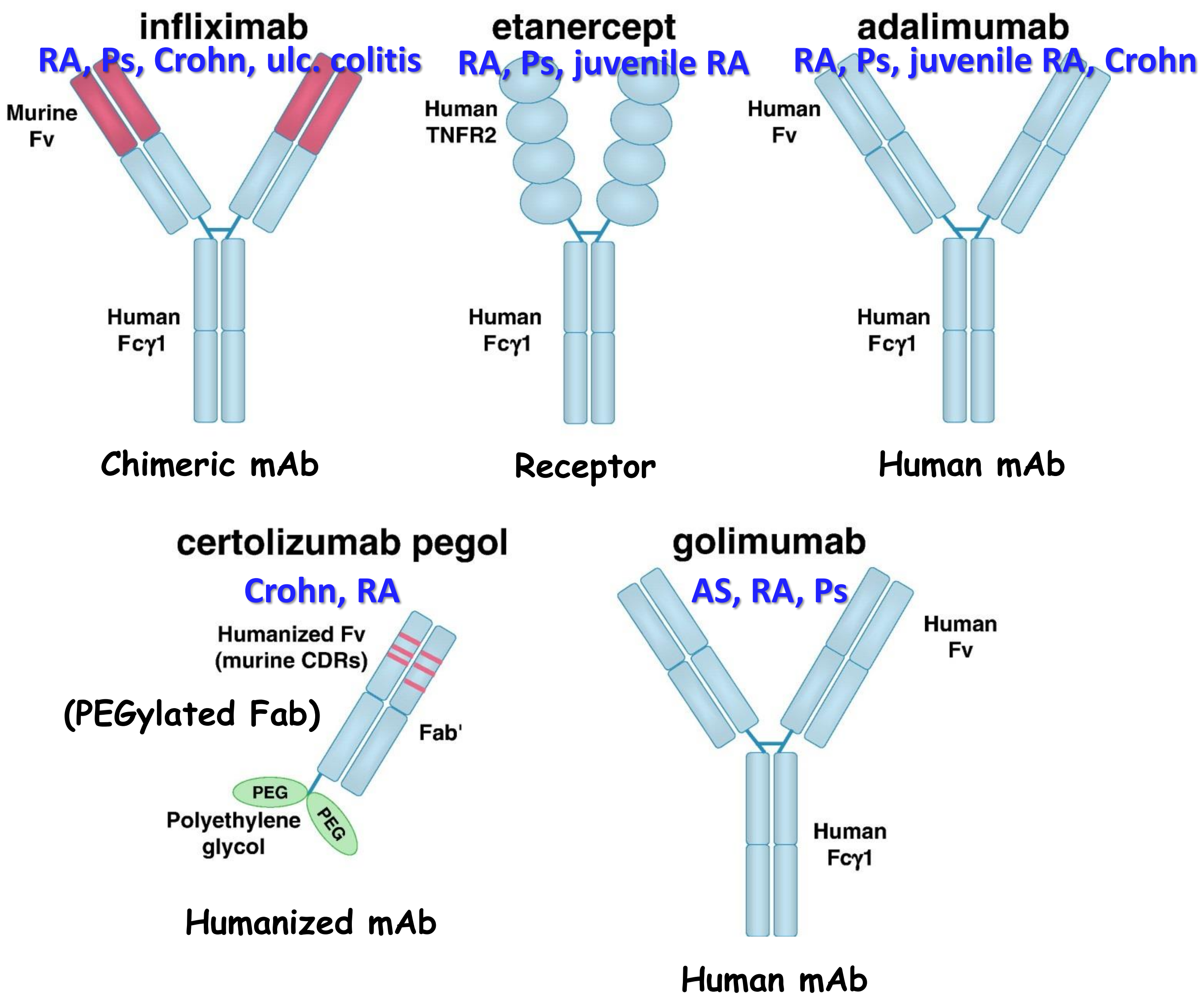
...zumab: anticorpo umanizzato

...mumab: anticorpo umano («fully human»)

...cept: molecola di fusione/recettore solubile

...ra: antagonista del recettore («fully human»)

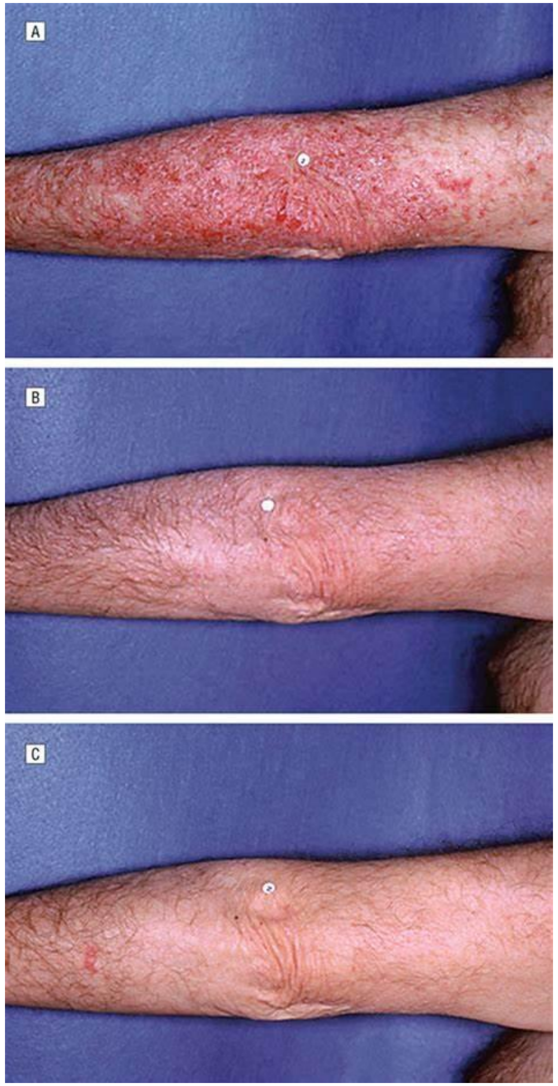
(Alcuni) Antagonisti del TNF



Tracey D et al Pharmacol & Therap, 2008

Gli antagonisti del TNF nella clinica (es. Etanercept)

Psoriasis activity in an etanercept-treated patient at baseline
(A, Psoriasis Area and Severity Index [PASI] = 18.7), at 12 weeks
(B, 59% improvement in PASI), and at 24 weeks
(C, 86% improvement in PASI).



Time 0

12 weeks

24 weeks

Gottlieb AB, Arch Dermatol. 2003
A Randomized Trial of Etanercept as Monotherapy for Psoriasis

Gli antagonisti del TNF nella clinica (es. Etanercept)

Patient at presentation, prior to treatment, showing widespread patches of erythema with overlying pustules affecting 90% of his body surface.

Patient after 4 weeks of treatment with etanercept, 50 mg subcutaneously per week, showing complete resolution of the skin lesions.

Successful Treatment With Etanercept of von Zumbusch Pustular Psoriasis in a Patient With HIV.
Mikhai M, Arch Dermatol. 2008

The New England Journal of Medicine 2001

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

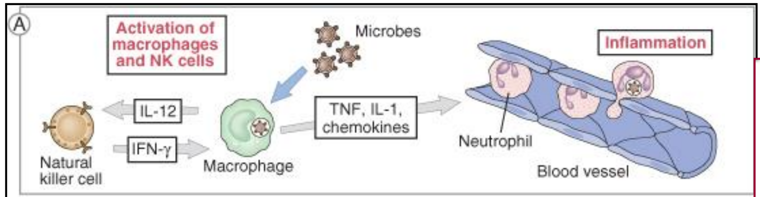
JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

From the Pulmonary Center, Department of Medicine (J. Keane, E.M.-L.), and the Pathology Department (J. Kasznica), Boston University School of Medicine, Boston; and the Center for Biologics Evaluation and Research, Office of Biostatistics and Epidemiology, Division of Epidemiology (S.G., R.P.W., M.M.B.), and Office of Therapeutics Research and Review (W.D.S., J.N.S.), Food and Drug Administration, Rockville, Md.

RESULTS: **There were 70 reported cases of tuberculosis after treatment with infliximab**, for a median of 12 weeks. **In 48 patients, tuberculosis developed after three or fewer infusions**. Of the 70 reports, 64 were from countries with a low incidence of tuberculosis. **The reported frequency of tuberculosis in association with infliximab therapy was much higher than the reported frequency of other opportunistic infections associated with this drug.**

CONCLUSIONS: **Active tuberculosis may develop soon after the initiation of treatment with infliximab. Before prescribing the drug, physicians should screen patients for latent tuberculosis infection or disease.**

LE CITOCHINE INFIAMMATORIE



B

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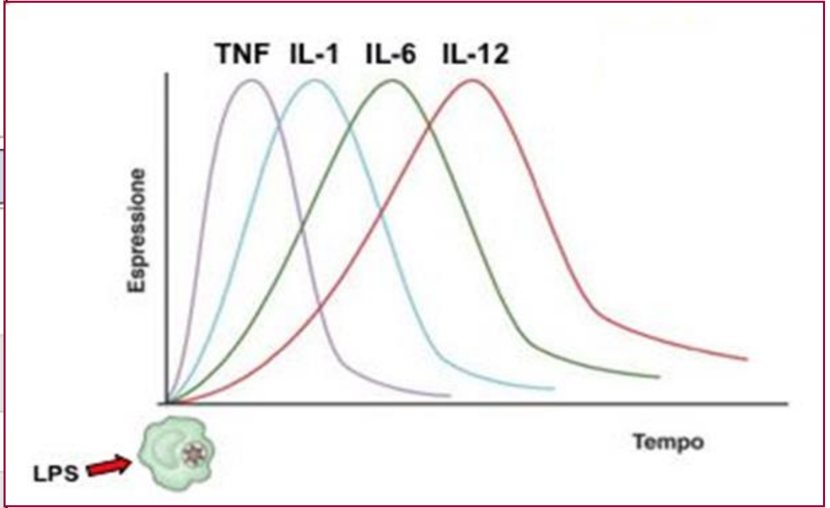
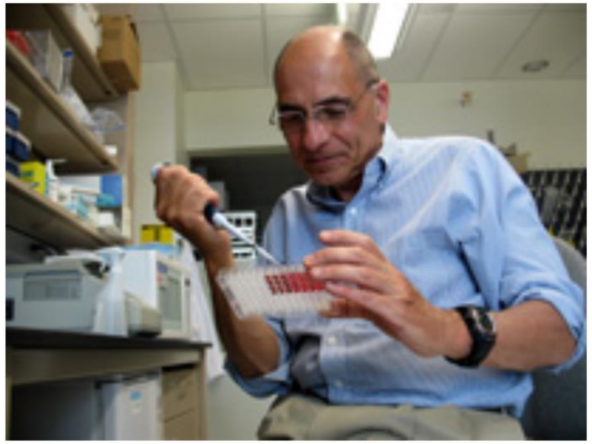


Joost Oppenheim

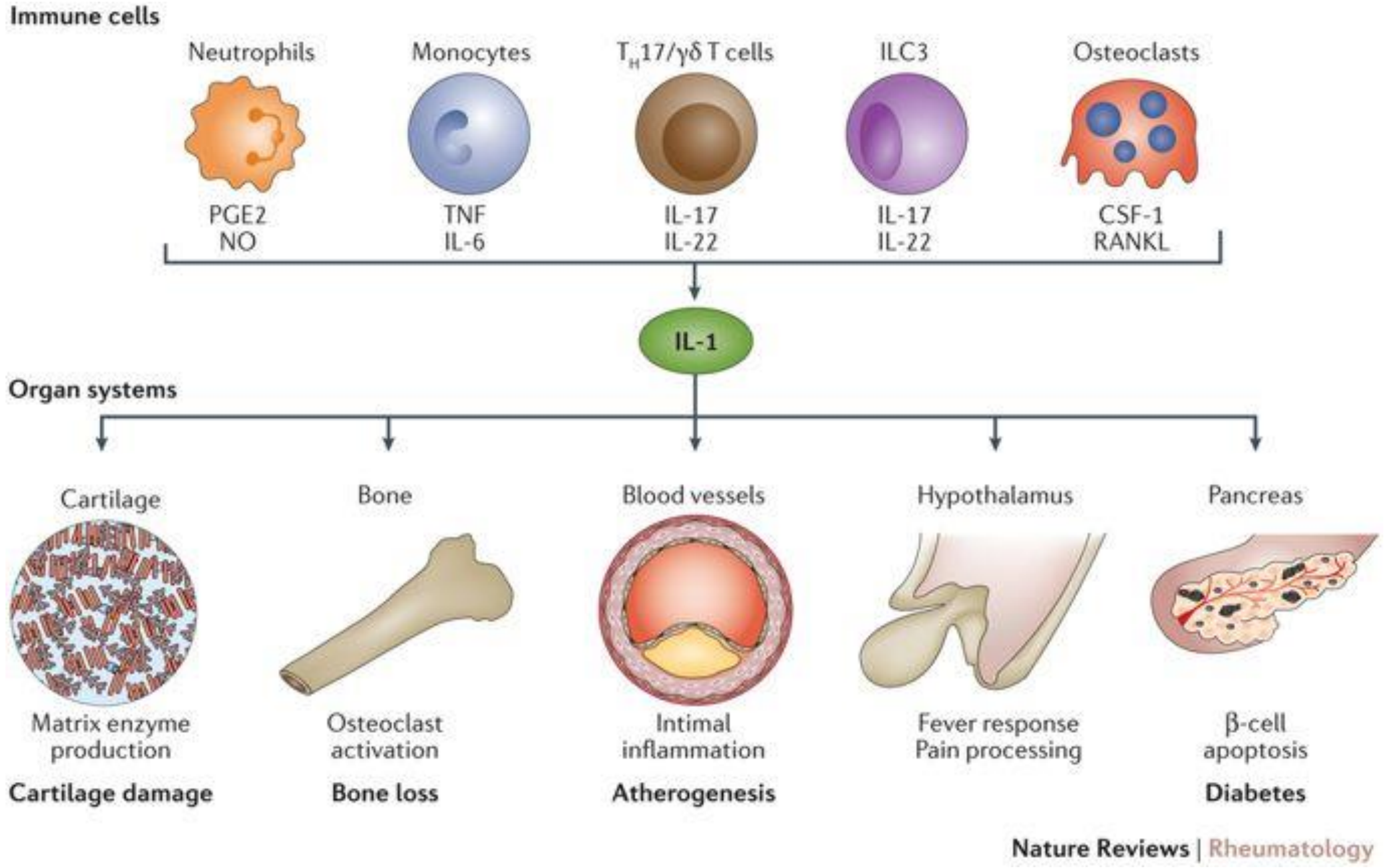


Charles Dinarello

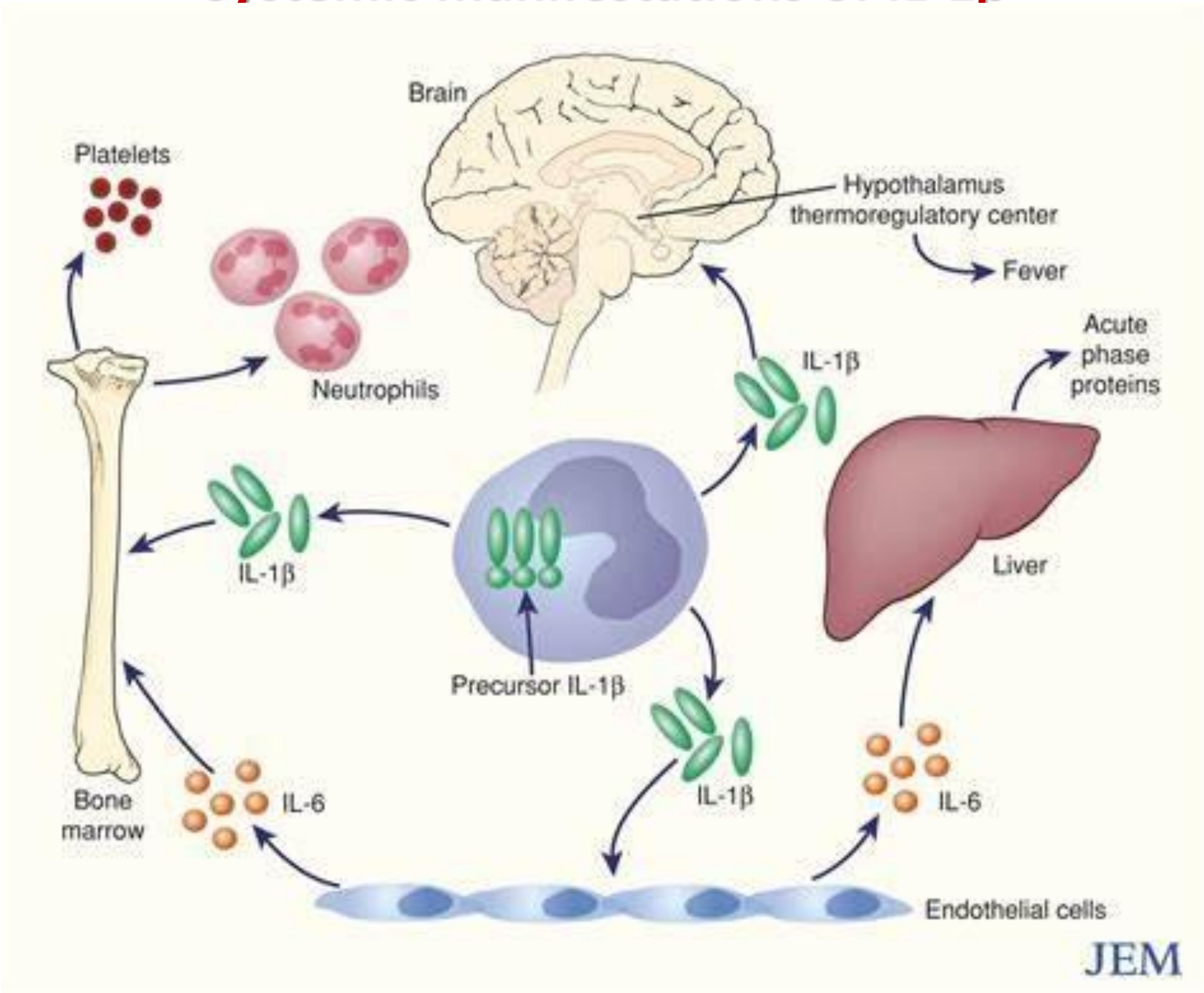
LA SUPERFAMIGLIA DELL'INTERLEUCHINA-1

Alberto Mantovani

Main (and many!) functions of IL-1



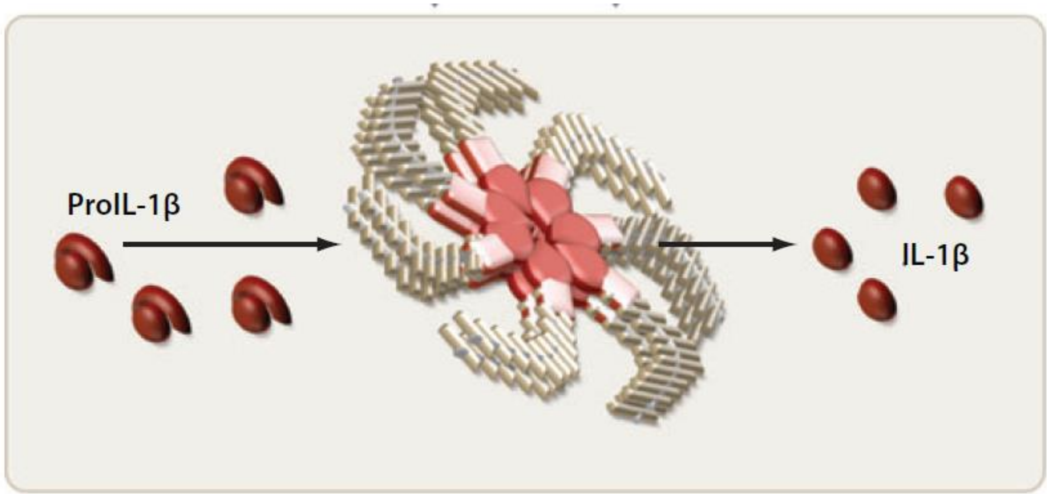
Systemic manifestations of IL-1β

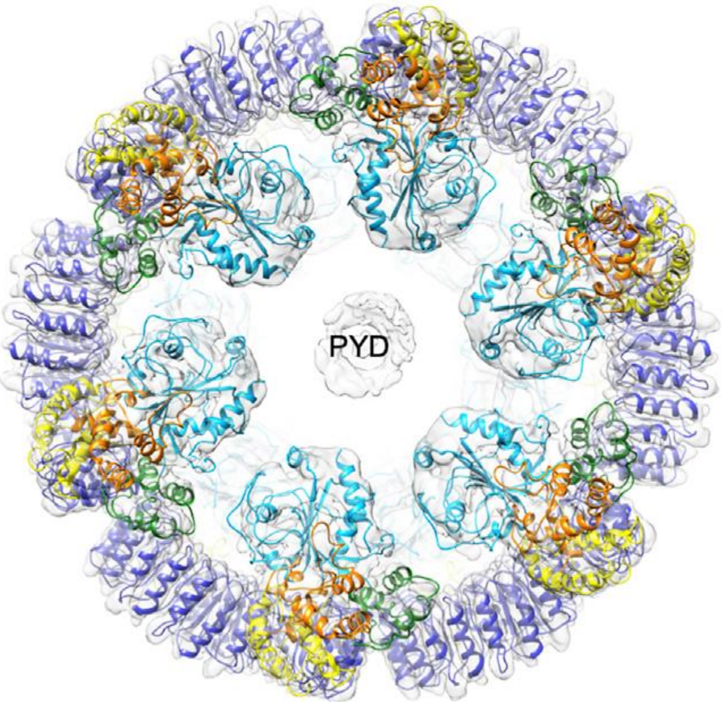


THE INFLAMMASOMES

The maturation of pro-inflammatory cytokines, such as IL-1β and IL-18 is mediated by the inflammasomes:

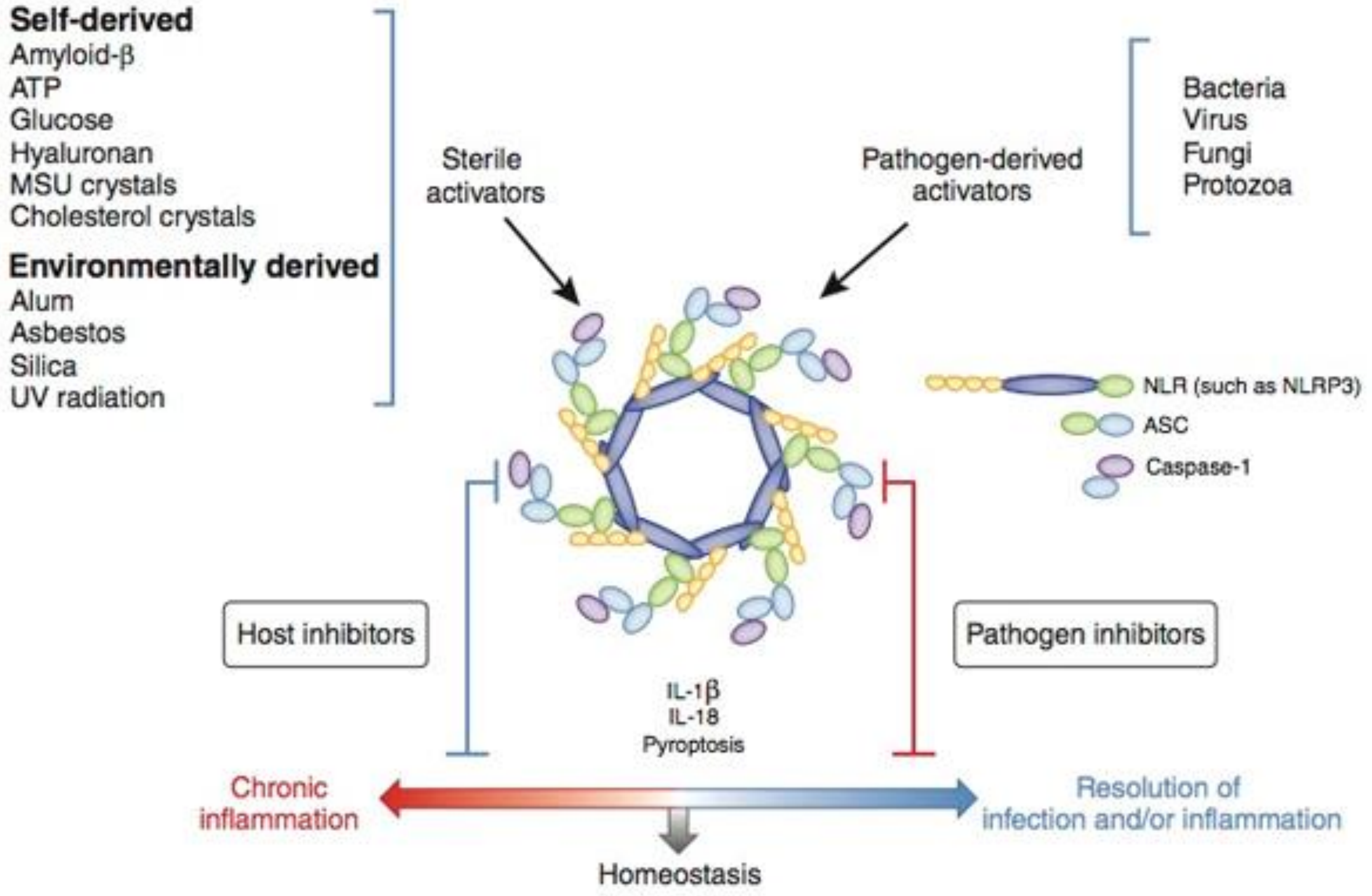
- ***molecular platforms activated by a plethora of microbial products, as well as endogenous host products associated with cellular stress and damage.***





Exogenous and endogenous activators of inflammasomes

Non solo PAMPs,
ma anche DAMPs…



Exogenous and endogenous activators of inflammasomes

Non solo PAMPs,
ma anche DAMPs…

NLRP1	
Bacillus anthracis lethal toxin (LeTx)	
MDP	
NLRP3	
Pathogens / PAMPs	**DAMPs**
Sendai virus	Extracellular ATP
Influenza	Hyaluronan
Adenovirus	Glucose
Encephalomyocarditis virus	MSU
Candida albicans	Amyloid-β
Saccharomyces cerevisiae	Skin irritants: trinitrophenylchloride, trinitrochlorobenzene, dinitrofluorobenzene
Staphylococcus aureus	Imidazoquinoline compounds (R837, R848)
Listeria monocytogenes	Silica
Neisseria gonorrhoeae	Asbestos
Bacterial pore-forming toxins	Alum

IPAF
Listeria monocytogenes
Salmonella typhimurium
Shigella flexneri
Legionella pneumophila
Pseudomonas aeruginosa
Cytosolic flagellin
AIM2
dsDNA

PAMPs, DAMPs, PRRs…

microbes → **PAMPs**

different source

same chemical structure

disruption of homeostasis → **DAMPs**

PAMPs, DAMPs → **PRRs** → evolved not only to detect microbes, but also to adapt to environmental changes

PRRs → macrophages

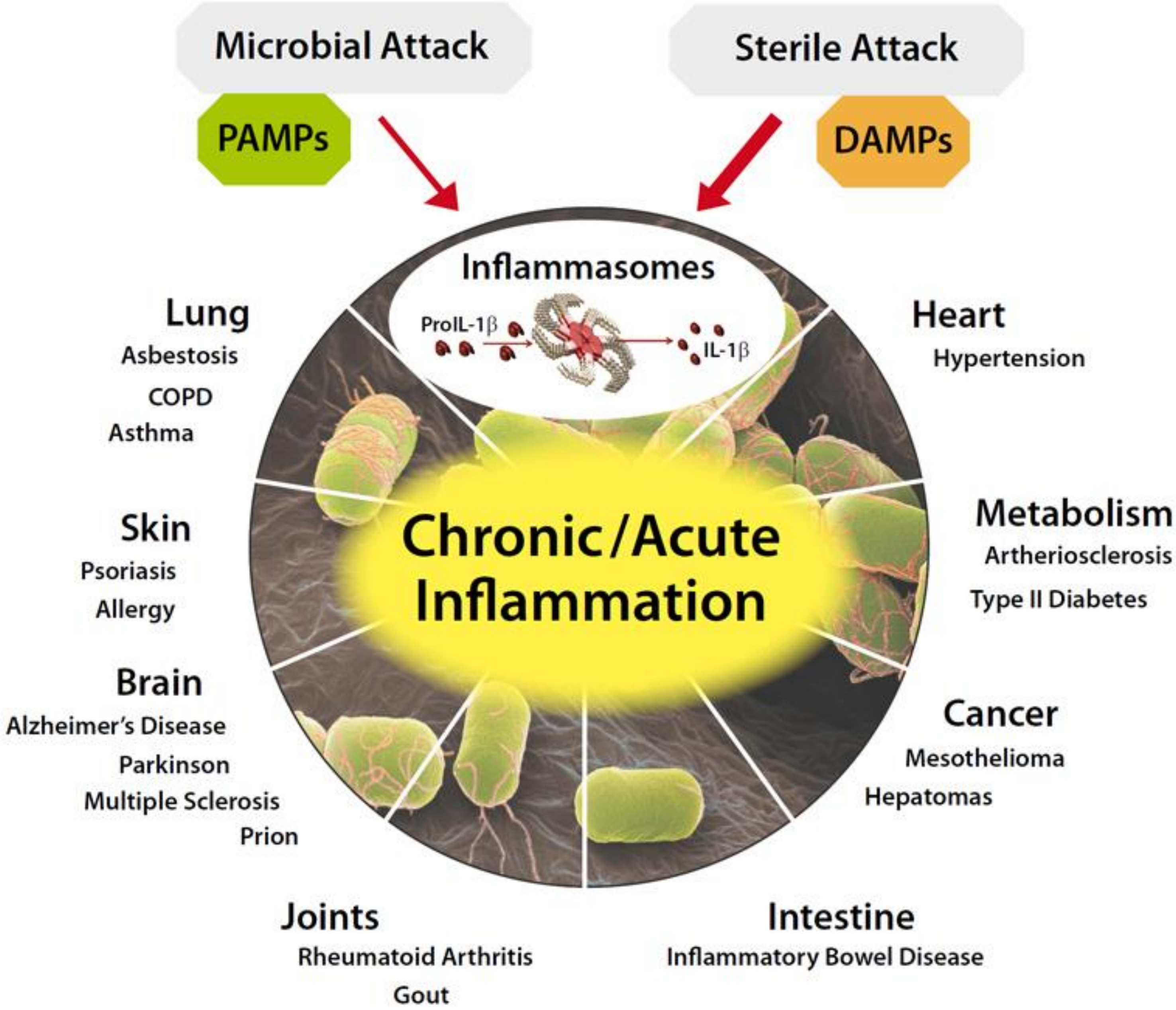
macrophages → earlier: anti-microbial cells

macrophages → now: anti-microbial cells
+
regulation of tissue homeostasis
&
detection of non-infectious threats

Lemaitre et al
Cell 1996

Drosophila TLR → development

Drosophila TLR → anti-microbial


Microbial Attack
Sterile Attack
PAMPs
DAMPs
Inflammasomes
ProIL-1β
IL-1β
Chronic/Acute Inflammation
Lung
Asbestosis
COPD
Asthma
Skin
Psoriasis
Allergy
Brain
Alzheimer's Disease
Parkinson
Multiple Sclerosis
Prion
Joints
Rheumatoid Arthritis
Gout
Intestine
Inflammatory Bowel Disease
Cancer
Mesothelioma
Hepatomas
Metabolism
Artheriosclerosis
Type II Diabetes
Heart
Hypertension

Role of IL-1 in disease (spec. NLRP3)

«Activation» disorders

Gout
Alzheimer’s disease
Macular degeneration
Type 2 diabetes
Atherosclerosis
Rheumatic diseases
IBD
Cancer

«Genetic» disorders

Periodic fever syndromes or CAPS
(cryopyrin-associated periodic syndromes)

Auto-inflammatory diseases

The term auto-inflammatory diseases was first proposed in 1999 to encompass a group of inherited disorders characterized by recurrent episodes of fever with inflammatory responses in multiple organs including the joints, skin, eyes, ears, and central nervous system. This group of diseases is characterized by gain-of-function mutations and over-production of IL-1β.

Auto-immune *versus* auto-inflammatory diseases

Dysfunctional cells	Dominant cytokines	Disease examples	Options for biologics
Autoimmune diseases			
T- and B lymphocytes	TNF, IL-6 and IL-17	• Rheumatoid arthritis • Crohn's disease • Psoriasis • Multiple sclerosis	• TNF blockers • Anti-IL-6 receptor mAb • Anti-IL-12/IL-23 mAb • Anti-IL-17 mAb • CTLA4 immunoglobulin • Rituximab; anakinra
Autoinflammatory diseases			
Monocytes and/or macrophages	IL-1α and IL-1β	• Hereditary diseases: CAPS; FMF; TRAPS; HIDS; PFAPA • Common (non-hereditary) diseases: adult and juvenile Still's disease; Schnitzler syndrome; hidradenitis suppurativa; gout; pseudogout; type 2 diabetes	• Anakinra • Rilonacept • Canakinumab • Gevokizumab • LY2189102 • Anti-IL-1α mAb • Anti-IL-1 receptor mAb • Oral caspase 1 inhibitors

Dinarello C, Nature Reviews Drug Discovery 2012

Role of IL-1 in disease

Disease*	Symptoms
Familial Mediterranean fever (FMF)	2–3 day episodes of fever, monoarticular arthritis, erythematous rash, and abdominal pain. Systemic amyloidosis
Familial-cold autoinflammatory syndrome (FCAS)‡	1–2 day episodes of fever, arthralgia, urticaria-like rash and conjunctivitis predominantly after cold exposure ***mildest***
Muckle–Wells Syndrome (MWS)	1–2 day episodes of fever, arthritis, limb pain and urticaria-like rash. Progressive neurosensory hearing loss and systemic amyloidosis ***more severe***
Neonatal-onset multisystem inflammatory disease (NOMID)§ **(CINCA)**	1–2 day episodes of fever. Chronic meningitis, uveitis, urticaria-like rash, deforming arthropathy, neurosensory hearing loss ***more severe***

Ting et al, Nature Reviews Immunol 2006

Neurological diseases to which IL-1 might contribute

Disease	Clinical evidence of a role for IL-1	Proposed role of IL-1
Alzheimer's disease	Increased expression of IL-1 is associated with plaques and tangles in brain parenchyma; polymorphisms in genes encoding IL-1 influence susceptibility	Excessive production and processing of β-amyloid precursor protein and phosphorylation of tau protein, the main components of plaques and tangles
Traumatic brain injury	Increased intracerebral expression of IL-1 early after injury, and increased concentration of IL-1 in cerebrospinal fluid	Increases neuronal excitability, induces neurotoxin production, increases leukocyte infiltration, activates microglial cells and promotes astrogliosis
Epilepsy	Increased expression of IL-1 in brain parenchyma; polymorphisms in genes encoding IL-1 might influence susceptibility	Increases neuronal excitability through modification of the balance between excitatory and inhibitory synaptic transmission
Parkinson's disease	Increased concentration of IL-1 in cerebrospinal fluid; polymorphisms in genes encoding IL-1 might influence susceptibility	Contributes to the degeneration of neurons in the substantia nigra
Stroke	Increased concentration of IL-1 in cerebrospinal fluid; polymorphisms in genes encoding IL-1 might influence susceptibility	Increases neuronal excitability, induces neurotoxin production, increases leukocyte infiltration, activates microglial cells and promotes astrogliosis

IL-1β plays a key role in a variety of ischemic, hypoxic, excitotoxic, traumatic, and degenerative conditions of the central nervous system!

Pathologic inflammasome activation

Pathologic activation of NLRs/inflammasomes, and associated diseases

Disease	Responsible factor	Effect
Hereditary periodic fevers		
Cryopyrinopathies (MWS, FCAS, NOMID)	Mutation in *CIAS1/NLRP3*	Overactive variants of NLRP3, overexpression of NLRP3 leading to facilitated inflammasome activation
FMF	Mutations in *MEFV*/pyrin	Possible promotion of ASC assembly
NLRP12 familial fever	Truncation mutations in NLRP12	Hereditary periodic fevers associated with arthralgia, and urticaria
Other genetic diseases		
Vitiligo	Mutations in NLRP1	Unknown
Crystal-induced diseases		
Gout	MSU crystals	Activation of the NLRP3 inflammasome
Pseudogout	Calcium pyrophosphate dehydrate	Activation of the NLRP3 inflammasome
Asbestosis	Asbestos	Activation of the NLRP3 inflammasome
Silicosis	Silica	Activation of the NLRP3 inflammasome
Other		
Alzheimer disease	β-Amyloid	Activation of the NLRP3 inflammasome
Contact hypersensitivity	Trinitrochlorobenzene, sodium dodecylsulfate	Activation of the NLRP3 inflammasome

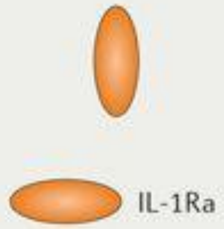
Anakinra!

ARTHRITIS & RHEUMATISM
Vol. 48, No. 4, April 2003, pp 927–934
DOI 10.1002/art.10870

Anakinra, a Recombinant Human Interleukin-1 Receptor Antagonist (r-metHuIL-1ra), in Patients With Rheumatoid Arthritis

A Large, International, Multicenter, Placebo-Controlled Trial

Roy M. Fleischmann,[1] Joy Schechtman,[2] Ralph Bennett,[3] Malcolm L. Handel,[4] Gerd-Rudiger Burmester,[5] John Tesser,[6] Dennis Modafferi,[7] Jennifer Poulakos,[7] and Gordon Sun,[7] for the 990757 Study Group

	Anakinra
	
Parameter	**IL-1Ra**
Structure Binding to IL-1α Affinity to IL-1β Half life Dose	Recombinant protein Yes None 5 hours 100 mg daily
Approved Off label use	RA, CAPS sJIA, AOSD, CPPD Gout, CPPD, HACD Schnitzler syndrome
In testing	–

Most patients with auto-inflammatory diseases exhibit a rapid response to treatment with Anakinra or with other therapeutic agents that block IL-1β effects.

These dramatic responses validate the importance of IL-1β overproduction as the mechanism of autoinflammatory diseases.

Drugs (2020) 80:1267–1292
https://doi.org/10.1007/s40265-020-01367-z

LEADING ARTICLE

Pharmaco-Immunomodulatory Therapy in COVID-19

John G. Rizk[1] · Kamyar Kalantar-Zadeh[2,3,4] · Mandeep R. Mehra[5] · Carl J. Lavie[6] · Youssef Rizk[7] · Donald N. Forthal[8,9]

Anakinra in COVID-19 patients!

386 publications!

Table 1 Summary of immunomodulatory agents for the management of COVID-19

Treatments	Dosing regimens under investigation	Route of administration under investigation	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Specific immunomodulators							
Anakinra	IV: 100 mg every 6 h (total daily dose: 400 mg) for 15 days; 200 mg every 8 h for 7 days; 300 mg od for 4 days, followed by 100 mg od SC: 100 mg od for 10 or 28 days. Alternative regimen: 100 mg every 12 h on days 1–3, then 100 mg od from days 4–10	IV, SC Note: IV route is currently not FDA-approved	Anti-cytokine, IL-1 receptor antagonist	Injection site reactions, upper respiratory tract infections, headache, nausea, diarrhea, sinusitis, flu-like symptoms, abdominal pain	Known hypersensitivity to *Escherichia coli*-derived proteins, anakinra, or any component of the product	Avoid use with anti-TNF agents due to higher rates of infections and neutropenia	Use caution in the elderly due to higher rates of infections in the elderly population In patients with CrCl < 30 and ESRD, use extended dosing intervals (every other day)

European Journal of Internal Medicine

Anakinra for patients with COVID-19: a meta-analysis of non-randomized cohort studies.

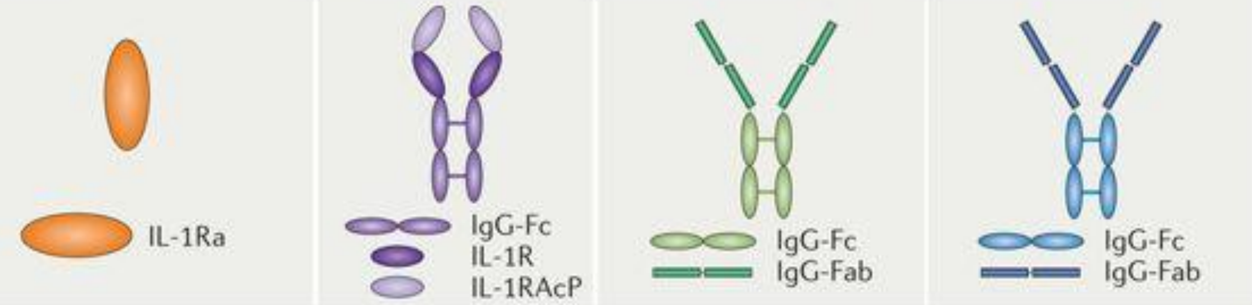
Laura Pasin[a,1], Giulio Cavalli[b,1], Paolo Navalesi[a,c], Nicolò Sella[a], Giovanni Landoni[d,*], Andrey G. Yavorovskiy[e], Valery V. Likhvantsev[f,g], Alberto Zangrillo[d], Lorenzo Dagna[b,h], Giacomo Monti[d]

Table 2
Outcomes.

Outcome	Number of included studies	Anakinra patients	Control patients	RR	95% CI	P for effect	I^2 (%)
Overall studies	4	111	73				
Mortality*	4	11/111 [10%]	30/73 [41%]	0.26	0.14 to 0.48	<0.0001	0
Need for invasive MV*	4	18/111 [16%]	26/73 [36%]	0.45	0.25 to 0.82	0.008	19
Bacterial infection	3	9/99 [9%]	2/63 [3%]	1.59	0.35 to 7.16	0.55	7
Thromboembolic events	3	13/99 [13%]	7/63[11%]	1.35	0.58 to 3.12	0.35	0
Elevated serum transaminases	3	13/99 [13%]	9/63 [14%]	0.81	0.21 to 3.13	0.11	55
Discharged from hospital with no limitations	2	20/47 [43%]	6/19[32%]	1.29	0.61 to 2.74	0.50	0

RR: relative risk; CI: confidence interval; P: p-value; MV: mechanical ventilation
* Additional data provided by corresponding author (Navarro-Millán)

Therapeutic inhibition of IL-1



	Anakinra	Rilonacept	Canakinumab	Gevokizumab
Parameter	**IL-1Ra**	**IL-1R/IL-1RAcP-Fc**	**Anti-IL-1β antibody**	**Anti-IL-1β antibody**
Structure	Recombinant protein	Fc fusion protein	IgG1 mAb	IgG2 mAb
Binding to IL-1α	Yes	Yes	No	No
Affinity to IL-1β	None	0.5 pmol	23 pmol	300 fmol
Half life	5 hours	8 days	26 days	22 days
Dose	100 mg daily	160 mg/week	4 mg/kg/4–8 weeks 150 mg single dose	–
Approved	RA, CAPS	CAPS (only USA)	CAPS, gout, sJIA	–
Off label use	sJIA, AOSD, CPPD Gout, CPPD, HACD Schnitzler syndrome	–	AOSD, Schnitzler syndrome	–
In testing	–	–	CVD, diabetes	CVD, diabetes, Behçet syndrome, pyoderma gangrenosum
Refs	143	144,145	146	147

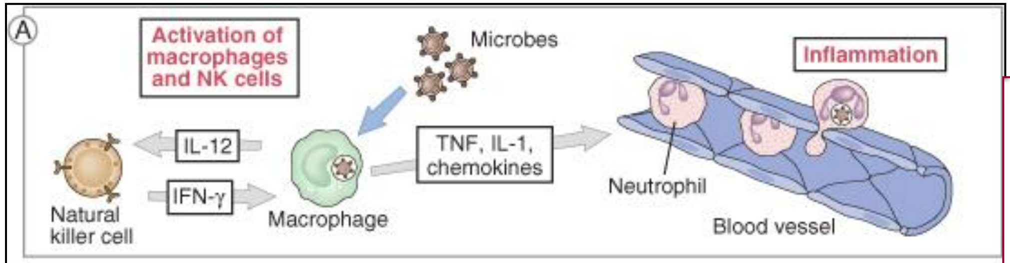
Nature Reviews | Rheumatology

Therapeutic agents that inhibit inflammasome components and their targeted diseases

Therapeutic agent	Target	Disease
Anakinra	IL-1 receptor	RA
Rilonacept	IL-1β, IL-1β	CAPS, diabetes, gout
Canakinumab	IL-1β	MWS, FCAS
GSK1070806	IL-18	B-cell non-Hodgkin's lymphoma, IBD
Glyburide	NLRP3 (indirectly)	Type 2 diabetes
16673-34-0	NLRP3 (indirectly)	Acute myocardial infarction
Pralnacasan (VX-740)	Caspase-1	RA
VX-765		MWS
Parthenolide	Caspase-1/NF-κB (IKKβ kinase activity)/ NLRP3 ATPase	Cancer
Bay 11-7082	NFκB (IKKβ kinase activity)/NLRP3 ATPase	Systemic lupus erythematosus
Cys-LT receptor antagonist	ASC oligomerization	Allergic rhinitis, asthma, nasal polyposis
AZD9056	P2X7	RA
CE-224535	P2X7	RA
GSK1482169	P2X7	RA

Ozaki E, Journal Inflammation Research 2015

LE CITOCHINE INFIAMMATORIE



B Cytokine	Principal cell source(s)	Principal cellular targets and biologic effects
Tumor necrosis factor (TNF)	Macrophages, T cells	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Liver: synthesis of acute phase proteins Muscle, fat: catabolism (cachexia) Many cell types: apoptosis
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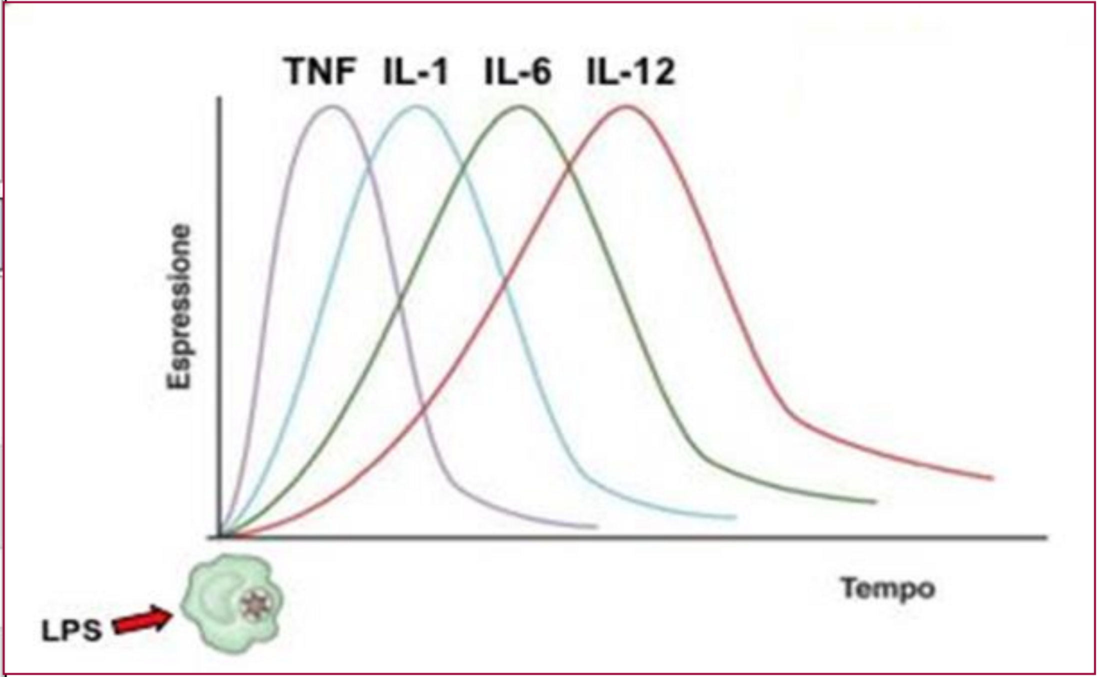
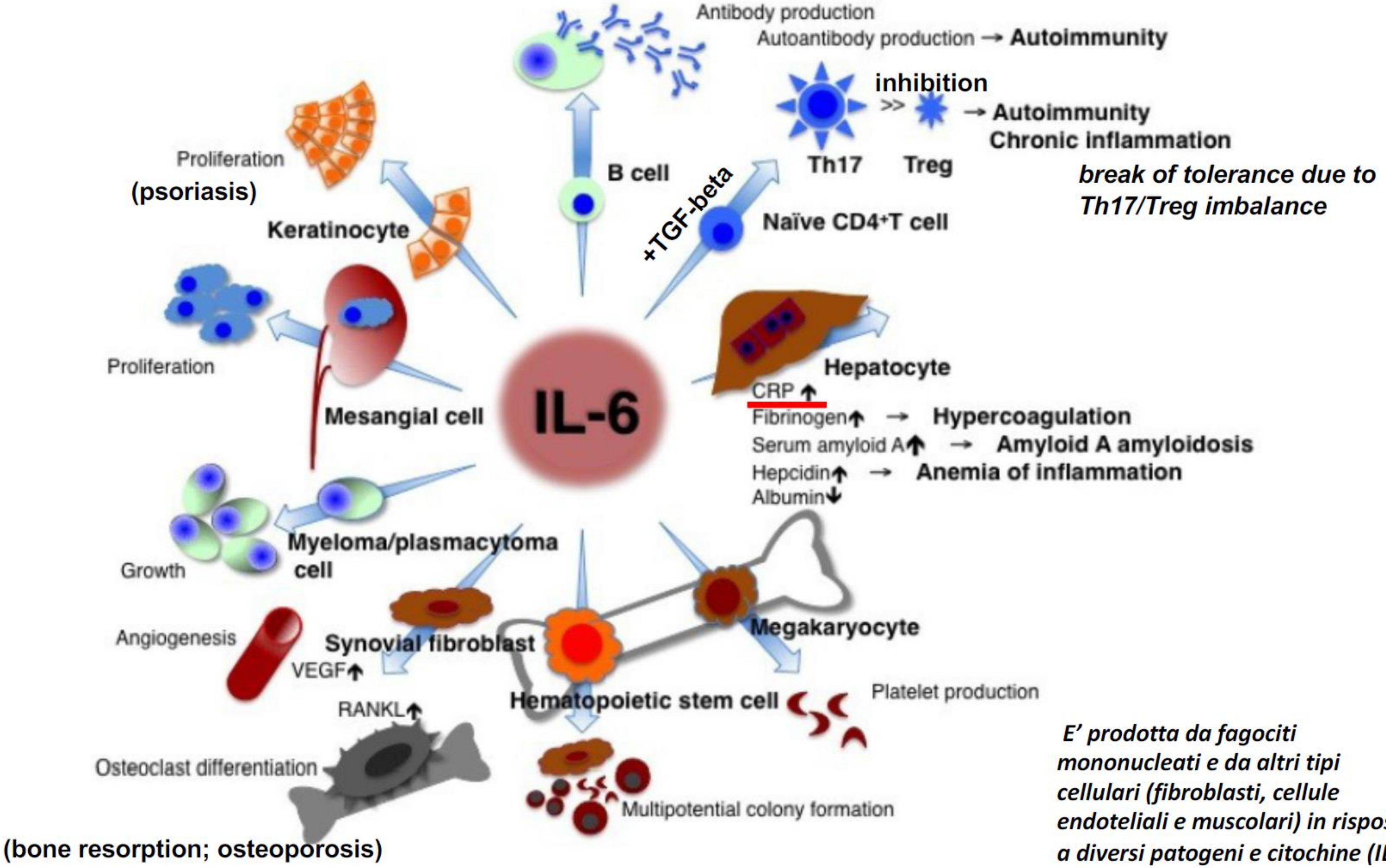
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T cells	Liver: synthesis of acute phase proteins B cells: proliferation of antibody-producing cells
Interleukin-15 (IL-15)	Macrophages, others	NK cells: proliferation T cells: proliferation
Interleukin-18 (IL-18)	Macrophages	NK cells and T cells: IFN-γ synthesis



IL-6 is a pleiotropic cytokine
(but its persistent and dysregulated production causes the onset and development of various autoimmune and chronic inflammatory diseases)



E' prodotta da fagociti mononucleati e da altri tipi cellulari (fibroblasti, cellule endoteliali e muscolari) in risposta a diversi patogeni e citochine (IL-1, TNF).

IL-6 nella clinica…

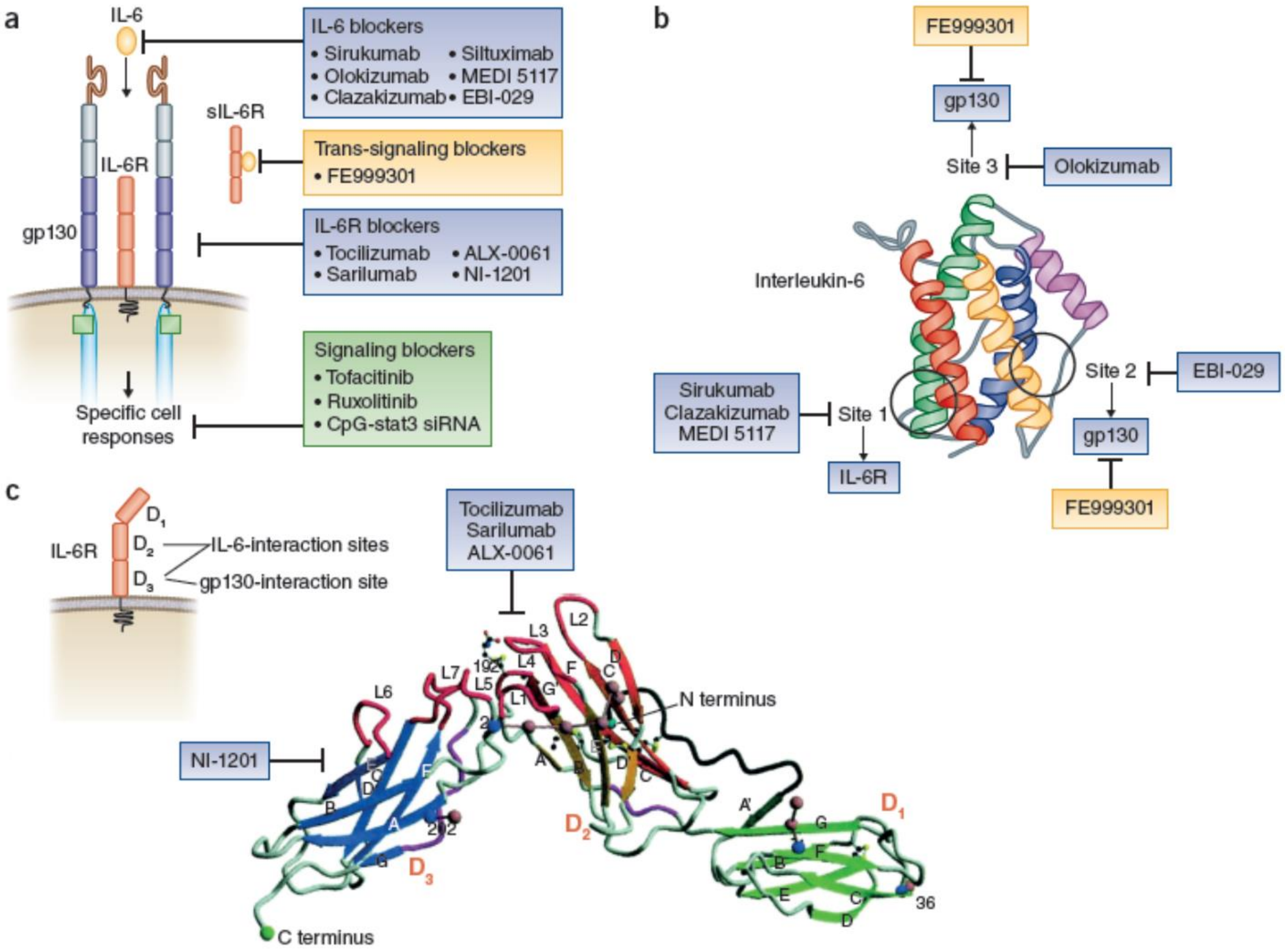
Table 2. Major Examples of Therapeutics for IL-6 Family Cytokines and Receptors

Targets	Therapeutics	Disease indications
IL-6	siltuximab[a] (anti-IL-6)	multicentric Castleman's disease
	clazakizumab (anti-IL-6)	antibody-mediated rejection of kidney graft, rheumatoid arthritis, psoriatic arthritis, etc.
	olokizumab (anti-IL-6)	rheumatoid arthritis
IL-11	oprelvekin[a] (recombinant IL-11)	severe thrombocytopenia
OSM	GSK2330811 (anti-OSM)	systemic sclerosis
CNTF	NT-501 (CNTF implant)	macular telangiectasia type 2
gp130	olamkicept (soluble gp130-Fc)	inflammatory bowel diseases
IL-6Rα	tocilizumab[a] (anti-IL-6Rα)	Castleman's disease, rheumatoid arthritis, systemic and polyarticular juvenile idiopathic arthritis, giant cell and Takayasu arteritis, cytokine release syndrome (chimera antigen-receptor T cell therapy)
	sarilumab[a] (anti-IL-6Rα)	rheumatoid arthritis
IL-11Rα	BMTP-11 (IL-11Rα-targeted proapoptotic agent)	cancer
Cytokine receptors	tofacitinib,[a] baricitinib,[a] etc. (JAK inhibitor)	rheumatoid arthritis, inflammatory bowel diseases, psoriasis, etc.

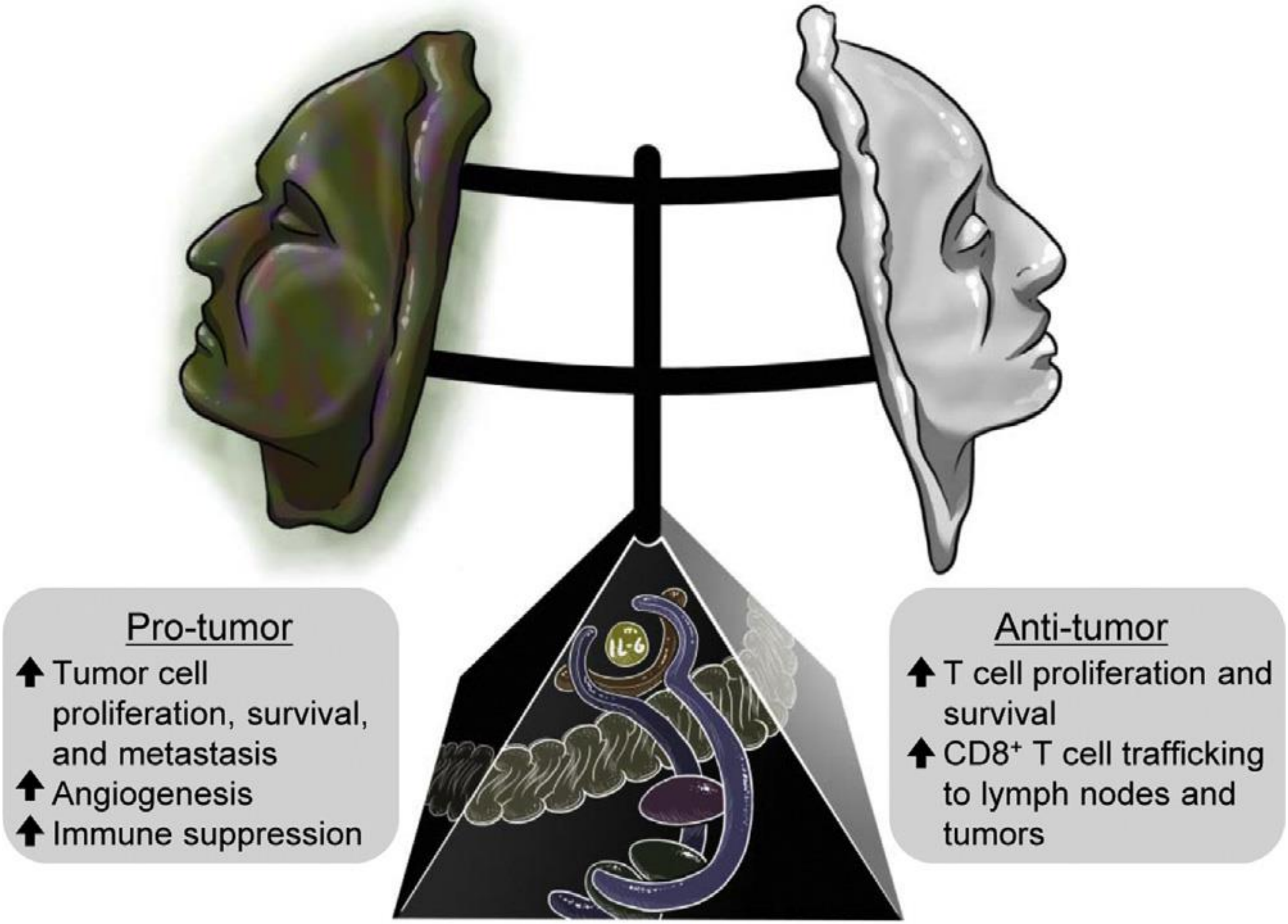
[a]Approved drugs.

Murakami M, Immunity 2019

Therapeutic targeting of IL-6 and its receptor

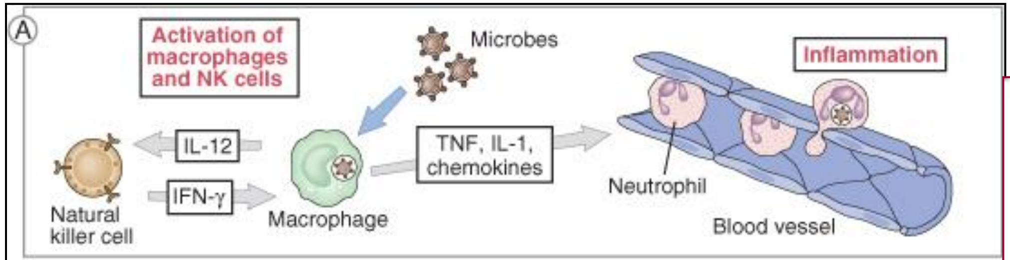


E nei tumori…



D.T. Fisher, Seminars in Immunology 2014

LE CITOCHINE INFIAMMATORIE



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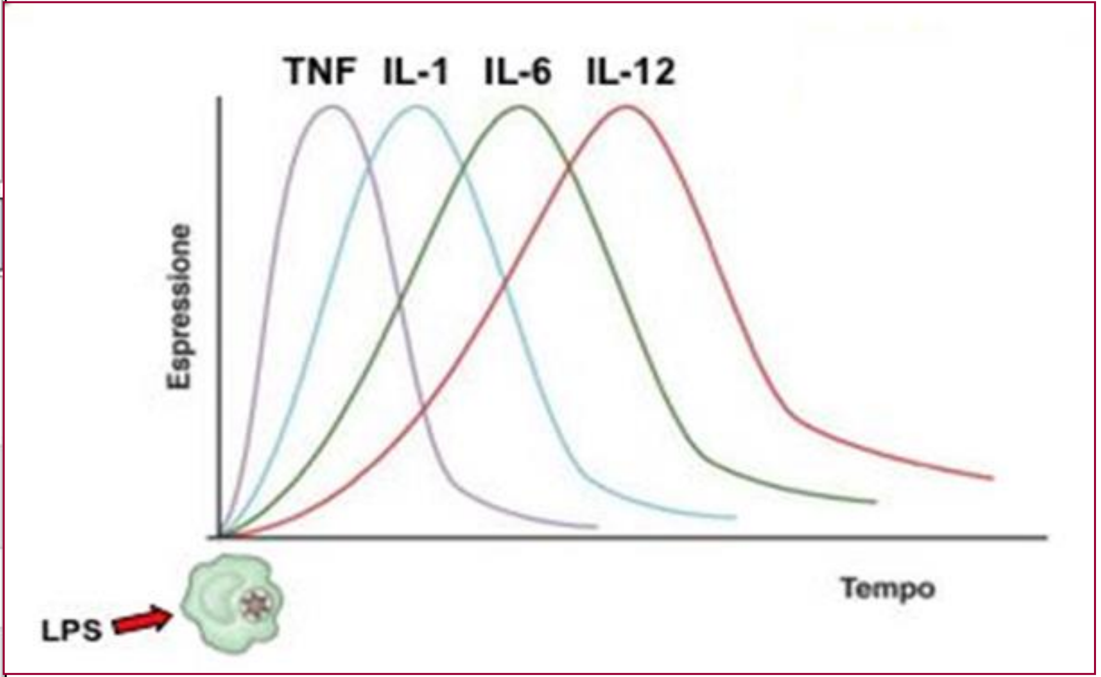


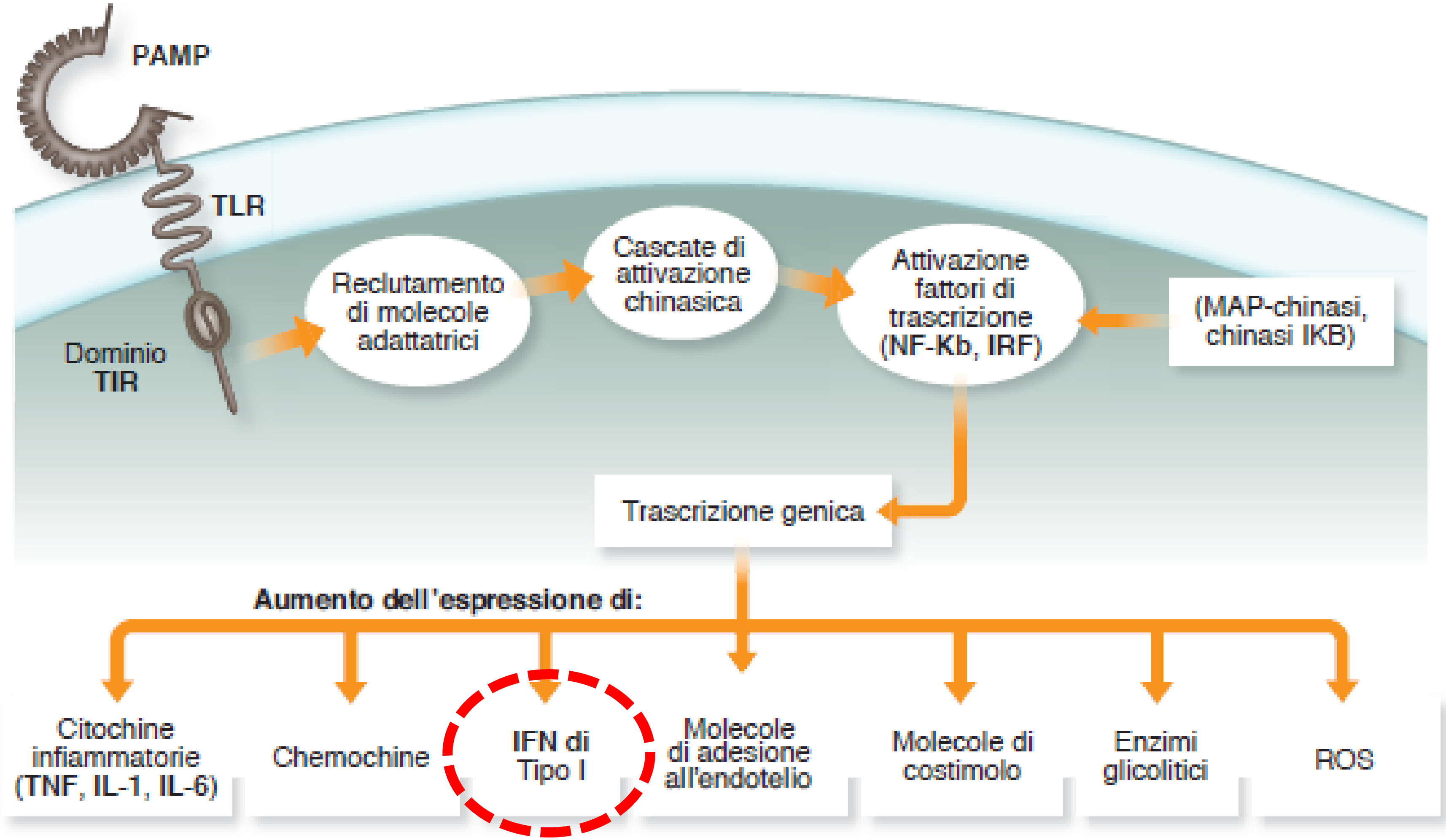


FIGURA 3.41.

Conseguenze biologiche dell'attivazione dei TLR. L'interazione dei PAMP con i diversi TLR induce nella cellula una serie di funzioni differenti, tutte volte a concorrere alla sua attivazione e allo svolgimento delle funzioni proprie del fagocita. In particolare, la cellula attivata produce una serie di citochine destinate ad attivare gli endoteli e di chemochine necessarie per il reclutamento cellulare nel sito di flogosi. La cellula potenzia anche l'espressione di molecole di costimolo (B7-1/2) che facilitano il compito di presentare l'antigene alle cellule dell'immunità acquisita. La cellula va anche incontro al cosiddetto *burst* ossidativo, che implica un incremento dell'attività glicolitica e della produzione di specie reattive dell'ossigeno (ROS), volte a favorire processi ATP-dipendenti quali la fagocitosi, nonché l'uccisione dei microbi fagocitati (radicali O_2, ossido nitrico),

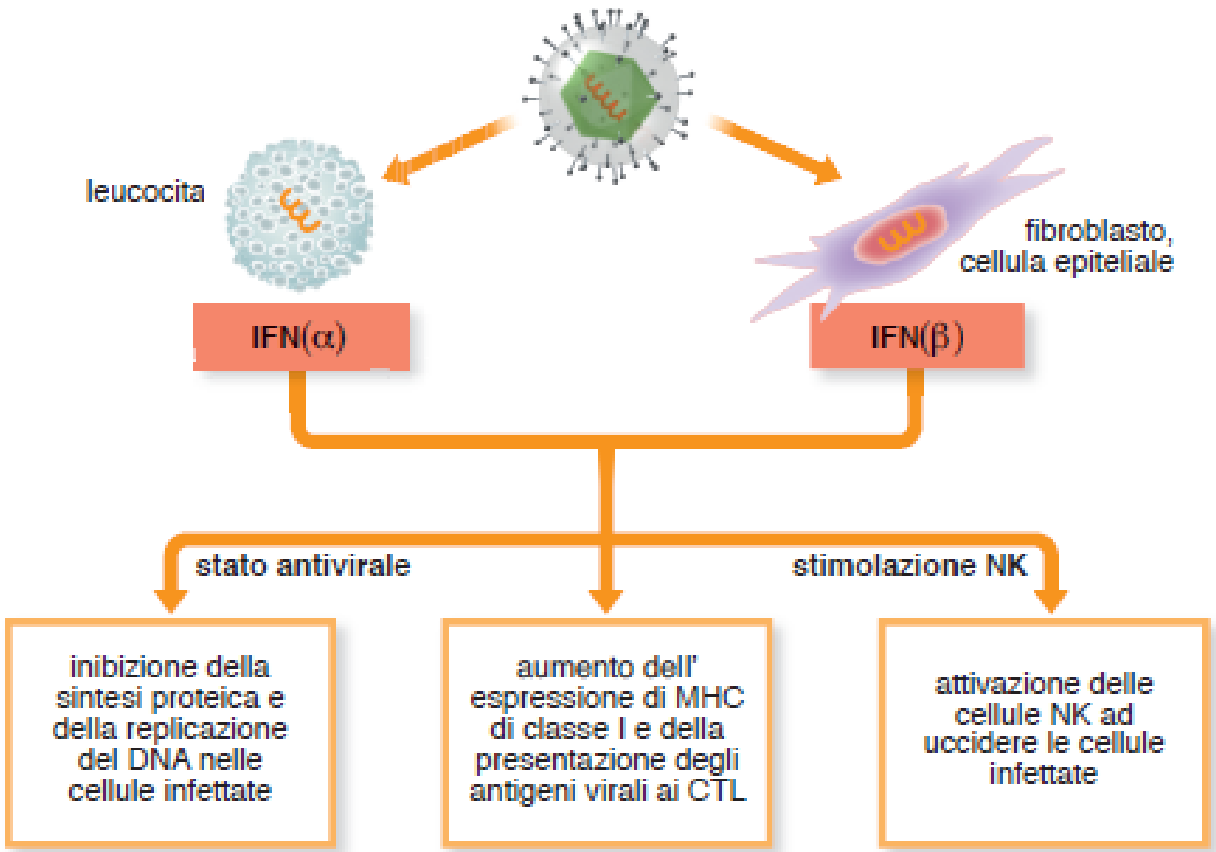
Amadori-Zanovello 2021

I mediatori solubili

Tre tipi di interferoni (IFN)

tipo	kD	specie	cellule produttrici	induttori principali
IFN-α (leucocitario)	18 - 20	> 20	monociti e molti altri tipi cellulari	virus
IFN-β (fibroblastico)	23	1	fibroblasti, epiteli	virus, citochine (TNF, IL-1)
IFN-γ (immune)	17	2	linfociti T, cellule NK	antigeni, mitogeni

Le azioni degli IFN di tipo I



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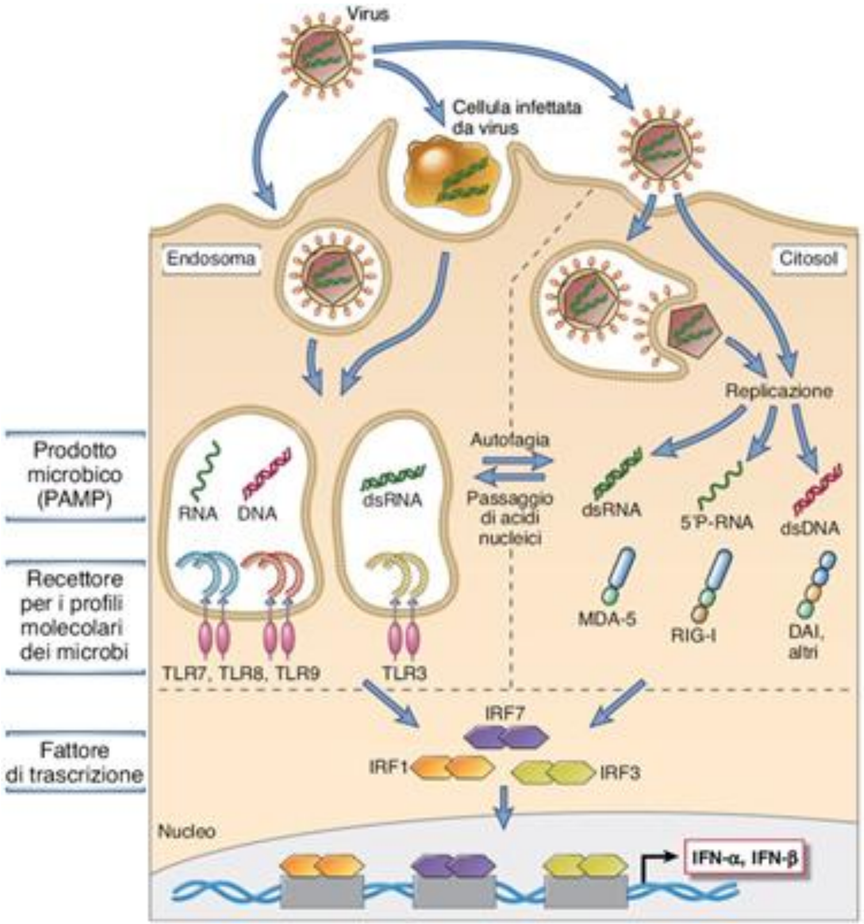
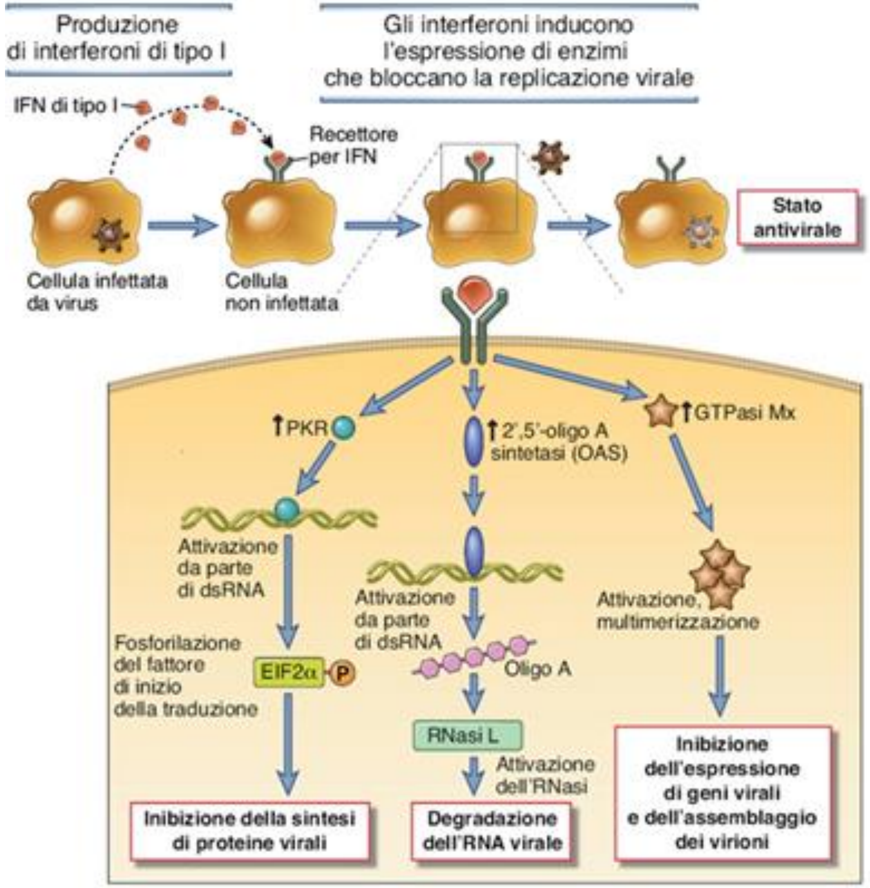
Le azioni degli IFN di tipo I





Attività biologiche degli IFN

Comuni ai tre tipi	Effetti	Preferenziali di IFN-γ	Effetti
attività anti-virale	previene l'infezione di nuove cellule		
attività anti-proliferativa	diminuisce la replicazione dei virus	attivazione di monociti e macrofagi	aumenta le funzioni fagocitiche e microbicide
induzione di MHC di classe I	rende le cellule infettate più "visibili" ai linfociti T citotossici	induzione di molecole MHC di classe II	aumenta la presentazione dell'antigene da parte delle Antigen-Presenting Cells (APC)
attivazione di cellule NK	aumenta l'uccisione delle cellule infettate	diminuzione della produzione di citochine di tipo TH2	favorisce la produzione di anticorpi opsonizzanti (IgG)
attivazione di linfociti T citotossici	aumenta l'uccisione delle cellule infettate	aumento della produzione di citochine di tipo TH1	aumenta la risposta TH1; attiva le cellule NK e i macrofagi

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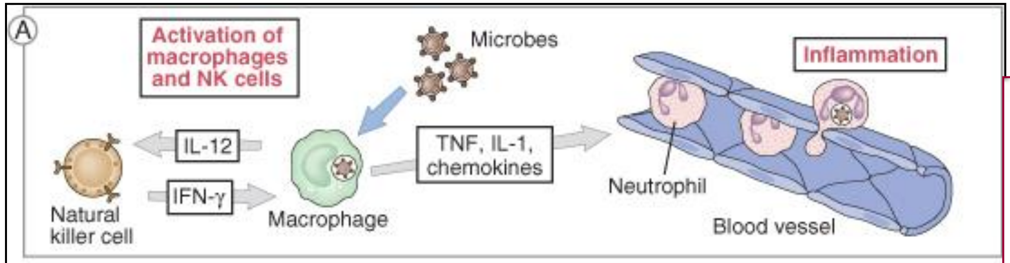
LE CITOCHINE INFIAMMATORIE



B

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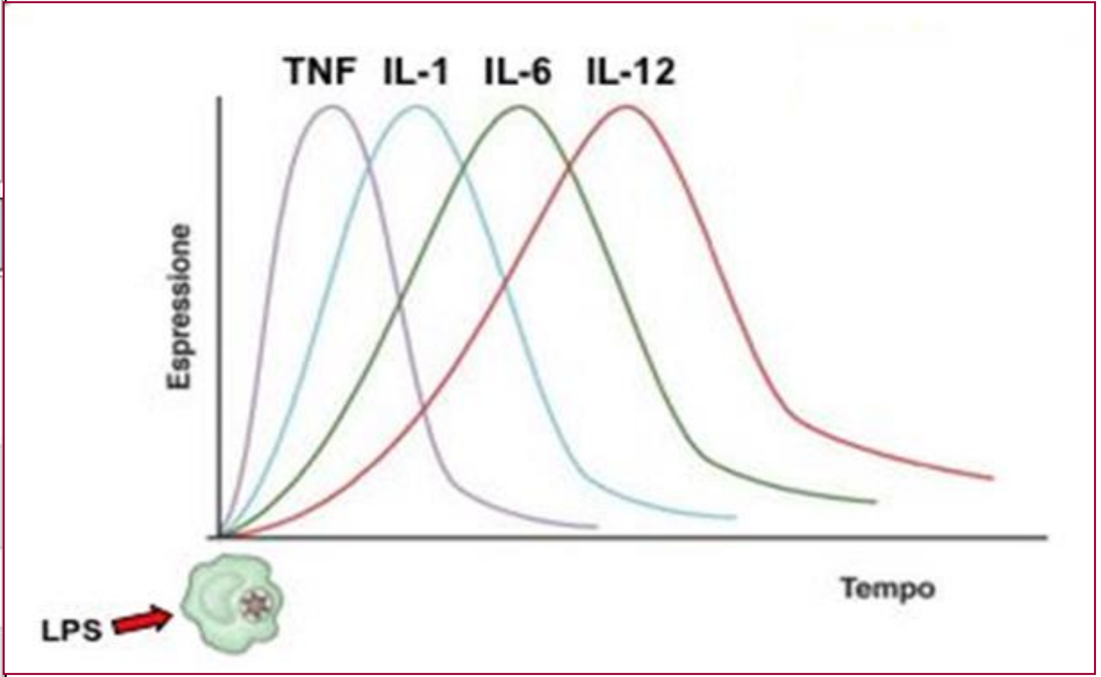
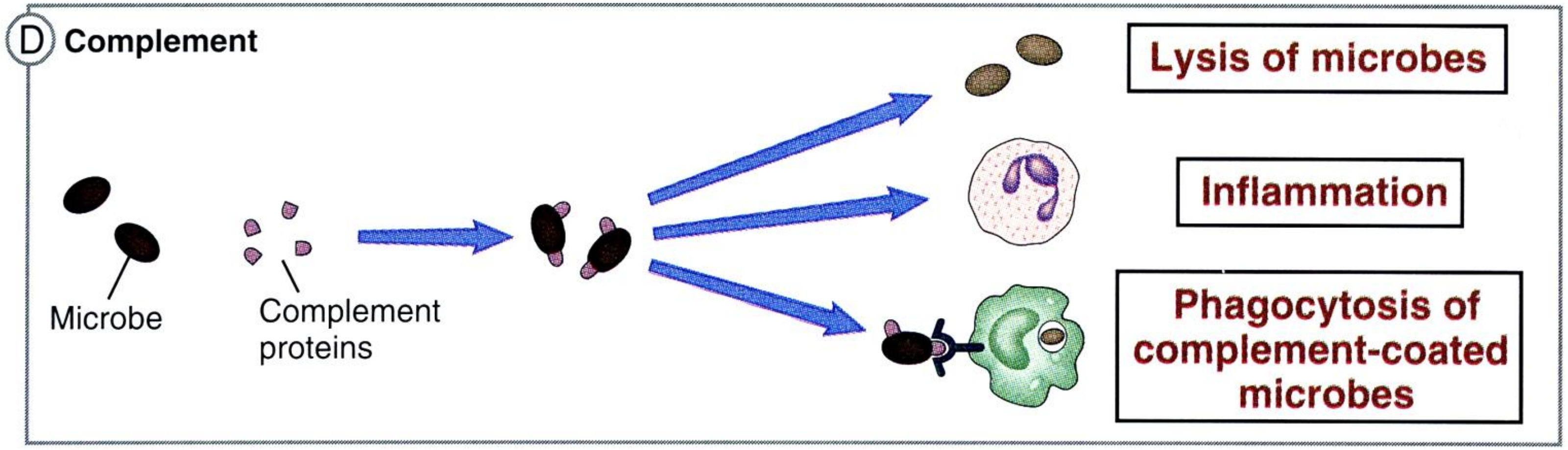


I MEDIATORI SOLUBILI DELL'IMMUNITA' INNATA

- LE CITOCHINE INFIAMMATORIE
- IL COMPLEMENTO
- LE COLLECTINE
- LA PROTEINA C-REATTIVA, LE PENTRAXINE
- I FATTORI DELLA COAGULAZIONE

I COMPONENTI SOLUBILI DELL'IMMUNITA' INNATA:

IL SISTEMA DEL COMPLEMENTO (C):
un sistema enzimatico del plasma



Alcuni frammenti del sistema del complemento interagiscono tra loro formando complessi funzionali che rimangono legati al patogeno: LISI DEL PATOGENO

Altri frammenti diffondono dal sito di attivazione: amplificazione della risposta immunitaria

Componenti solubili del sistema immunitario:
IL SISTEMA DEL COMPLEMENTO (C)

- **Il sistema del Complemento (C) è costituito da circa 30 proteine plasmatiche presenti in circolo in forma di zimogeni. Le proteine del C sono sintetizzate dal fegato e dalle cellule del sistema immunitario.**

- **Il sistema del C viene rapidamente attivato in risposta ad una infezione, e svolge un ruolo fondamentale nella difesa contro numerose infezioni.**

- **L'attivazione del C dipende da un meccanismo "a cascata" estremamente potente e finemente regolato in ogni passaggio.**

- **Le proteine del C hanno attività enzimatica: ogni componente, una volta attivato, catalizza il taglio proteolitico del componente successivo, determinando la formazione di due frammenti.**

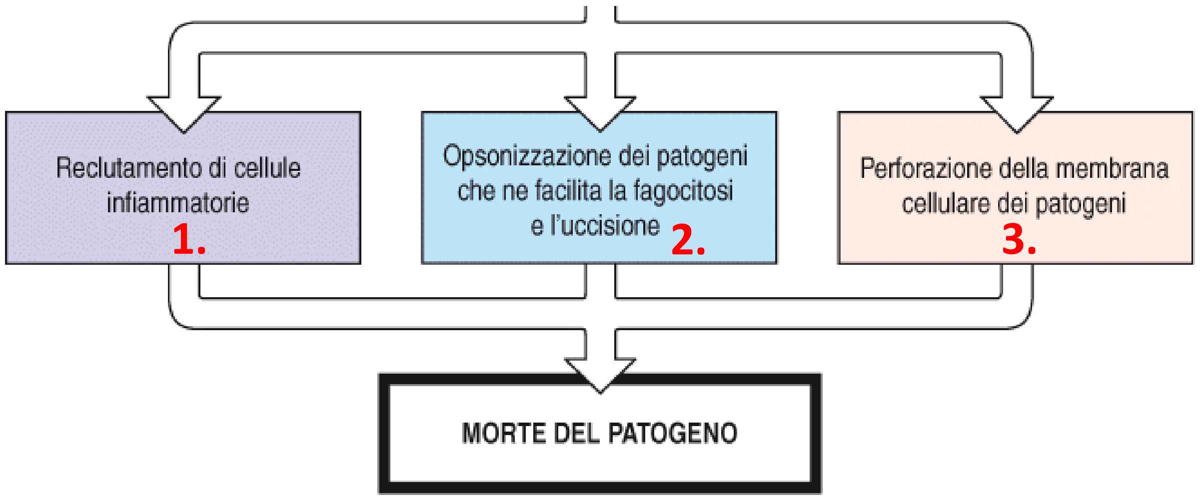
- **I diversi frammenti del C esplicano le funzioni biologiche.**

La cascata del complemento può essere attivata con tre modalità diverse:

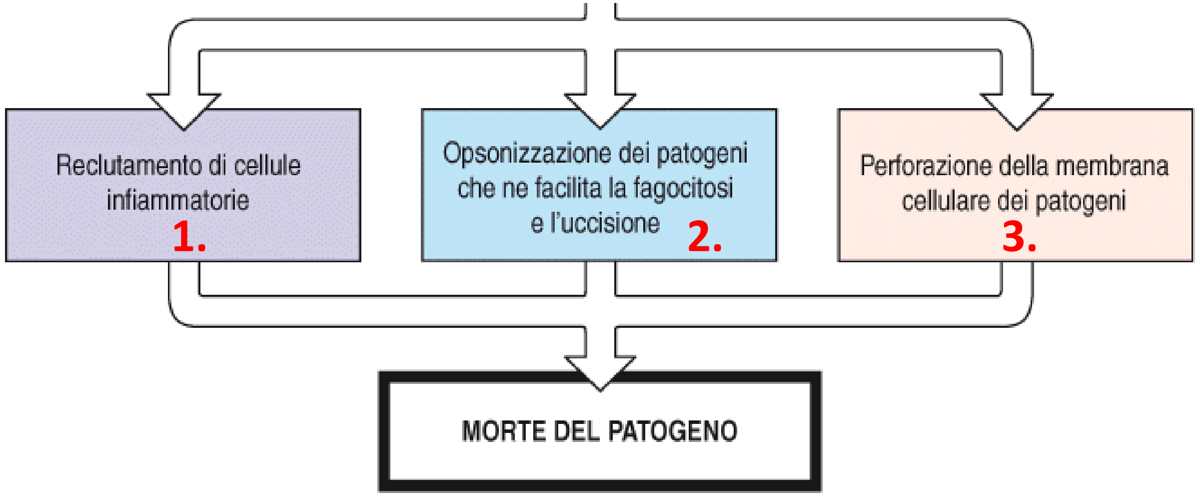
- VIA CLASSICA: l'attivazione avviene ad opera di alcune classi di anticorpi che hanno legato un antigene;

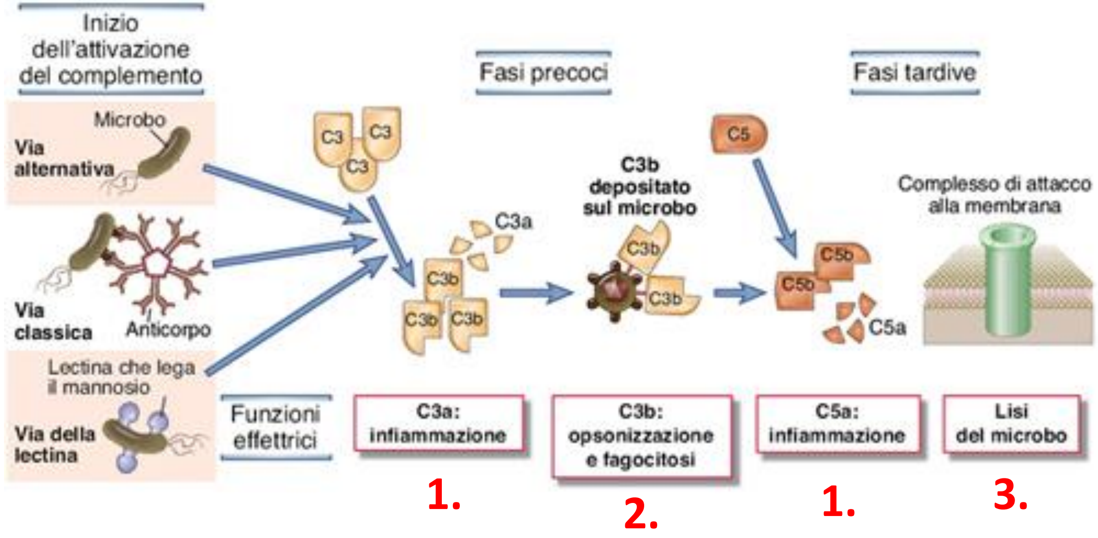
- VIA ALTERNATIVA: l'attivazione avviene ad opera di alcune componenti della superficie microbica, in assenza di anticorpi

- VIA DELLA LECTINA: è attivata da una lectina in seguito al suo legame a particolari carboidrati presenti sulla parete cellulare dei microbi (residui di mannosio).

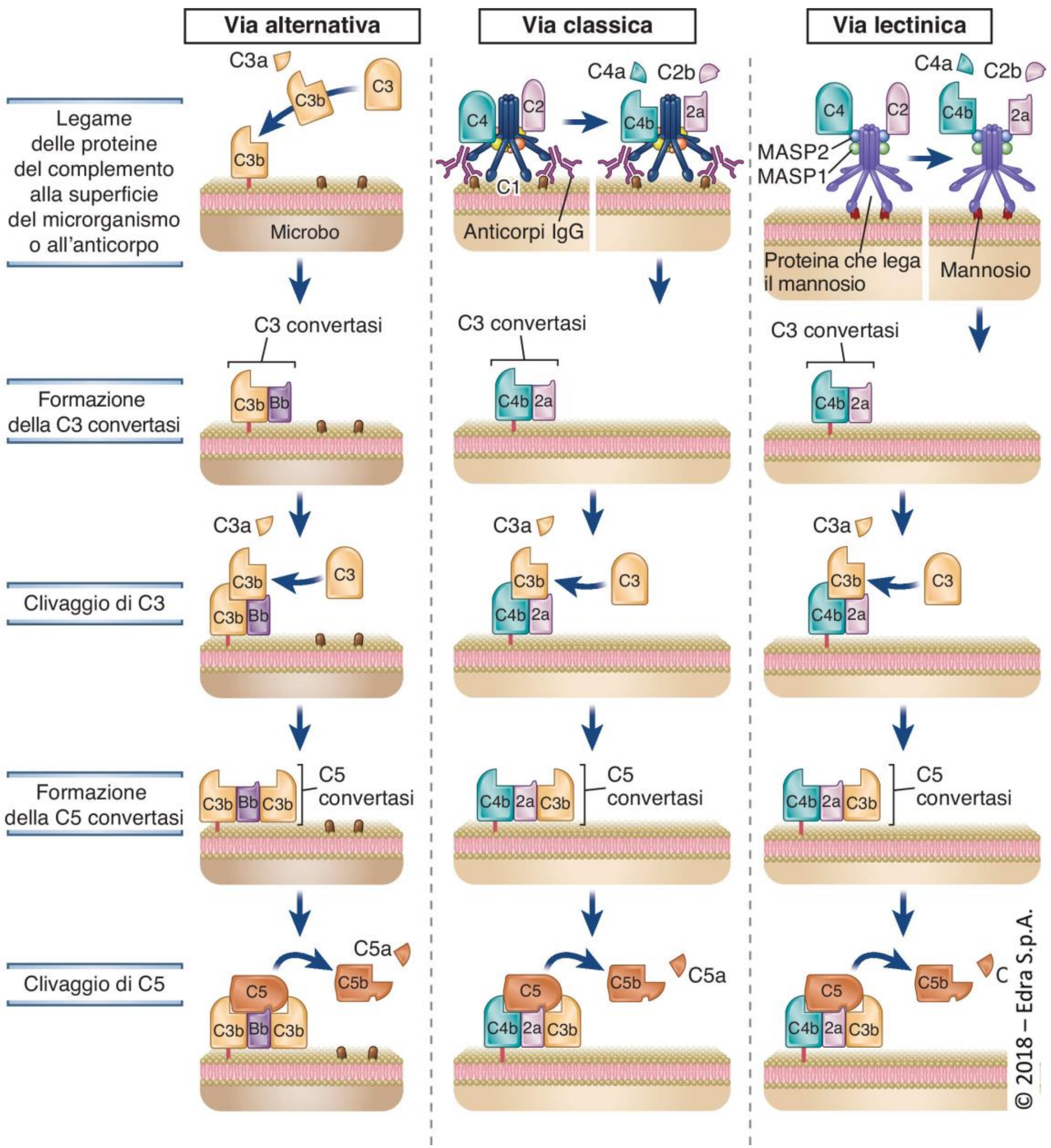


ATTIVITA' DEL COMPLEMENTO



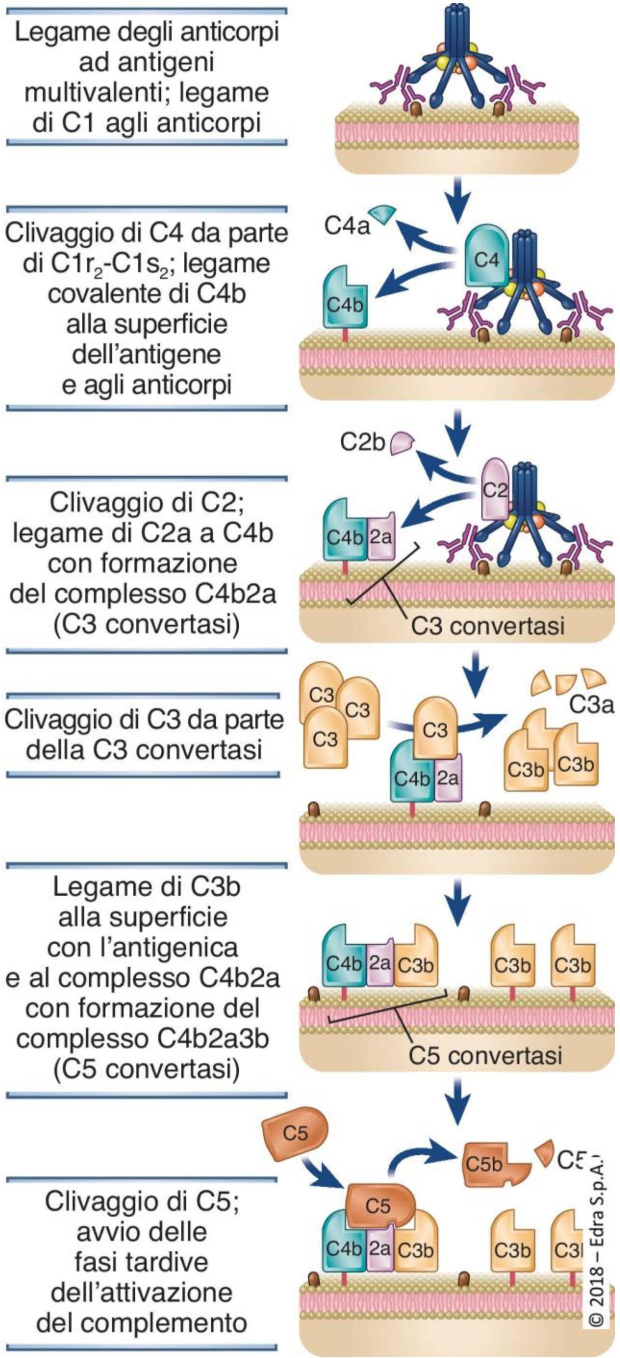


Componenti solubili del sistema immunitario:
LA CASCATA DEL COMPLEMENTO (C)

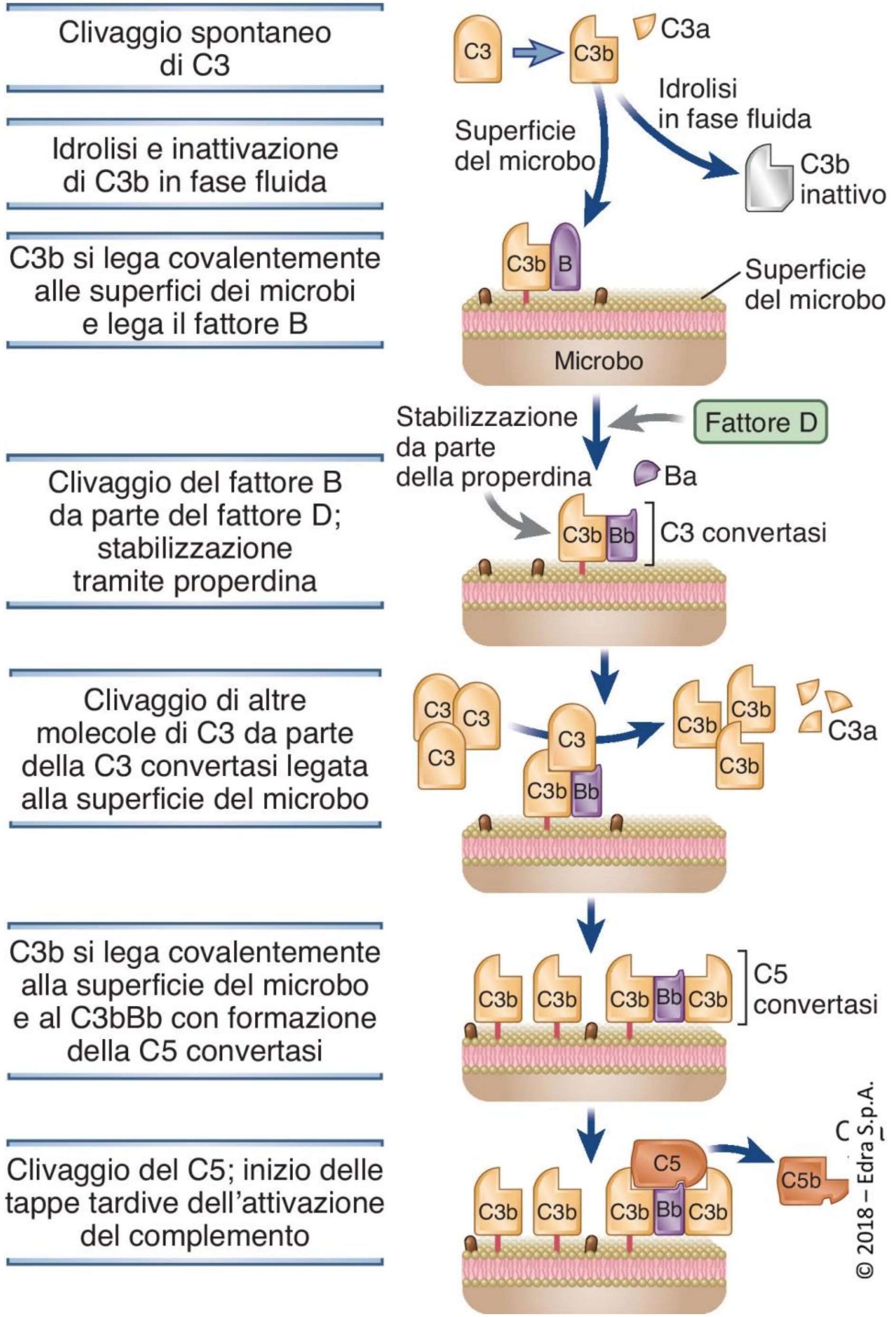


MASP: mannan-binding lectin-associated serine protease

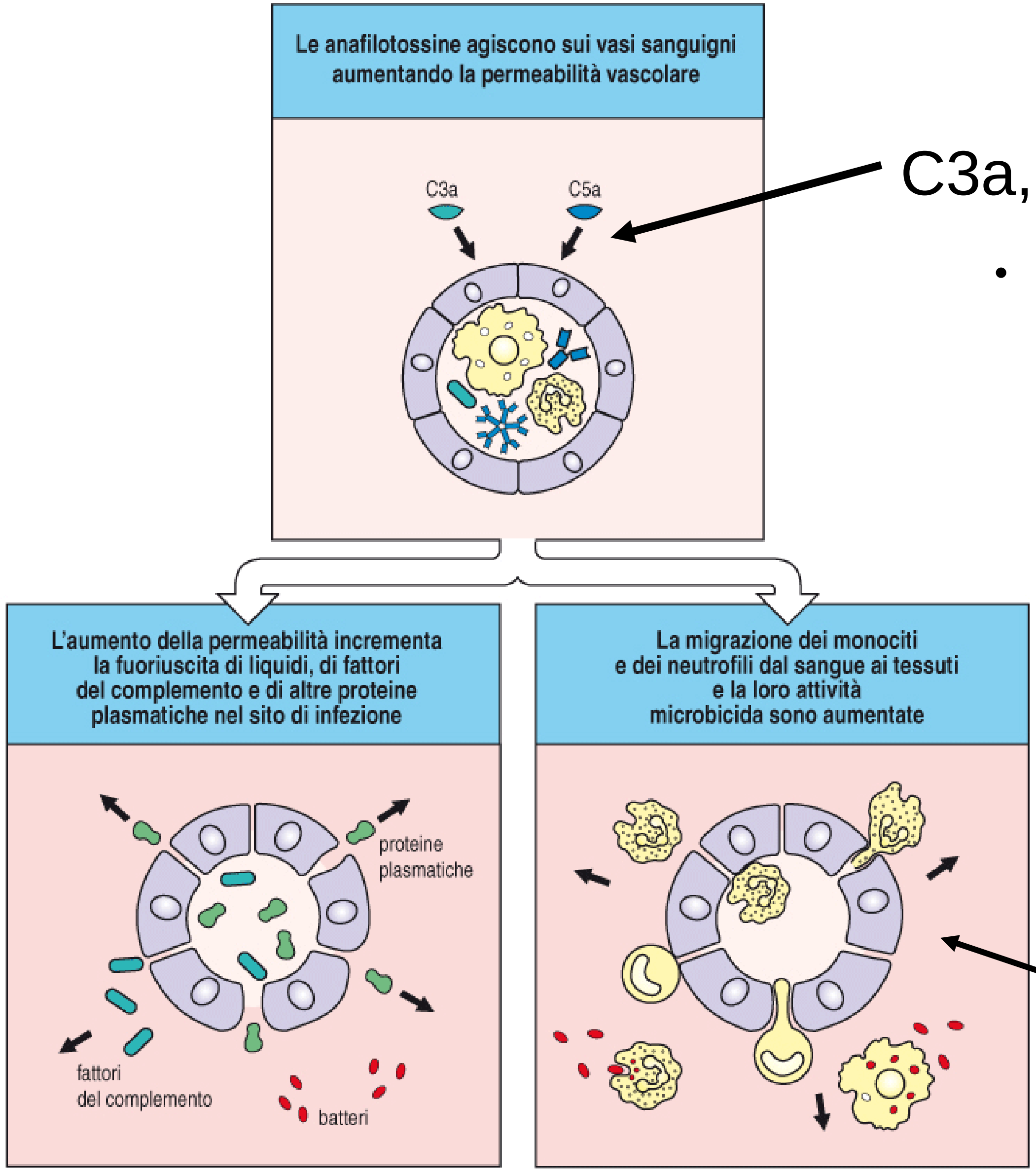
Via classica



Via alternativa



1. INDUZIONE DI REAZIONI INFIAMMATORIE LOCALI (da parte dei piccoli frammenti C3a e C5a)

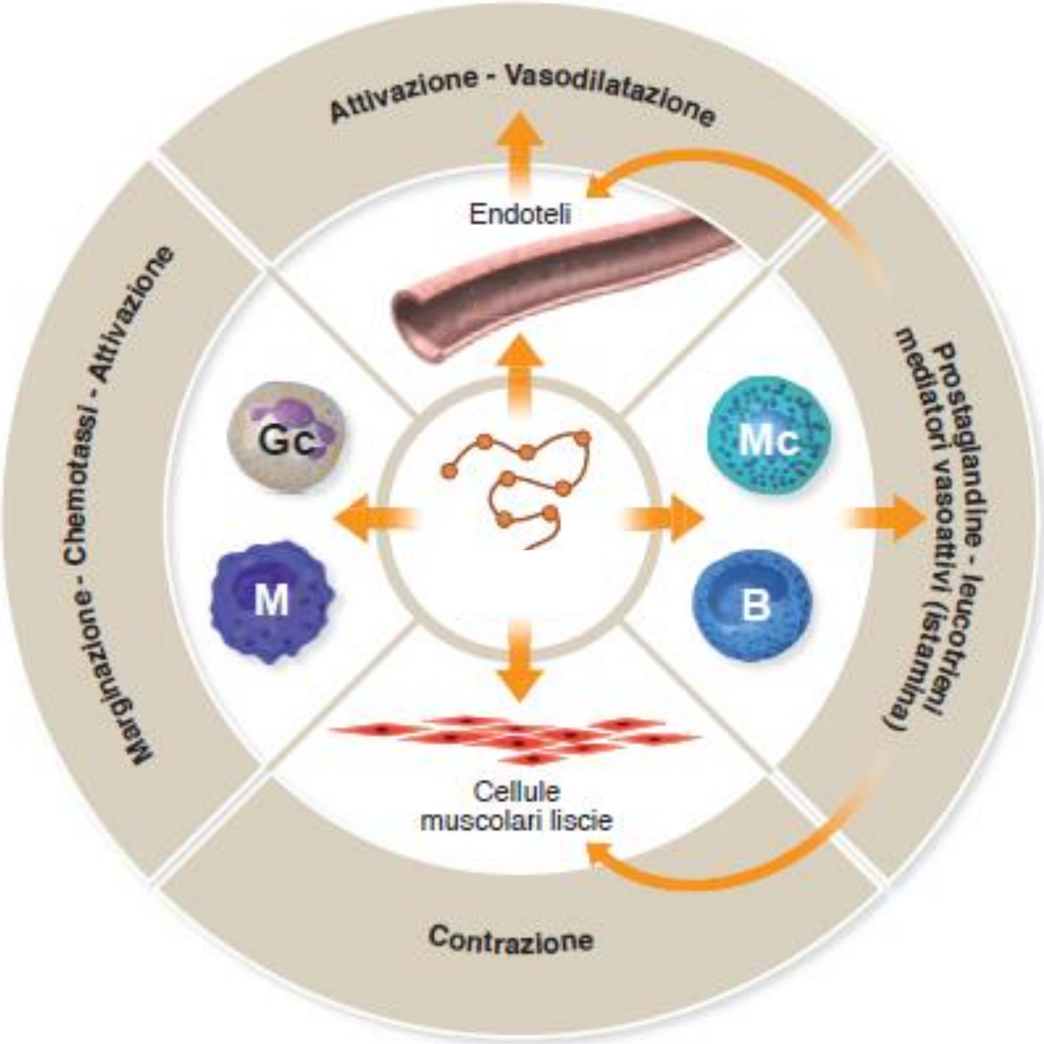


C3a, C5a (anafilotossine)

- Rilascio di istamina dai mastociti (vasodilatazione)

Migrazione di MONOCITI E NEUTROFILI nel sito di INFEZIONE (FAGOCITOSI!)

Le azioni delle anafilotossine



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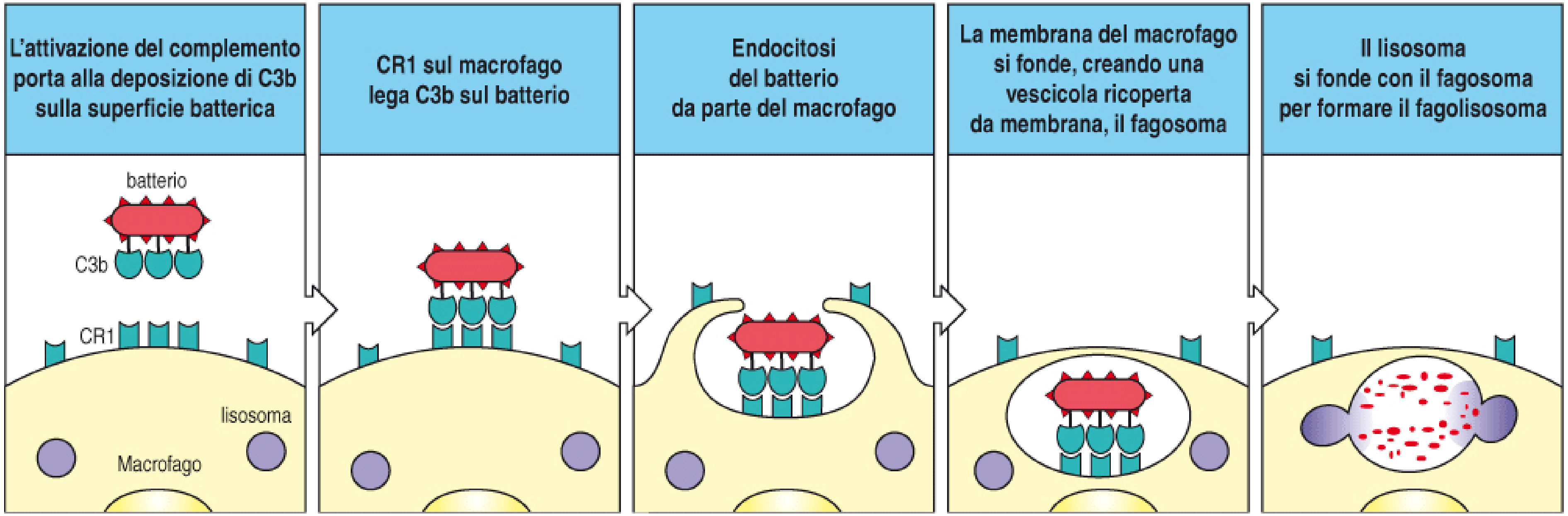
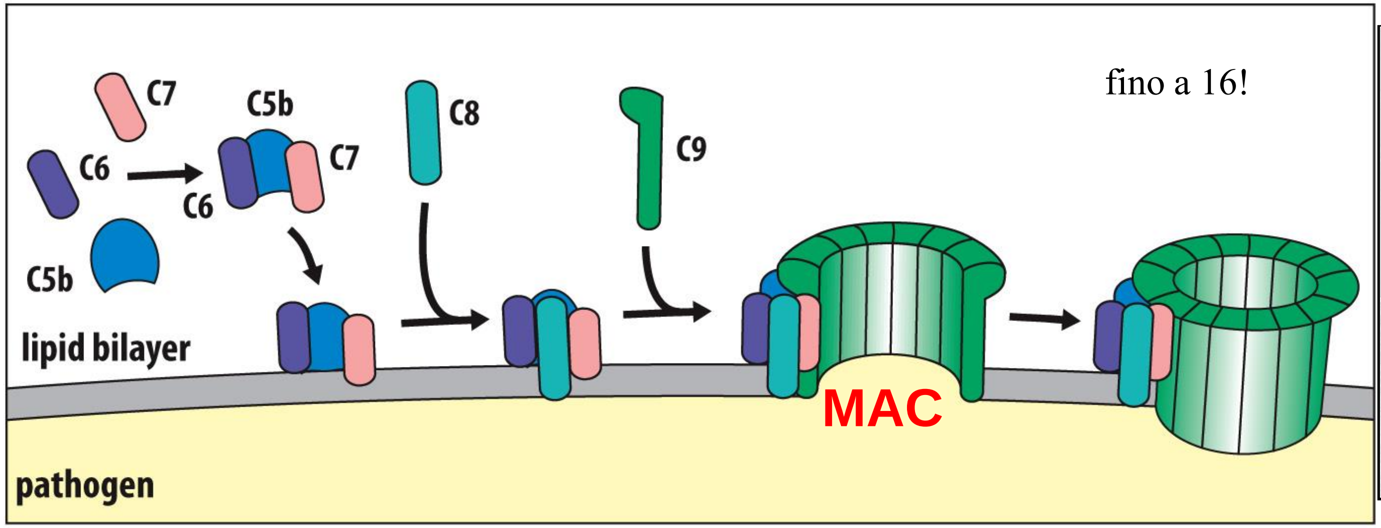
2. OPSONIZZAZIONE E FAGOCITOSI



I fagociti esprimono diversi recettori per il frammento C3b (CR1, CR3, CR4)

3. L’assemblaggio del complesso di attacco alla membrana da parte dei frammenti C5b-C9 forma un poro nel doppio strato lipidico ed è responsabile della lisi (MAC: Membrane Attack Complex)



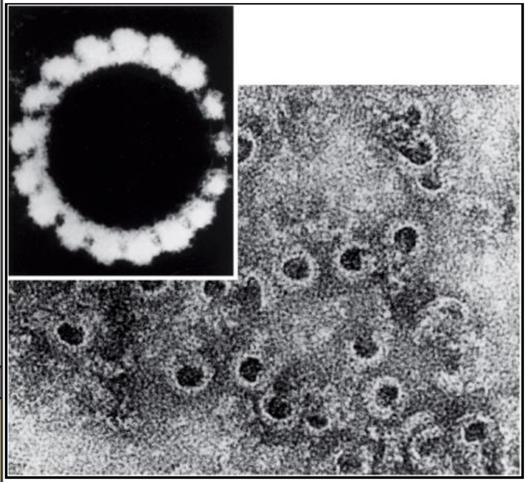


Figure 2.13 (part 1 of 2) The Immune System, 4th ed. (© Garland Science 2015)

FORMAZIONE DI PORI SULLA MEMBRANA DEL PATOGENO!

Figure 7-12a
Kuby IMMUNOLOGY, Sixth Edition
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Figure 7-12b
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Figure 7-12c
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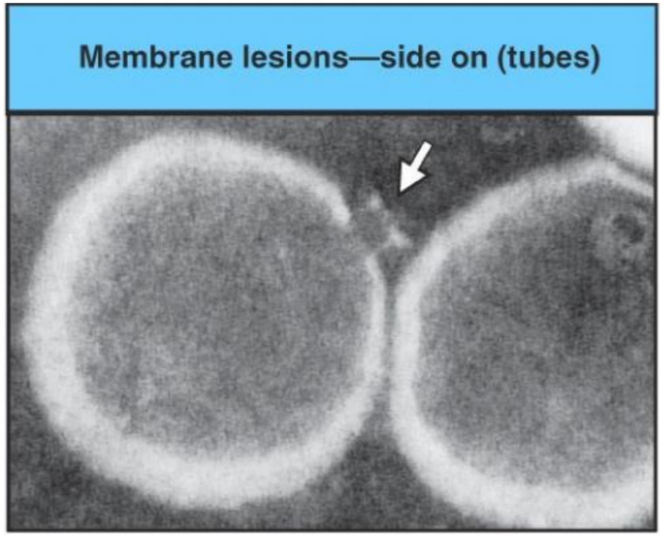
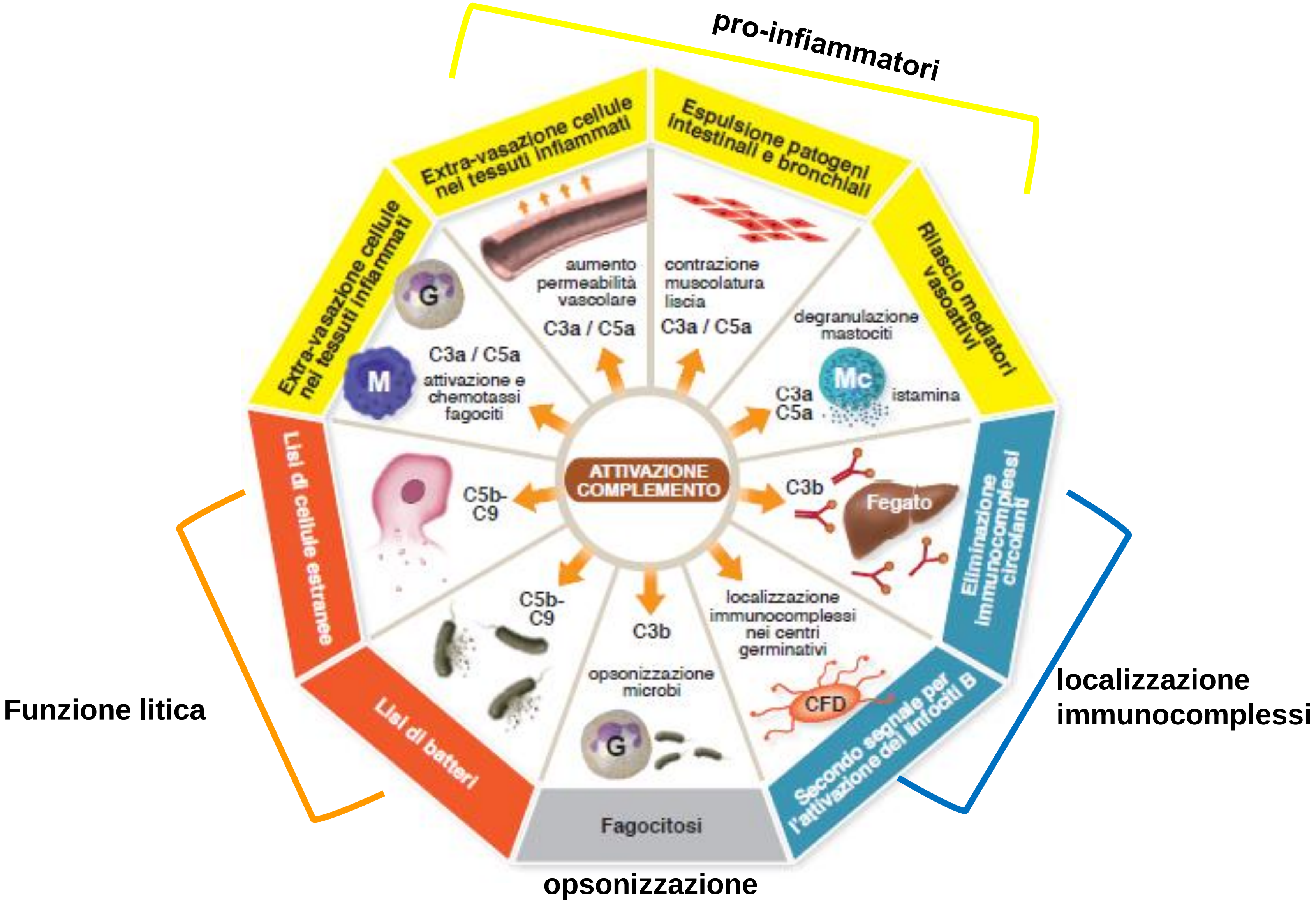


Gli effetti dell'attivazione del complemento



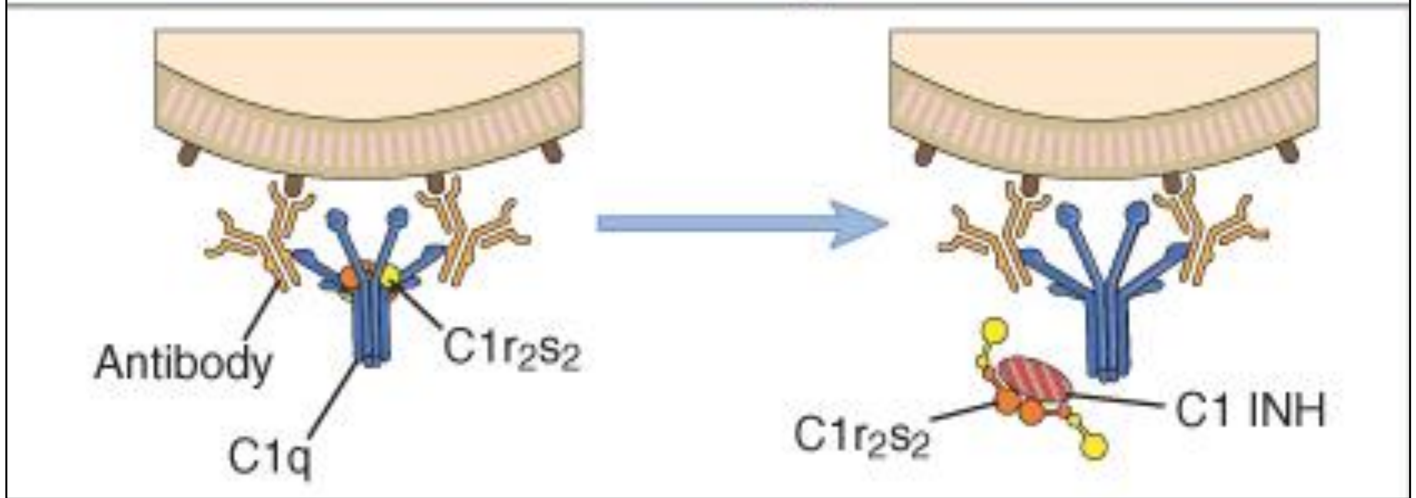
Amadori-Zanovello 2021

Proteine Regolatorie del Sistema del Complemento

Proteine di controllo della via classica e alternativa	
Nome (simbolo)	**Ruolo nella regolazione dell'attivazione del complemento**
Inibitore C1 (C1INH)	Si lega a C1r,C1s attivato, rimuovendolo da C1q
Fattore accelerante il decadimento (DAF)	Proteina di membrana che sposta Bb da C3b e C2b da C4b
CD59 (protectina)	Previene la formazione del complesso di attacco alla membrana su cellule allogeniche o autologhe. Molto espresso sulle membrane

C1q si lega agli anticorpi complessati con l'antigene, con conseguente attivazione di C1r2s2

C1 INH previene l'attivazione di C1r2s2



Deficienza di C1-inibitore :
edema angioneurotico ereditario o EDEMA di QUINKE

- episodi ricorrenti di edema a carico della cute e delle mucose
- dolori addominali associati a vomito e diarrea
- ostruzioni a carico delle vie respiratorie