# Zánět

MUNI | RECETOX

Mgr. Jan Kučera, Ph.D.
150663@mail.muni.cz

# Definice zánětu

**Souhrn reakcí na porušení integrity organismu**

- Ochrana proti infikování
- Lokalizace poškození
- Regenerace, zahojení

**Inzult** (patogenní faktor) vyvolávající zánětlivou reakci

- Biologický (mikroorganismy, parazité)
- Fyzikální (záření, termické vlivy)
- Chemický (toxiny, žíraviny)
- Metabolický (hypoxie, poruchy metabolismu)

# Rozdělení zánětu

## Dle ohraničení

- lokální
- systémový

## Dle dynamiky

- akutní
- chronický

## Dle efektu

- obranný
- autoagresivní (deregulovaný, delokalizovaný)

# Symptomy zánětu

## Makroskopická úroveň

- **calor** – vyšší teplota
- **rubor** – zarudnutí, erytém
- **tumor** – zduření, otok
- **dolor** – bolest

*(Celsus, De Medicina, 1. století)*

- **functio laesa** – porucha funkce *(R. Virchow, 19. století)*

## Mikroskopická úroveň

- alterace – změny v tkáni
- exsudace – zánětlivý exsudát (tekutina a proteiny), buňky (infiltrát)
- proliferace - tvorba granulační a vazivové tkáně (jizva)

exsudát:
serózní
nehnisavý
hnisavý
fibrinózní
gangrenózní

http://penelope.uchicago.edu/Thayer/E/Roman/Texts/Celsus/home.html

# Průběh zánětu

**Produkty buněk a traumatizovaných tkání vedou k:**

- Zvýšení permeability cév (při poranění krátká vazokonstrikce), prostup plazmatické tekutiny do extravaskulárního prostoru
- Zvýšení přilnavosti endotelií, exprese adhezivních molekul, usnadňující migraci lymfocytů
- Změny v regulaci teploty
- Ovlivnění nervových zakončení

Souhra složek nespecifické (vrozené) a specifické imunity, v závislosti na délce trvání zánětu a intenzitě

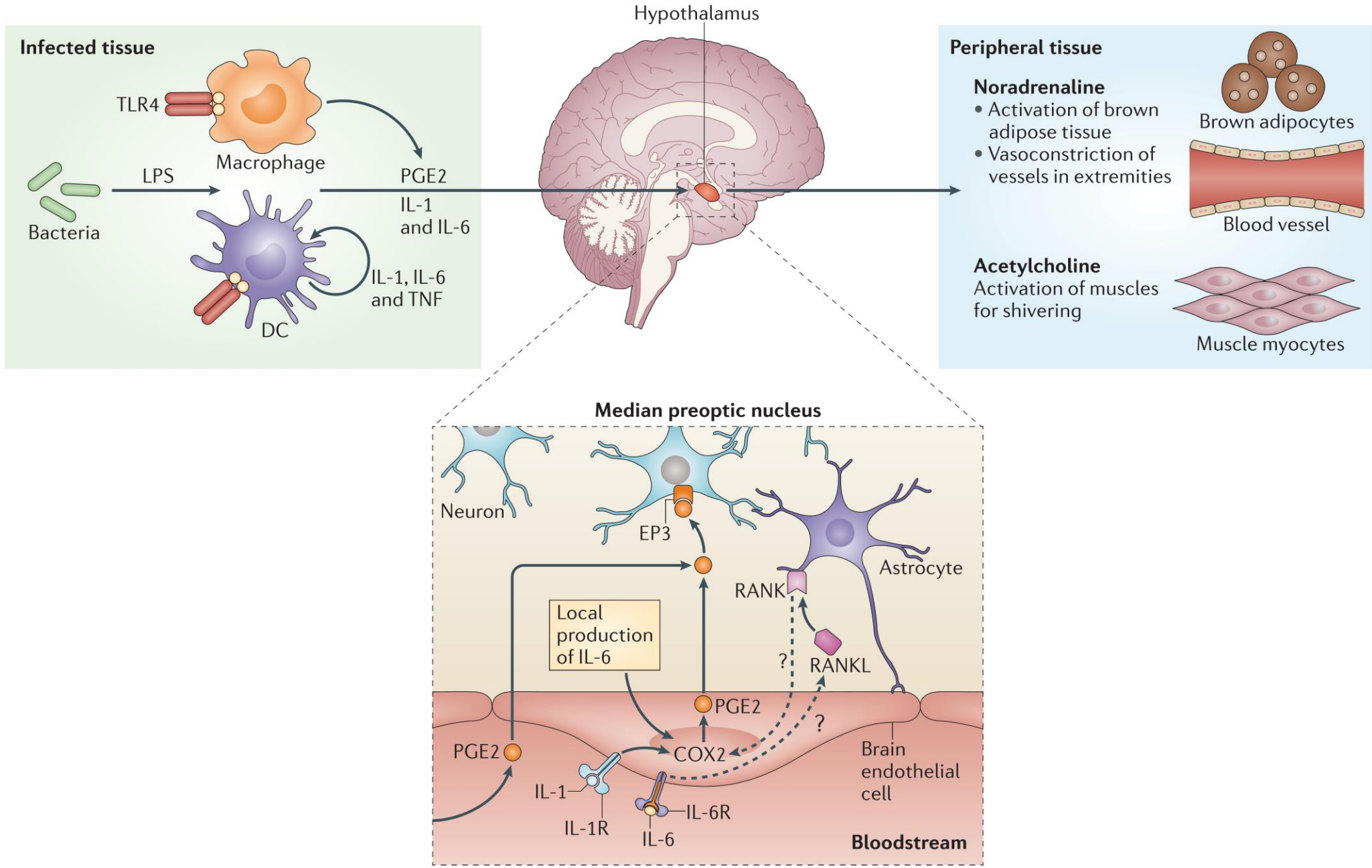
# Horečka

## Zvýšení tělesné teploty v klidu účinkem patogenního podnětu

- Infekční agens, trauma, inkompatibilní transfuze
- Zvýšená produkce prozánětlivých cytokinů (**IL-1, TNF, IL-6**), prostaglandiny (pyrogeny)
- Působení na hypotalamické termoregulační centrum

## Účinky (mediátorů) horečky na funkce organismu

- Nervový systém (bolest, únava, spavost)
- Kardiovaskulární systém (zvýšený tep, +1 °C => +10 tepů za minutu)
- Metabolismu (urychlení látkové přeměny, 40 °C => 50% navíc)
- Respirační systém (zrychlené dýchání)
- Trávicí systém (snížená činnost, porušena resorpce živin)
- Ledviny (snížená tvorba moči, bílkovina v moči)




https://www.semanticscholar.org/paper/Fever-and-the-thermal-regulation-of-immunity%3A-the-Evans-Repasky/1f6af26441b91283fa996849daba93b073c3d200

# Systémy realizující zánětovou odpověď

- Leukocyty
- Endotel
- Destičky
- Plazmatický koagulační systém
- Komplement
- Proteiny akutní fáze

# Vrozená imunita

## ne až tak úplně nespecifická… rozeznávání:

- **Pathogen-associated molecular patterns (PAMPs)**
  - pocházejí z mikroorganismu, evolučně konzervované molekuly typické pro patogeny
  - bakteriální sacharidy (lipopolysacharidy, také LPS, manóza), nukleové kyseliny (bakteriální nebo virální DNA nebo RNA), bakteriální peptidy (flagelin), peptidoglykany a lipoteichoická kyselina (gram pozitivní bakterie), N-formylmethionin, lipoproteiny a glukany, chitin

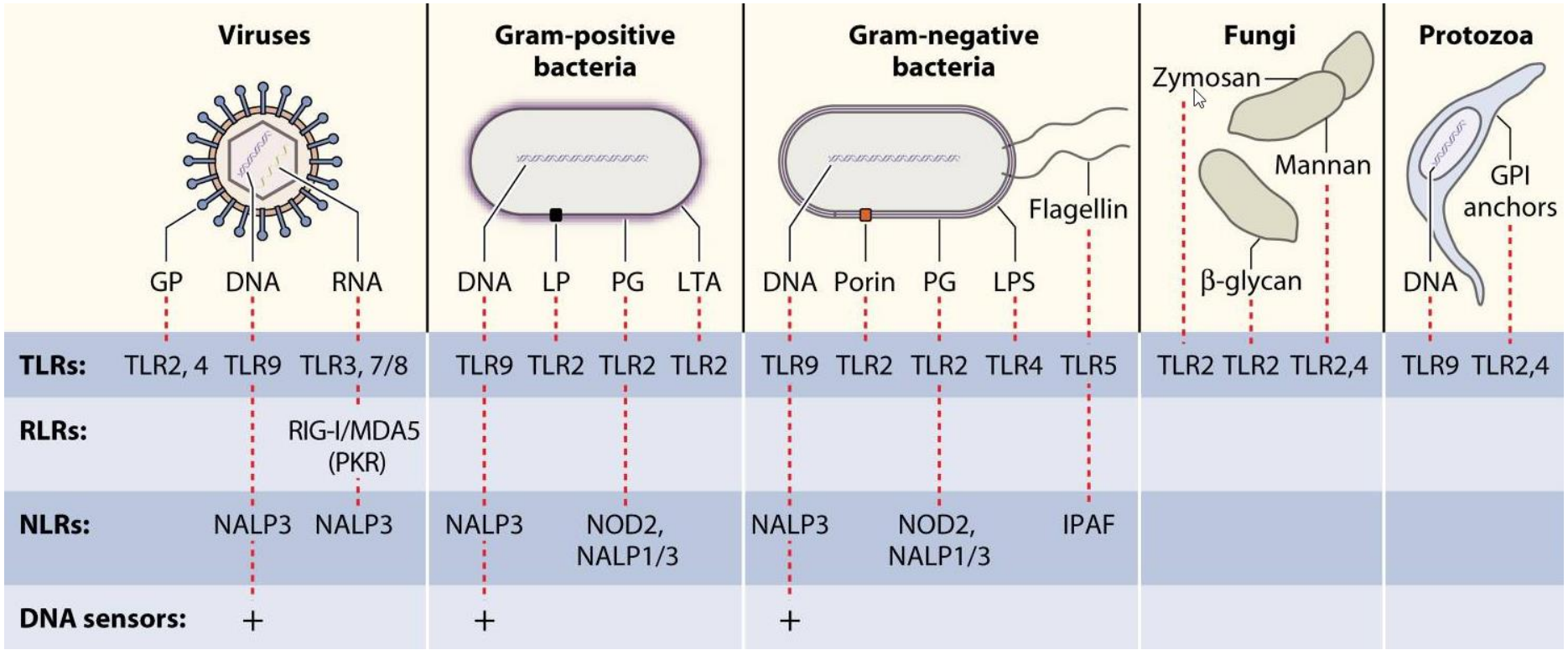
- **Damage (danger)-associated molecular patterns (DAMPs)**
  - pocházejí ze stresovaných nebo poškozených buněk hostitele, záleží často na kontextu
  - HSPs, HMBG1, hyaluronan, ATP, adenosin, kyselina močová, heparin sulfát, DNA, RNA, TNF-α, IL-1β, IFNα

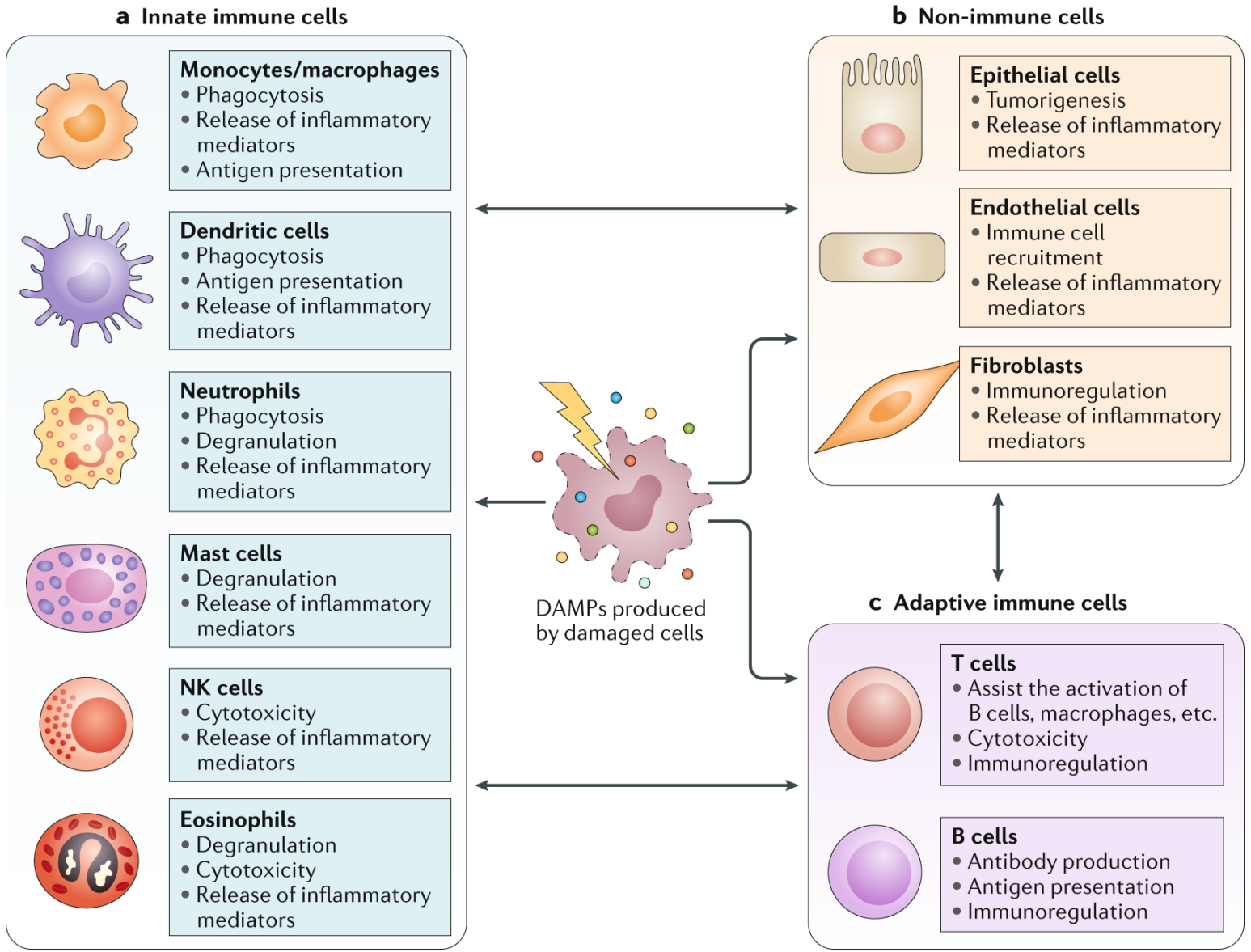
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3443751/

## PAMPs a DAMPs jsou rozpoznávány prostřednictvím:

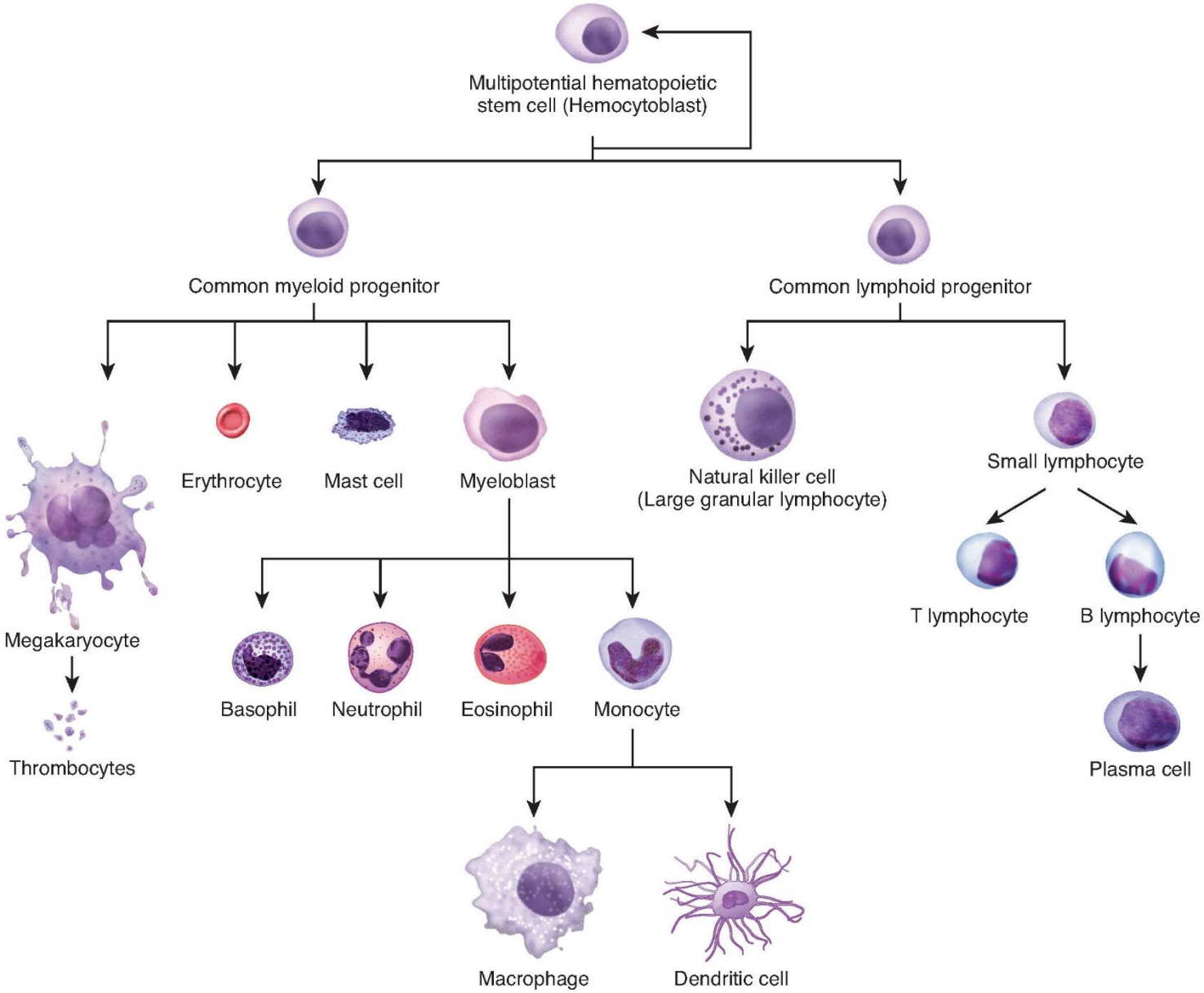
- **Pattern recognition receptory (PRRs)**
  - především na buňkách prezentujících antigen (ale i mimo buňky imunitního systému)
  - membránové Toll-like receptory (TLRs)
  - membránové C-type lectin receptory
  - cytoplazmatické retinoid acid-inducible gene I (RIG-I)-like receptory (RLRs)
  - cytoplazmatické nucleotide-binding oligomerization domain (NOD)-like receptory (NLRs)

- Po rozpoznání a navázání na receptor dochází k **aktivaci buněk** a **expresi molekul modulujících zánět** (cytokiny, chemokiny, adhezivní molekuly)
  - rychlá, relativně nespecifická reakce (minuty), bez imunologické paměti

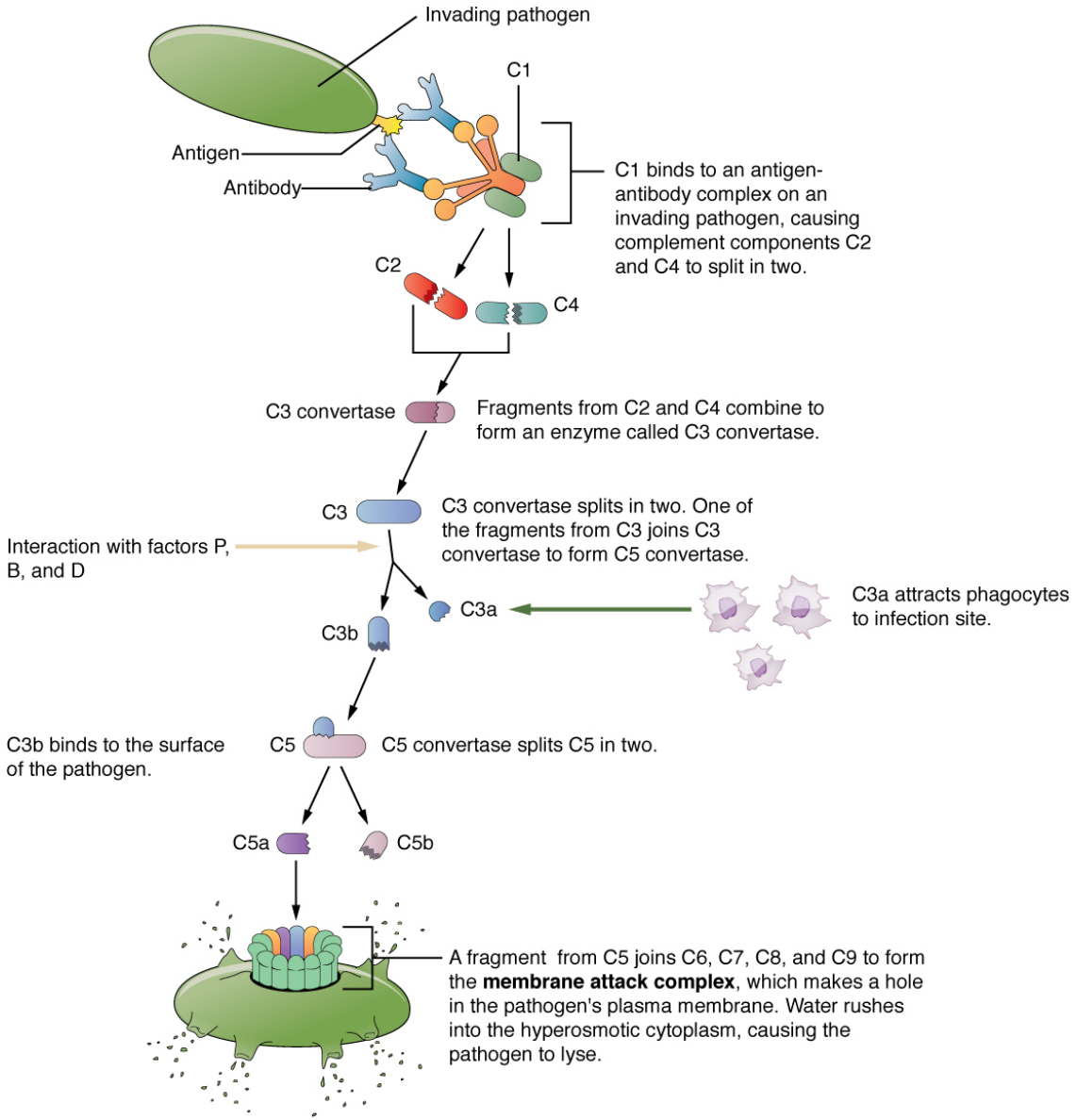




# Leukocyty

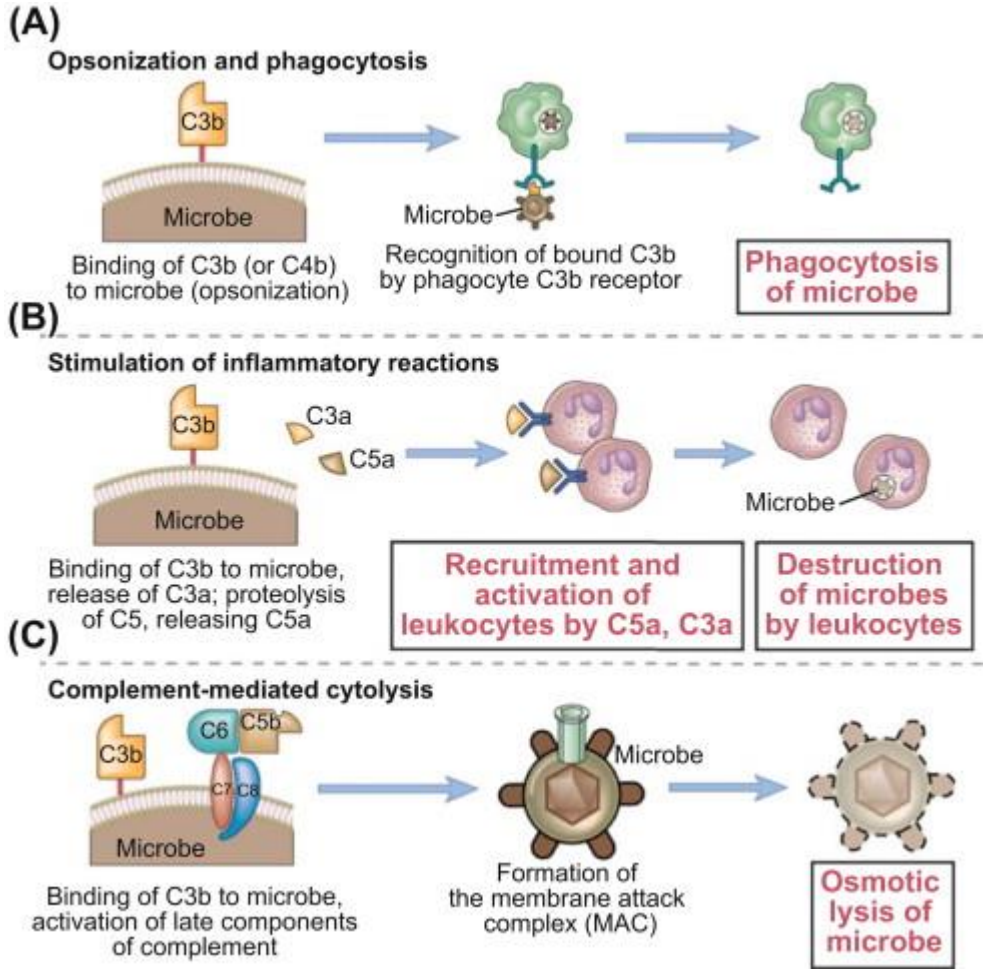

Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Plasma cell
Macrophage
Dendritic cell

# Komplementový systém

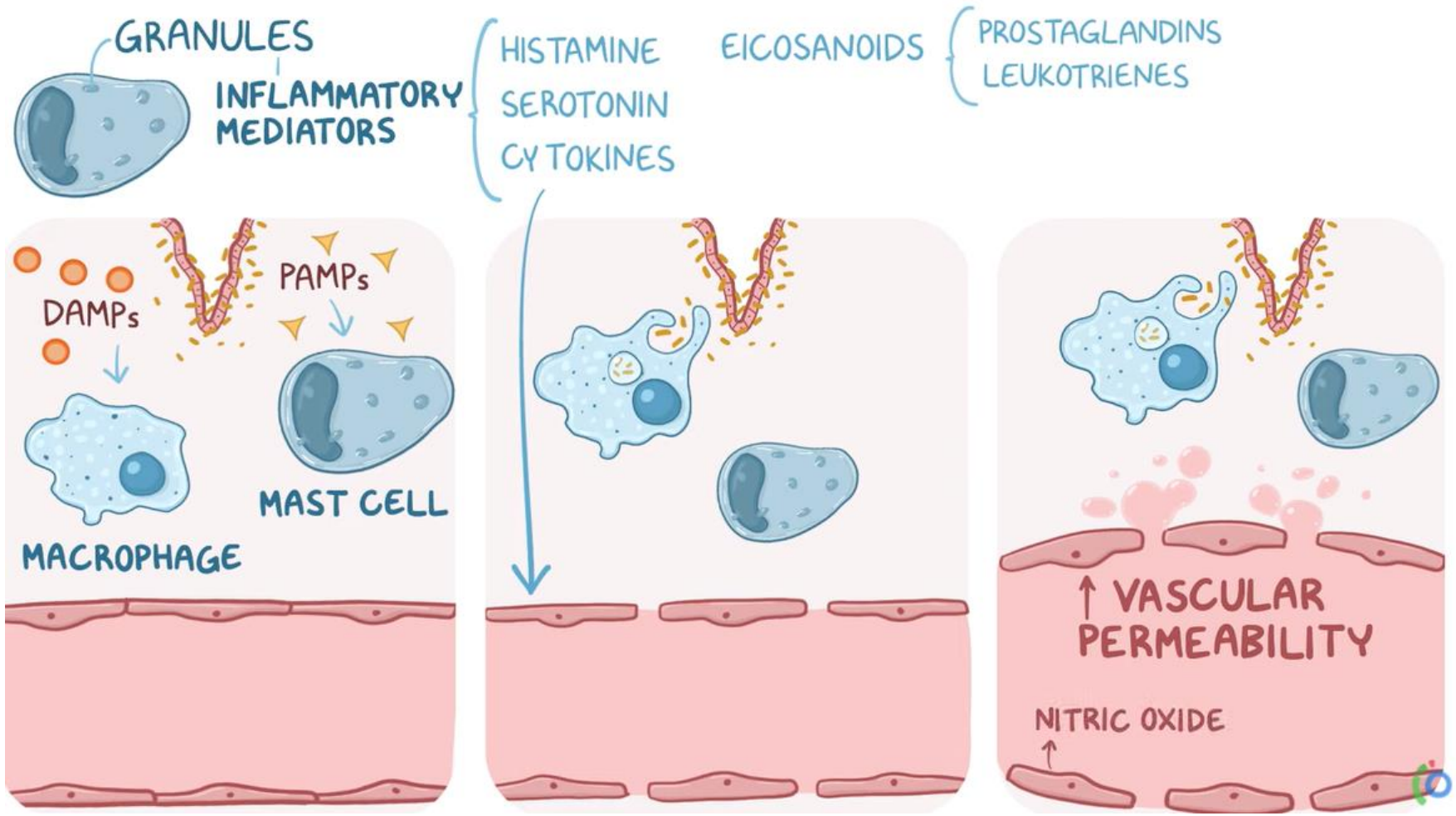



https://upload.wikimedia.org/wikipedia/commons/0/0b/2212_Complement_Cascade_and_Function.jpg

# Komplementový systém




https://www.sciencedirect.com/topics/engineering/complement-cascade




https://www.youtube.com/watch?v=LaG3nKGotZs&ab_channel=Osmosis

# Endotel

Udržování cévního tonu, vazoaktivita, adheze

## Exprese receptorů

**P-Selectin, E-selectin**

**ICAM, intercellular adhesion molecule**

JAM, junctional adhesion molecule

PECAM1, platelet/endothelial cell adhesion molecule 1

VE-cadherin, vascular endothelial cadherin

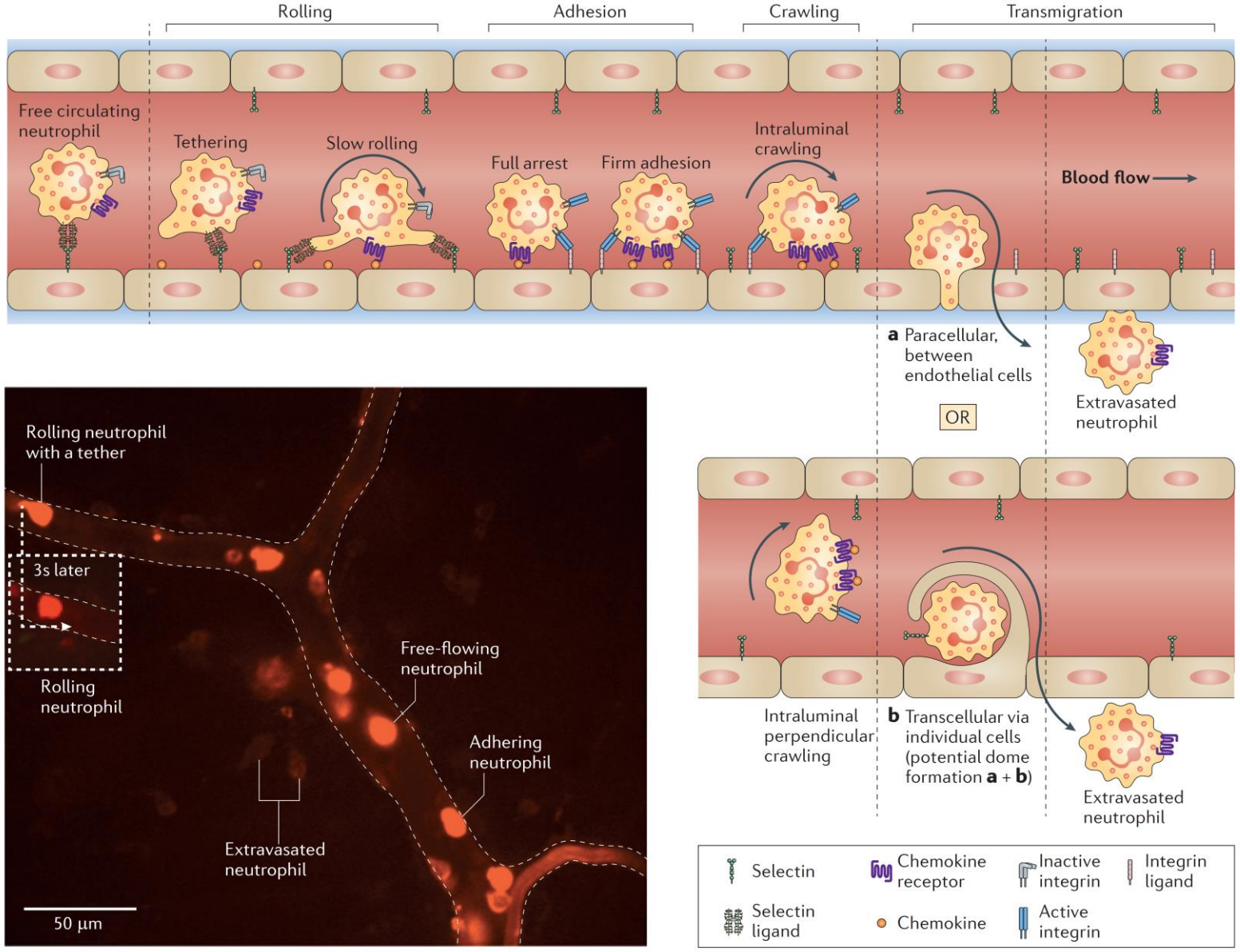
VCAM1, vascular cell adhesion protein 1

## ligandy

PSGL1, P-selectin glycoprotein ligand 1

LFA1, lymphocyte function-associated antigen 1

VLA4, very late antigen 4



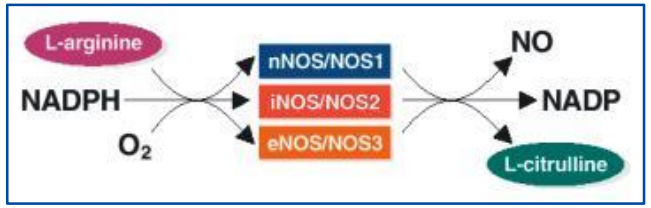

https://www.nature.com/articles/nri3399

# Regulace vazodilatace

## Oxid dusnatý (NO)

klíčová role ve vazodilataci, antitrombická aktivita

Produkován **NO-syntázou**




- konstitutivní i inducibilní formy enzymu (nNOS, eNOS, iNOS)
- regulace průtoku krve cévami, difúze NO z endotelií do buněk hladké svaloviny, inhibice krevních destiček
- riziko vzniku peroxynitritu ($ONOO^-$) a oxidativního poškození okolí

## Prostacyklin (PGI2)

- lipidový mediátor, syntetizován z kyseliny arachidonové (membránové fosfolipidy)
- enzym cykolooxygenáza

SCIENCE



# EDITORIAL

## The Molecule of the Year

The Molecule of the Year is nitric oxide, NO, a molecule of versatility and importance that has burst onto the scene in many guises. In the atmosphere it is a noxious chemical, but in the body in small controlled doses it is extraordinarily beneficial. It helps maintain blood pressure by dilating blood vessels, helps kill foreign invaders in the immune response, is a major biochemical mediator of penile erections, and is probably a major biochemical component of long-term memory. These are just a few of its many roles, which are just beginning to be discovered, and they are discussed in the accompanying Molecule of the Year story (p. 1862). That NO plays so many roles is not surprising because the same biological second messengers usually are used in many diverse systems, but a gas was indeed a surprise for an endogenous role, and a labile and toxic gas even more so. As the first surprise of such an unlikely agent was overcome, the gas as a messenger seemed logical because it could pass through biological membranes readily and oxidize foreign substances.

NO's role in sexual dysfunction, that of impotence, supports further a new liberation from old mental straitjackets. The future is sure to bring more insights into the effect on complex processes such as IQ, bad behavior, and alcoholism by single genes or chemical reactions. Many people will be happy to learn that some forms of sexual dysfunction may not be caused by psychiatric disorders or the failure of a marriage but may instead reflect a deficiency in a chemical reaction that can be compensated for by medical treatment. New research on the role of NO may also lead to new insights into the loss of memory, which is so debilitating to so many.

This year's Molecule of the Year once again shows that scientific rewards can come from pursuing unconventional thinking. The recent presidential election focused on the persistent question of providing jobs and correcting ailing economies. Hopefully, the political and social scientists advising our leaders will pursue these problems with the same creativity that characterized the research on NO. The new, the unexpected, and the incongruous will be needed to address these social problems. In addition, our elected officials as well as the general public must face unpleasant realities, including the need for the United States to work hard to maintain its standard of living in a competitive world and the need to be open-minded enough to welcome unexpected solutions such as gaseous messengers.

Every year *Science* picks a Molecule of the Year along the lines described in our editorial of 22 December 1989. Molecule is a term we use to emphasize that we are honoring the discovery rather than the people who made the discovery, not because people are unimportant but because many other awards honor the discoverers, and most discoveries involve the contributions of many people. As in the case of "people prizes," there are many "runner-up" discoveries that are extremely important to humanity but, in our opinion, are not yet quite as developed as our winner. For example, one of our runners-up, the discovery of the structure of nitrogenase, has no immediate industrial application, but the way enzymes fix nitrogen is bound to be of great importance to agriculture. As more intense farming and cheaper fuel become the necessities of the future, better mechanisms for nitrogen fixation become more important. Enzymes certainly appear to have solved the problem better than man-made solutions so far. The hope is that the enzyme mechanism and the chemical knowledge can be combined to make a new solution that will benefit millions. The widespread use of supercomputers is not a sudden event, but the increased utility of this powerful tool in industry and science for applications such as aircraft design and oil exploration will solve many problems that were previously beyond approach.

All of the runners-up are discussed in the accompanying story. This year they are an impressive group ranging from discoveries that are already being applied, such as fetal diagnosis and treatment (in utero treatment of a fetus to correct its deficiencies and transplanting fetal tissue to adults with Parkinson's disease), to those that are now far enough along so that application seems inevitable, for example, antisense RNA. In addition, there are landmarks such as the mapping of chromosomes Y and 21, which will certainly lead to medical discoveries, and the use of magnetic resonance imaging to diagnose medical problems and to locate areas of the brain identified with specific thought processes. Those who sometimes question the advances of science should think for a moment about the incredible developments that have slipped into everyday life without headlines. The Molecule of the Year and the runners-up are a good place to start for the discoveries that will inevitably make the future better than the past.

**Daniel E. Koshland, Jr.**



https://science.sciencemag.org/content/258/5090/1861

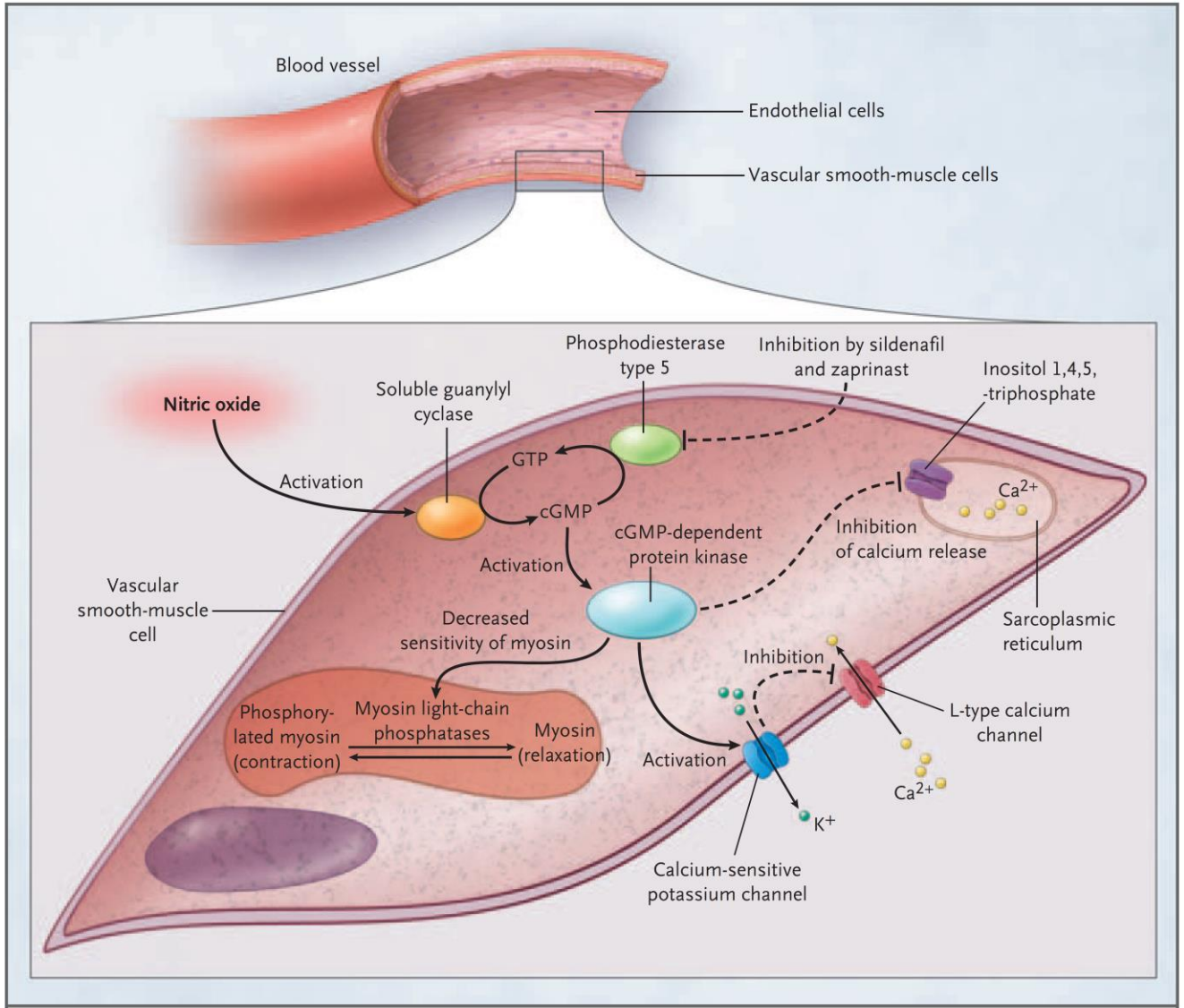



**Figure 1. Regulation of the Relaxation of Vascular Smooth Muscle by Nitric Oxide.**

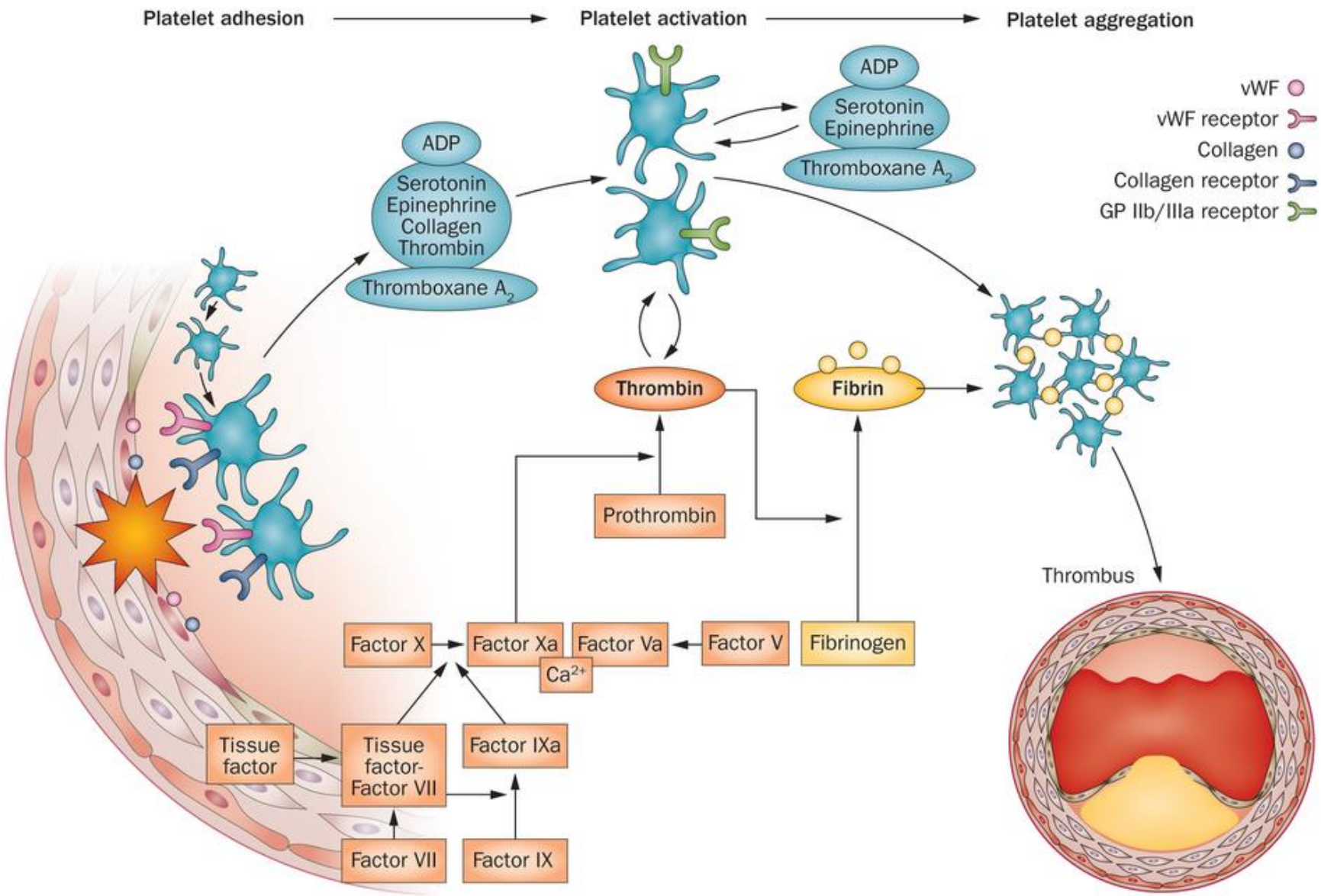
Nitric oxide activates soluble guanylyl cyclase, leading to the activation of cyclic guanosine 3′, 5′-monophosphate (cGMP)–dependent protein kinase (cGKI). In turn, cGKI decreases the sensitivity of myosin to calcium-induced contraction and lowers the intracellular calcium concentration by activating calcium-sensitive potassium channels and inhibiting the release of calcium from the sarcoplasmic reticulum. cGMP is degraded by phosphodiesterase type 5, which is inhibited by sildenafil and zaprinast. GTP denotes guanosine triphosphate.

# Prozánětová a hemostatická role endotelu

## vazokonstrikce, aktivace krevních destiček a plazmatického koagulačního systému

- endotelin 1
- tromboxan A2
- noradrenalin
- enzym konvertující angiotenzin (ACE), angiotenzin II
- von Willebrandův faktor (vWf)
- tkáňový faktor
- exprese membránových fosfolipidů => vhodná matrix pro aktivaci destiček a plazmatického koagulačního systému

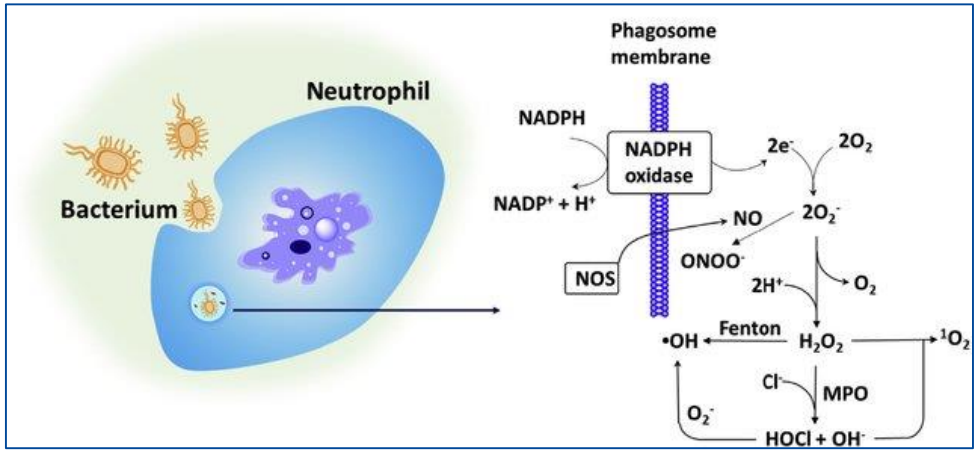
# Plazmatický koagulační systém a destičky

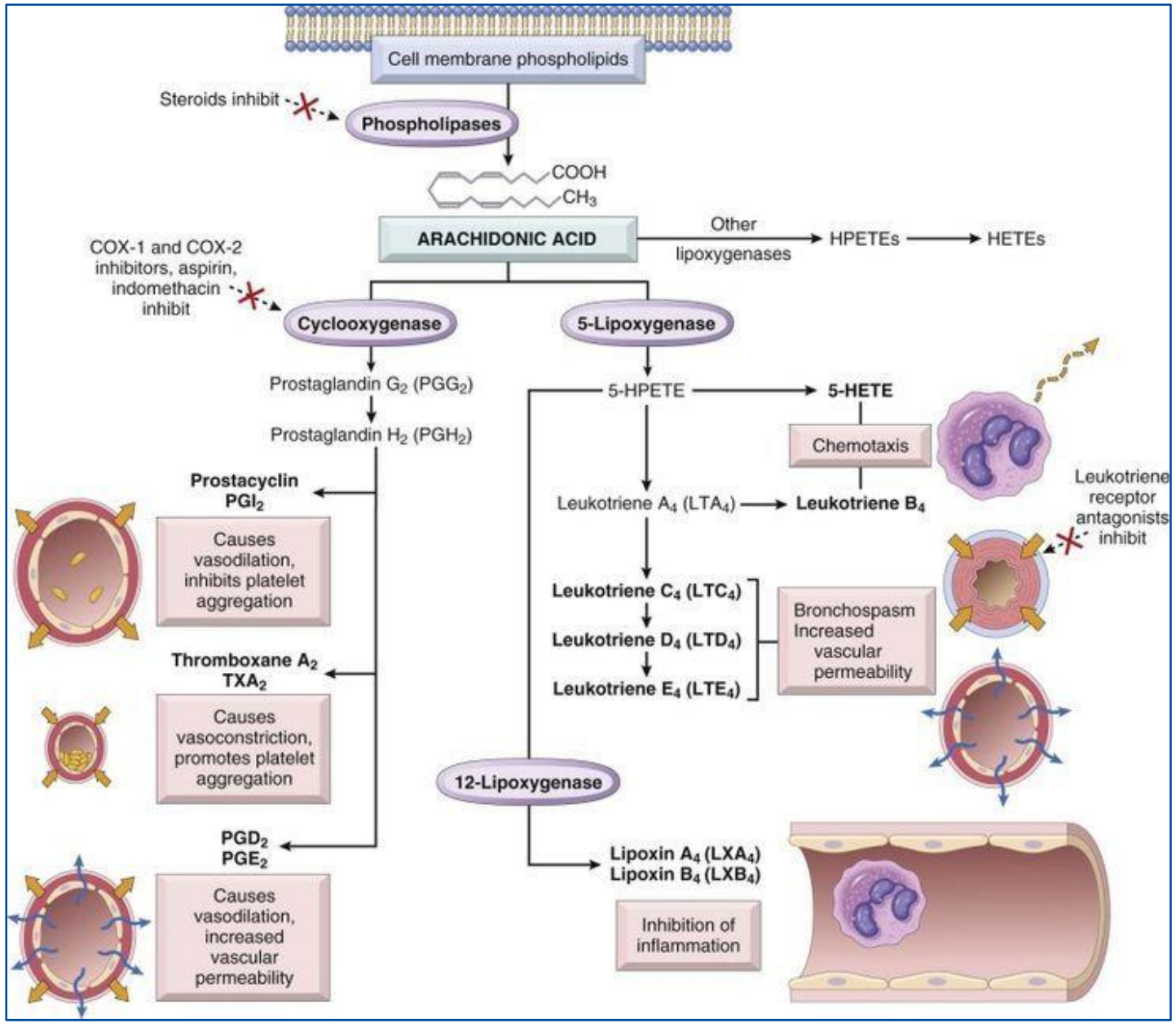



https://blog.antiaging.com/wp-content/uploads/2016/07/thrombus-evolution.jpg

# Mediátory zánětu

- lipidové mediátory
- volné radikály (ROS)



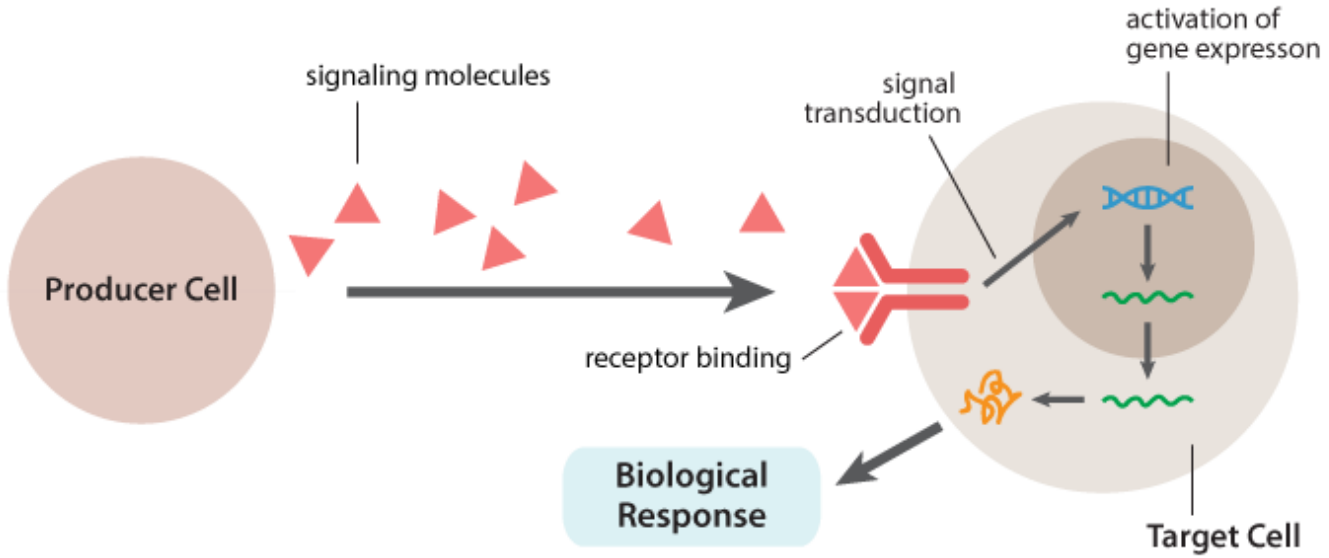

https://www.researchgate.net/publication/321466965_Bioanalytical_Methods_for_Hypochlorous_Acid_Detection_Recent_Advances_and_Challenges/figures?lo=1

# Mediátory zánětu

## Cytokiny

**Různorodá skupina malých proteinů secernovaných za účelem komunikace mezi buňkami**

- Autokrinní, parakrinní a endokrinní účinky
- Působení v překrývajících se sítích, redundance, často pleiotropní efekty, závislé na buněčném kontextu




https://old.abmgood.com/marketing/knowledge_base/growth_factors_cytokines_introduction.php

- **Interferony**

  Regulace nespecifické imunity, antivirové a antiproliferativní účinky (IFNα, IFNβ, IFNγ, IFNλ)

- **Interleukiny**

  Růst a diferenciace leukocytů (IL-1, IL-6, IL-12, IL-17, IL-18, IL-4, IL-10, IL-11, IL-13)

- **Chemokiny**

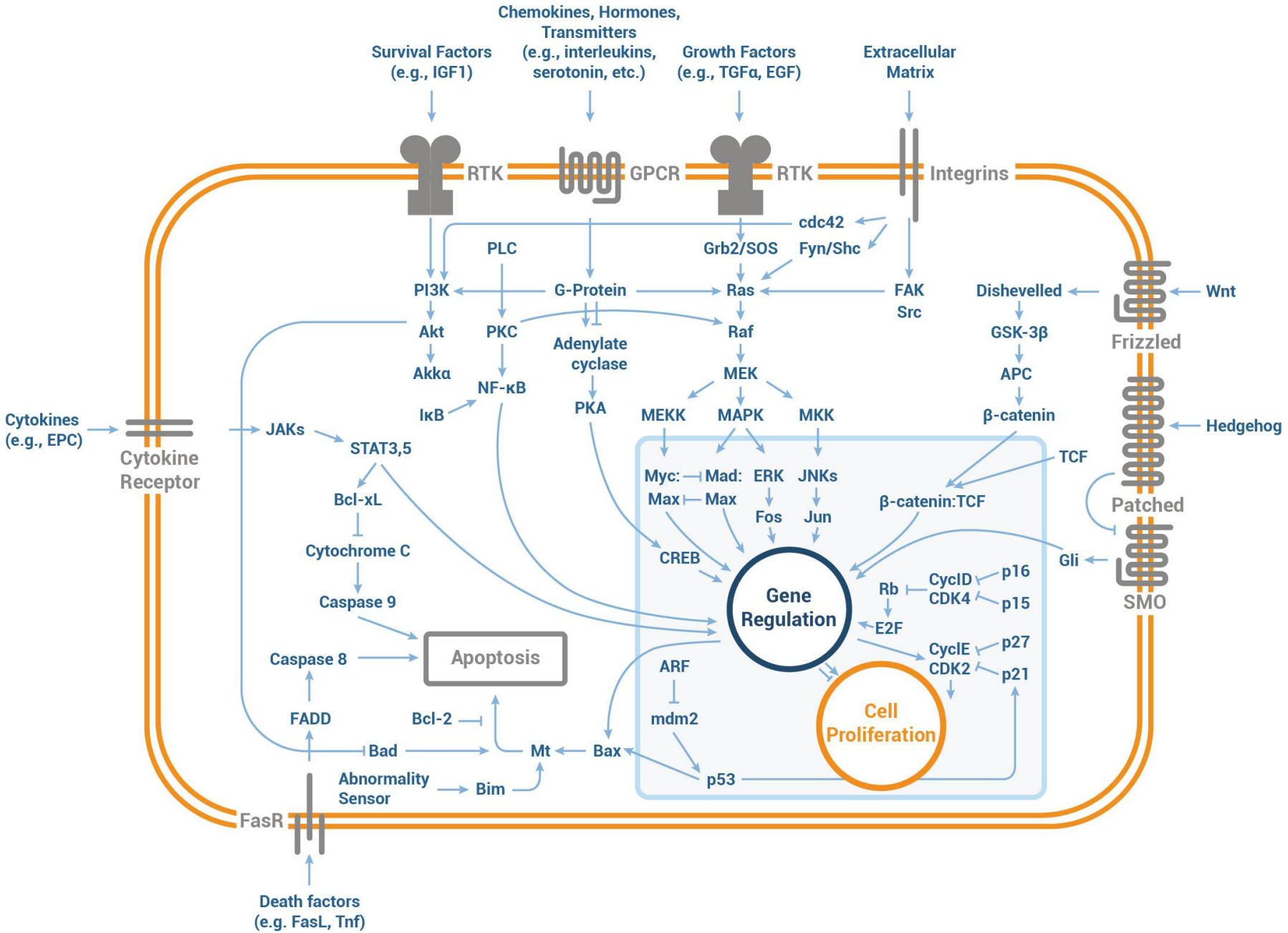
  Chemotaxe (IL-8, MCP1, RANTES)

- **Kolonie stimulující faktory**

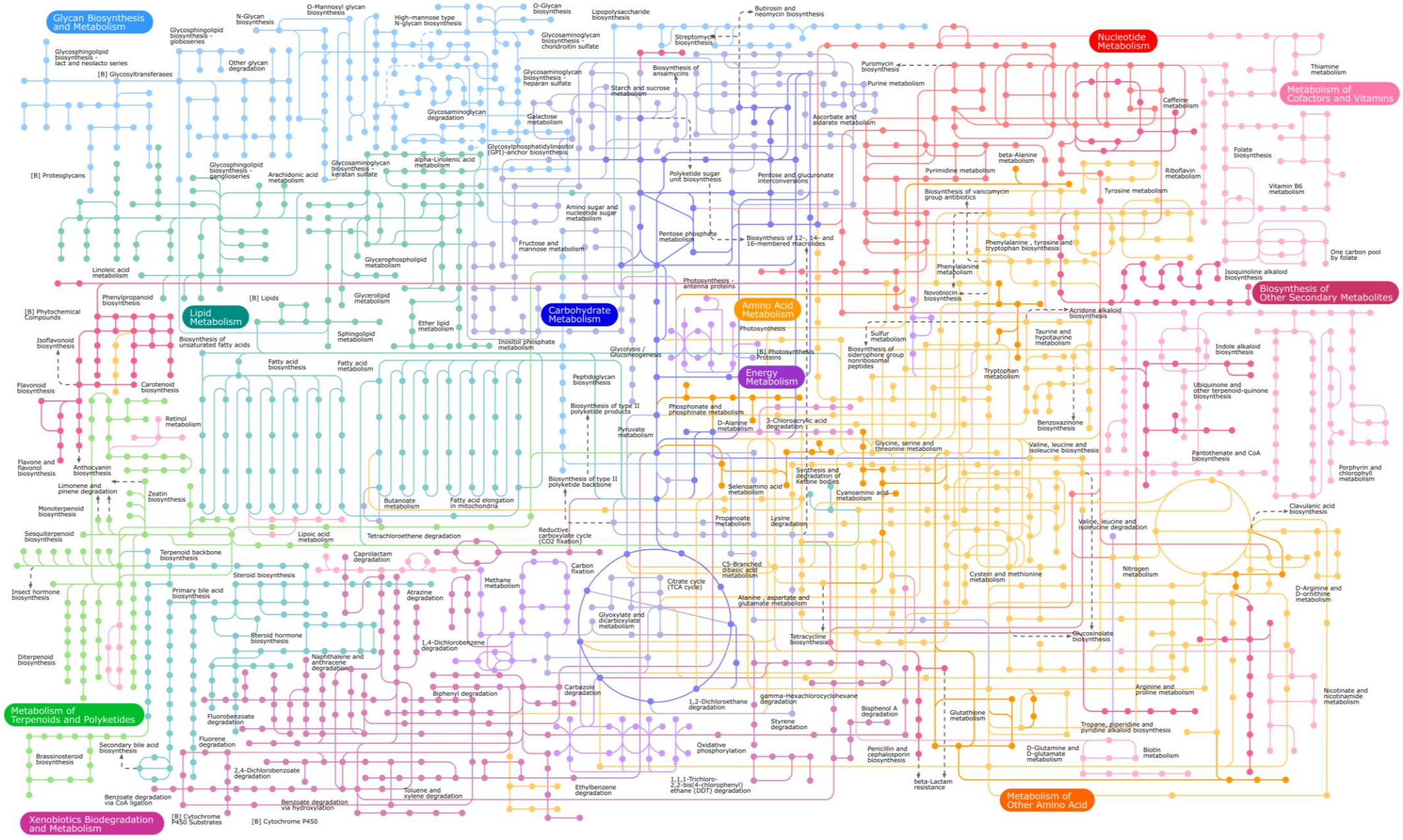
  Stimulace progenitorů, podpora růstu a diferenciace (M-CSF, GM-CSF, G-CSF)

- **Tumor nekrotizující faktory**

  Prozánětlivé působení, aktivace cytotoxických T lymfocytů (TNFα, TNFβ)




https://www.omicscouts.com/en/signallingscout.html




https://mokaspetridish.files.wordpress.com/2013/08/metabolic_map.png

# Systémový zánět, souhra působení inzultu a cytokinů

**SIRS** (syndrom systémové zánětové odpovědi, systemic inflammatory response syndrome)

- teplota nad 38 °C nebo pod 36 °C
- tep nad 90/min
- dechová frekvence nad 20/min nebo CO2 pod 32 mmHg
- leukocyty nad 12 tis./µl nebo pod 4 tis./µl nebo víc jak 10 % nezralých forem

**Sepse**

SIRS z infekčních příčin

(i původně neinfekční rozvinutý SIRS zpravidla přechází v sepsi – selhání mikrocirkulace střevní stěny, proniknutí bakterií do cirkulace)

**MODS** (syndrom multiorgánového selhání, Multiple organ dysfunction syndrome)

přítomnost takových změn orgánových funkcí že homeostáza nemůže být udržena bez intervence

- primární MODS – přímé působení inzultu (těžké trauma, cirkulační selhání)
- sekundární MODS – autoagresivní působení zánětu

Syndrom akutní dechové tísně (ARDS, acute respiratory distress syndrome, adult respiratory distress syndrome)

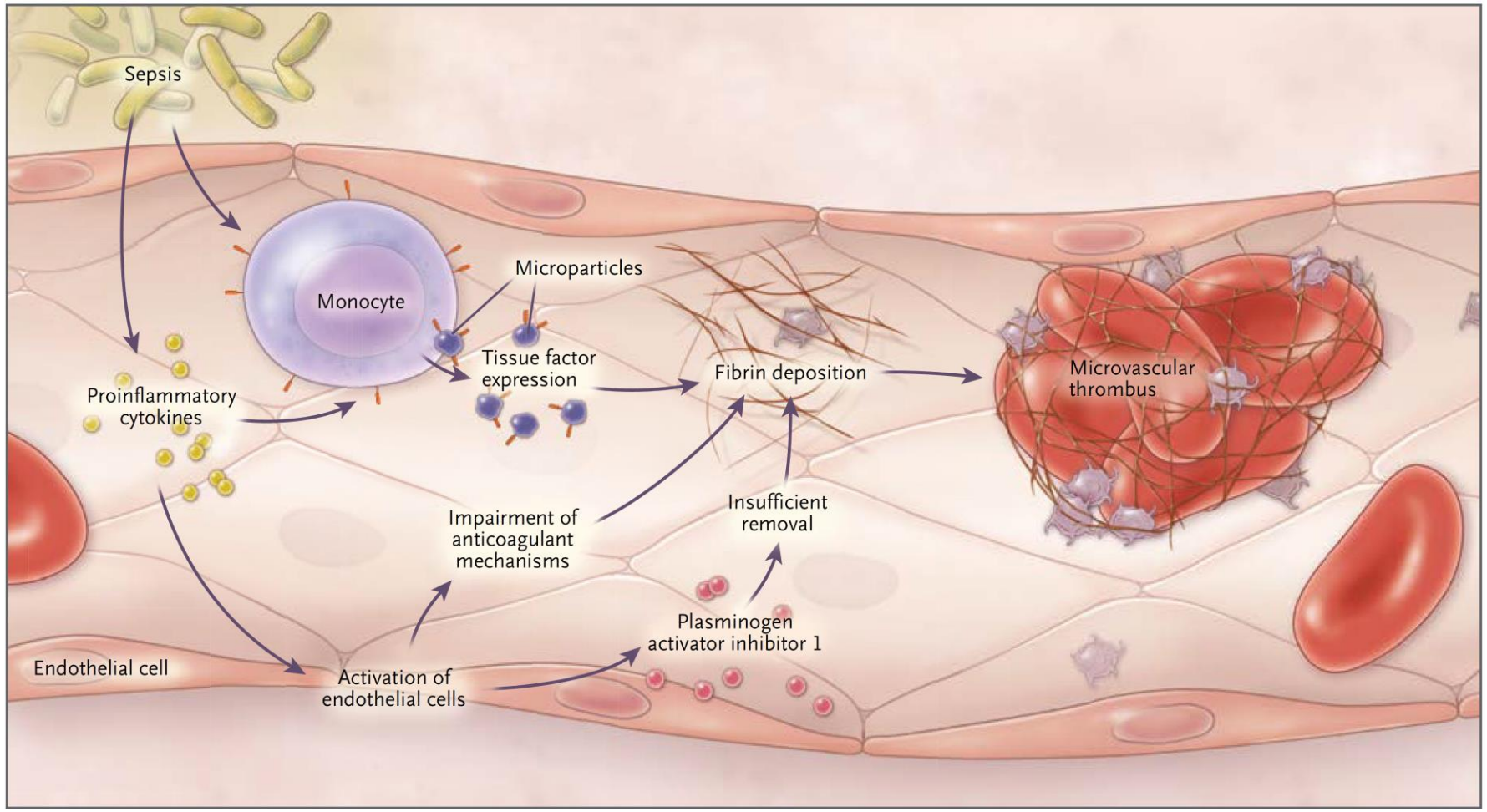
- zvýšená propustnost plicních kapilár
- akumulace tekutiny v parenchymu a alveolech
- poškození epitelu alveolů

https://www.ncbi.nlm.nih.gov/books/NBK547669/

# Diseminovaná intravaskulární koagulace (DIC)

**systémová aktivace koagulace** (infekce, trauma, nádory, porodní komplikace, potransfusní reakce)

- intravaskulární depozice fibrinu => trombózy, ischemie a orgánová selhání
- vyčerpání destiček a koagulačních faktorů => krvácení




https://www.nejm.org/doi/10.1056/NEJMra1208626

# Cytokiny se bouří…

„…while the general concept of an excessive or uncontrolled release of proinflammatory cytokines is well known, an actual definition of what constitutes a cytokine storm is lacking…“

## cytokinová bouře (hypercytokinemie)

- deregulace působení prozánětlivých cytokinů
- systémové působení vedoucí k MODS

ORIGINAL ARTICLE BRIEF REPORT

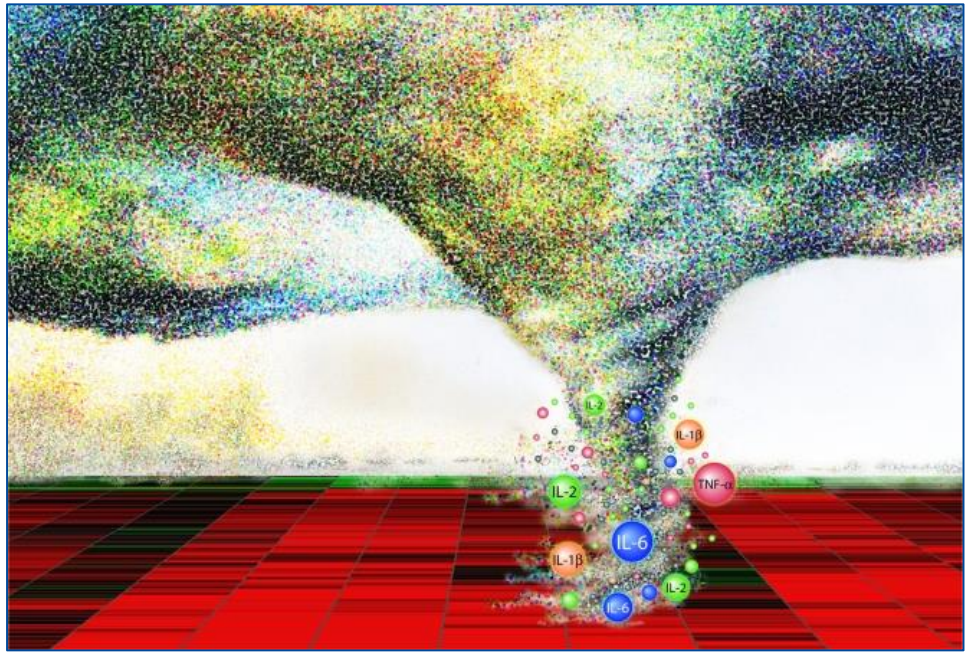
### Shock and Multiple-Organ Dysfunction after Self-Administration of Salmonella Endotoxin

Angelo M. Taveira da Silva, Helen C. Kaulbach, Francis S. Chuidian, David R. Lambert, Anthony F. Suffredini, and Robert L. Danner

ORIGINAL ARTICLE BRIEF REPORT

### Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

**1 hour** – simultaneously, the six men begin suffering excruciating headaches, shivering, back pain, gut pain, diarrhoea, swelling and nausea
**4 hrs** – all have fevers, are flushed, their blood pressure drops dangerously low and their hearts start to race. Blood tests show their lymphocytes and monocytes are fast vanishing.
**5 hrs** – one patient begins fighting for his breath. All suffer lung pain. They are all given steroids and other medications to ease inflammation.
**12 hrs** – the patient fighting for his breath is so bad that he has to be taken into intensive care and put on a ventilator to keep him alive. Suntharalingam decides to take all the volunteers into intensive care as a precaution.
**24 hrs** – two people are on ventilators, and the four others need support with breathing.
**48 hrs** – the four least affected men start to recover, but all six begin to suffer multi-organ failure, and have to be attached to kidney machines…

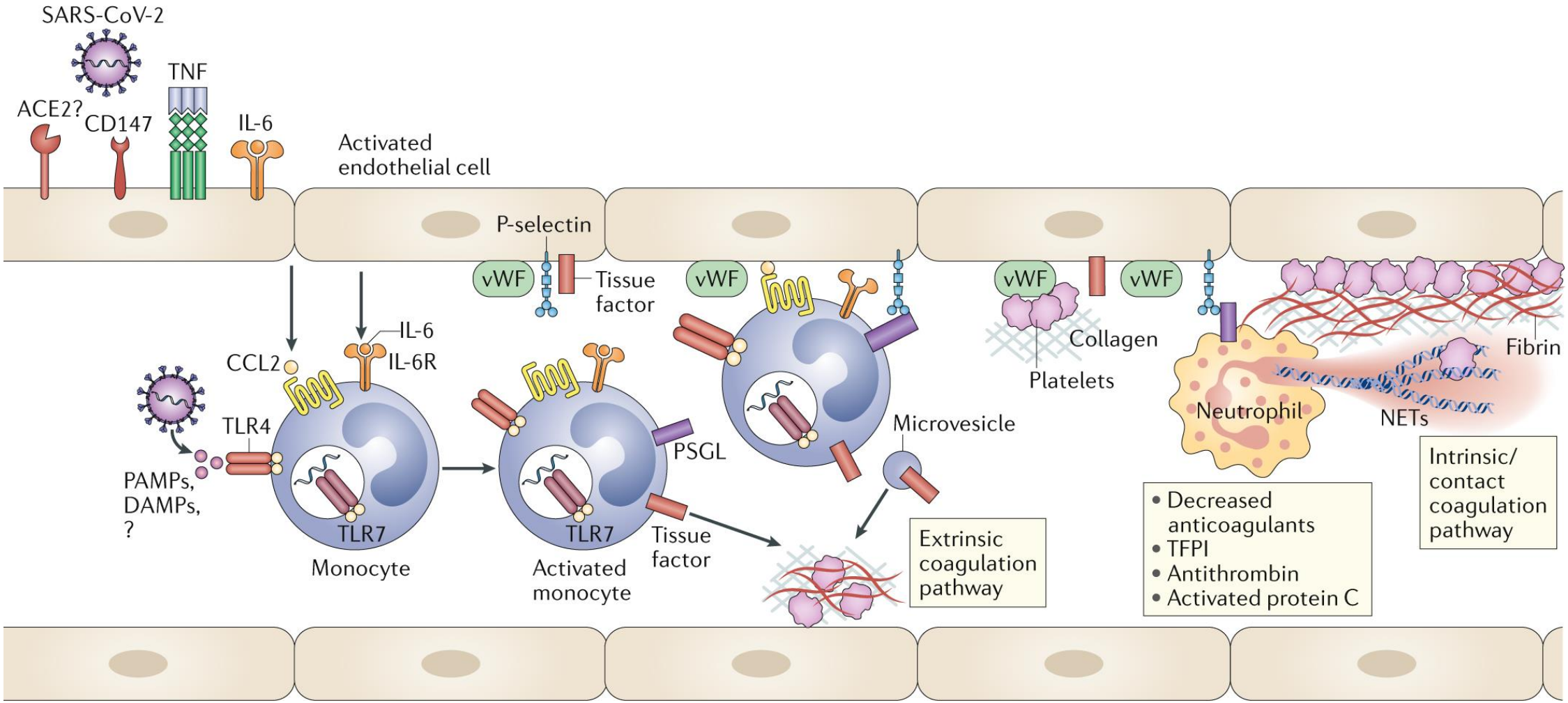



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294426/

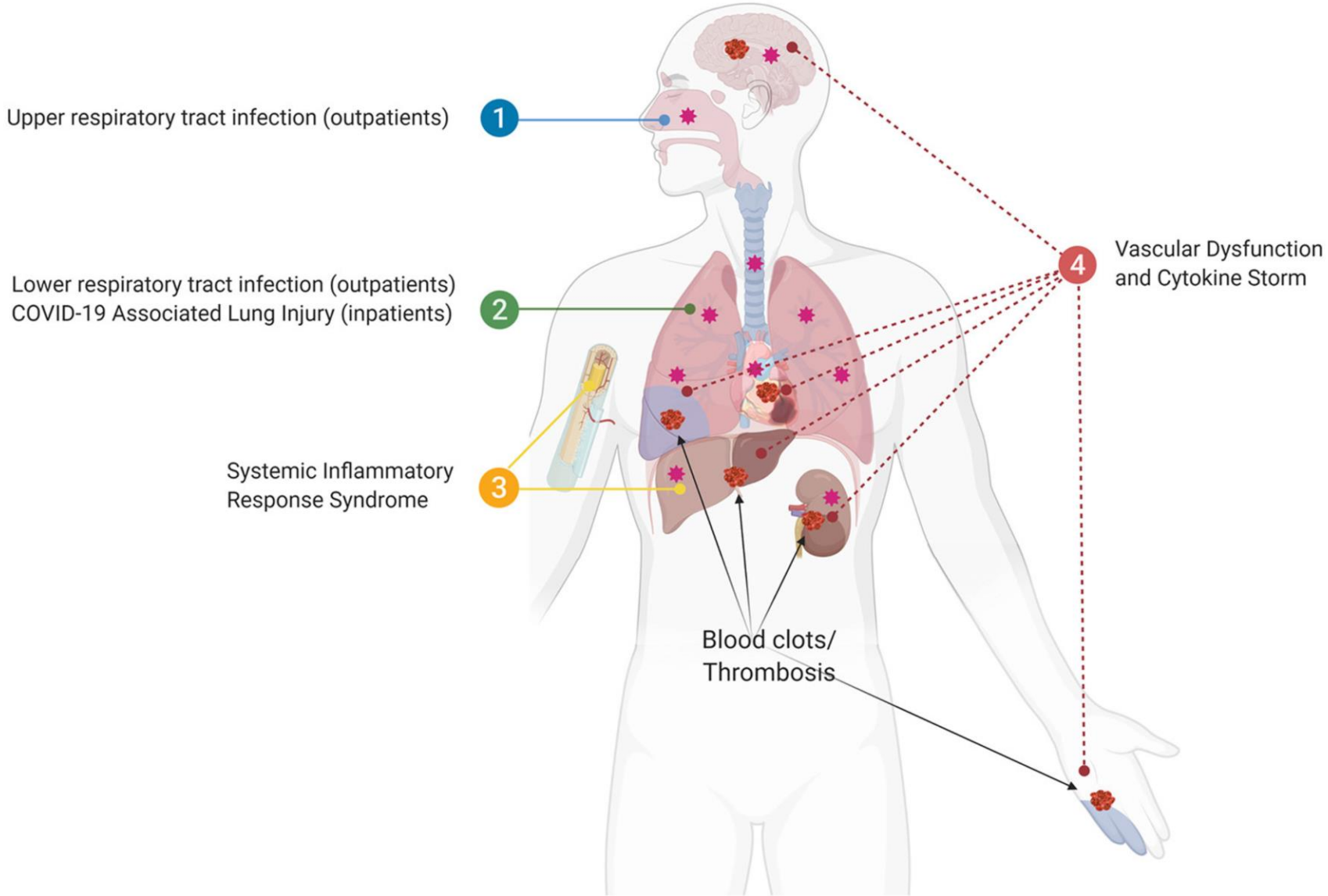
# Co stojí za náchylností k cytokinové bouři?

- hyperfunkční varianty Toll-like receptorů (TLR1, TLR4)?
- polymorfismy v SOCS (supresory cytokinové signalizace)?
- original antigenic sin?
- imunosenescence, Inflamm-aging
- environmentální faktory?
- vitamin D status?
- Something Completely Different?

# SARS-CoV-2 koagulopatie

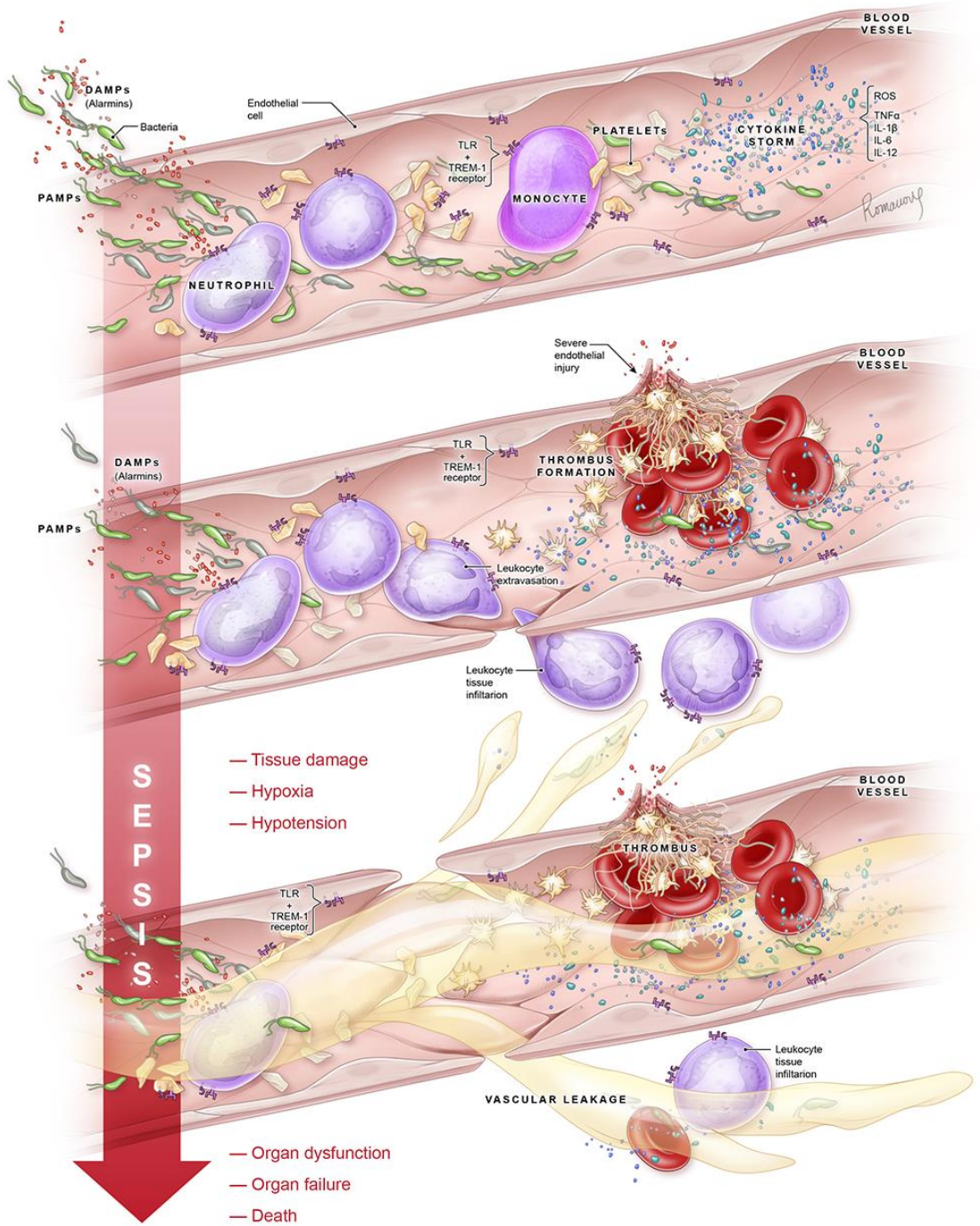



https://www.nature.com/articles/s41577-020-0331-4/figures/2




https://www.frontiersin.org/files/Articles/564628/fimmu-11-01626-HTML/image_m/fimmu-11-01626-g001.jpg

# Sepse



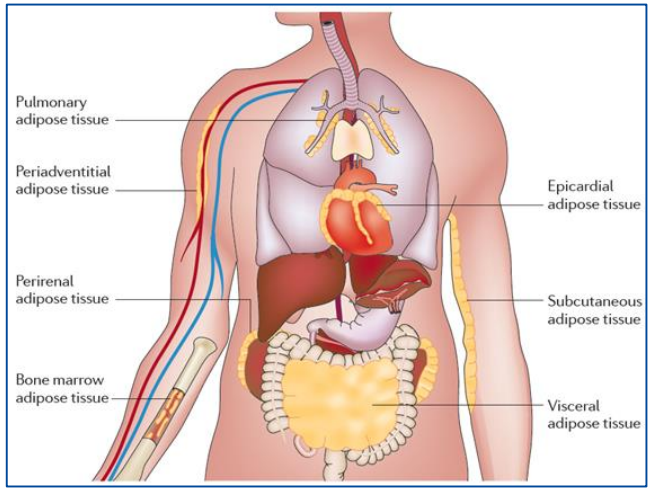

https://mariaromanova.org/illustration.html#gallery-3

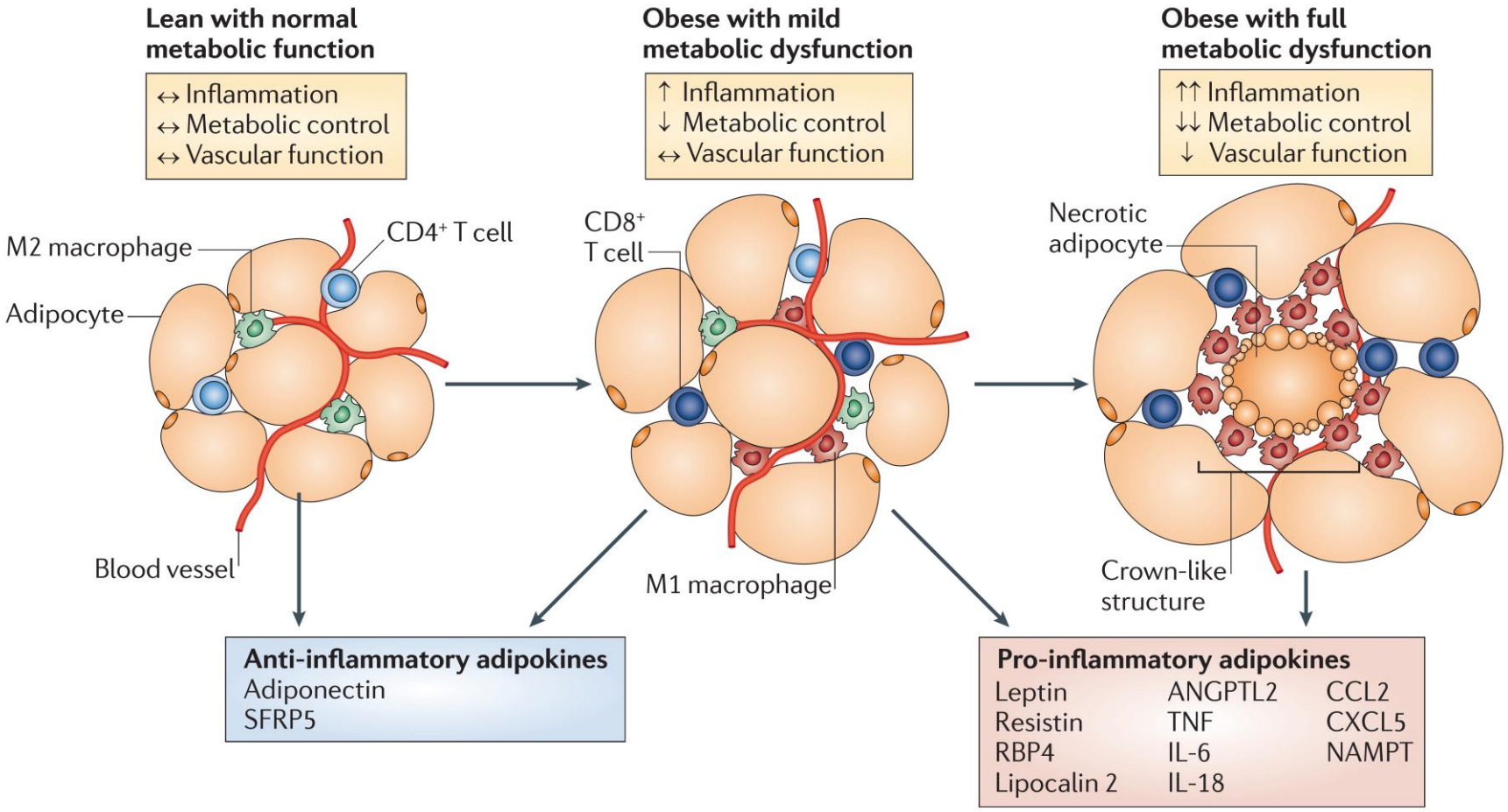
# Chronický zánět

- perzistující infekce (TBC, Syfilis, Lepra)
- prolongovaná expozice iritantům
- opakované akutní záněty
- primárně chronický zánět – nízce virulentní agens, sterilní zánět (silikóza)
- autoimunitní záněty (trvalé ukládání imunokomplexů)
- neznámé příčiny

# Chronický zánět

## obezita jako chronický zánětlivý stav




https://www.semanticscholar.org/paper/Adipokines-in-inflammation-and-metabolic-disease-Ouchi-Parker/b409ed2312330ef9a123f5eb700e93537ee9c21c/figure/3

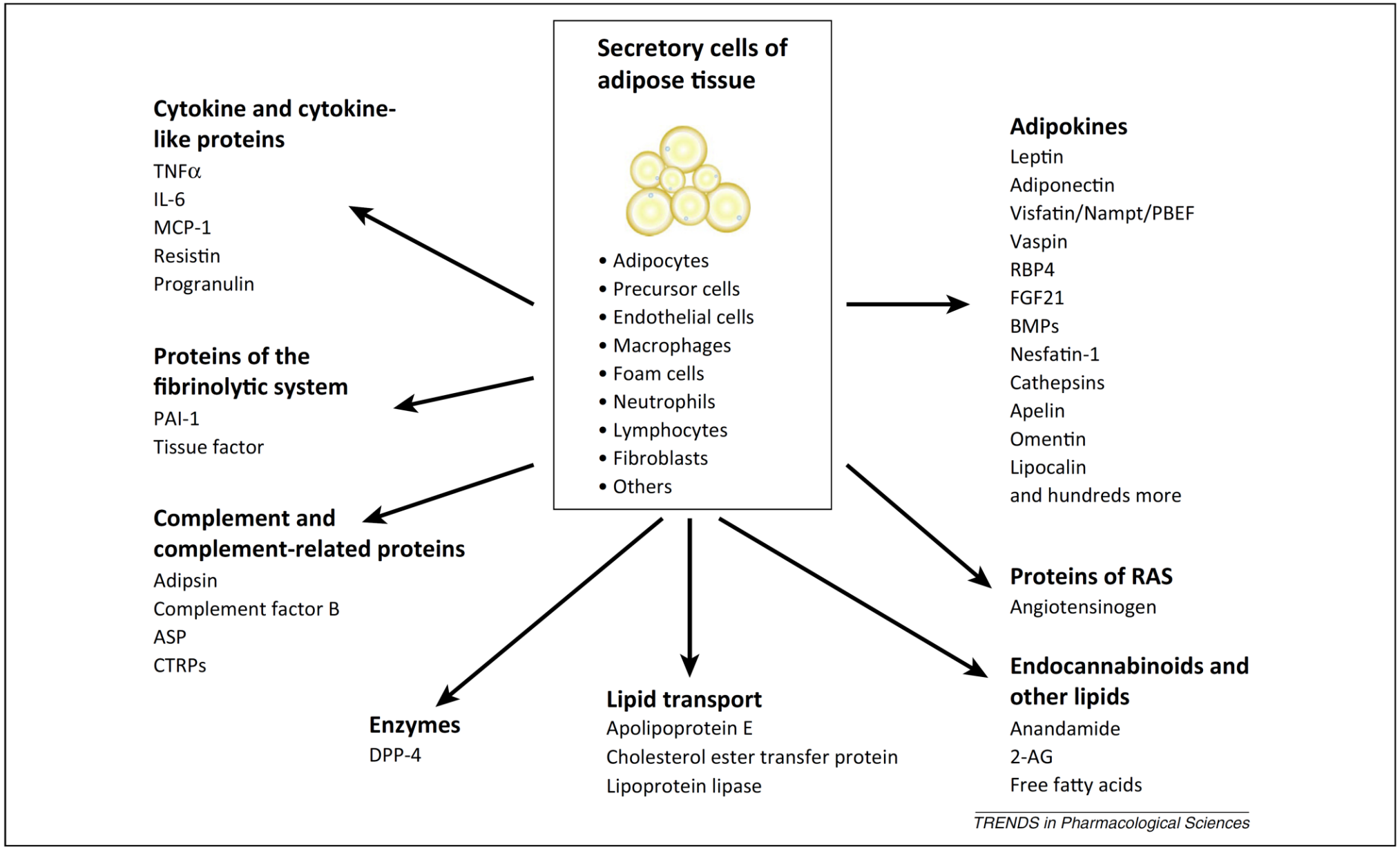
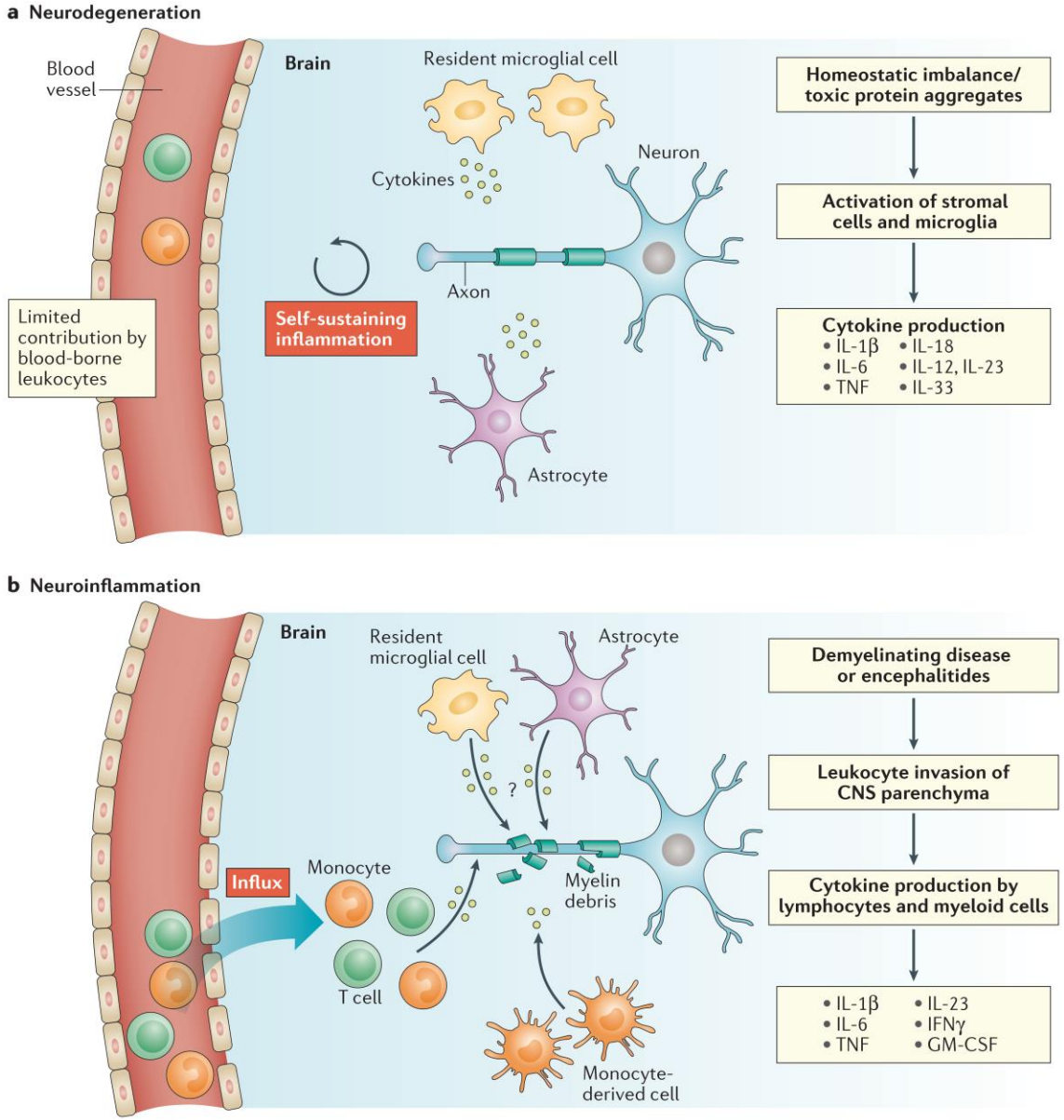



**Figure 1**. Factors released or secreted by adipose tissue. Adipocytes, immune cells, fibroblasts, endothelial cells, and others contribute to the release of metabolites, lipids, and adipokines. Examples of adipose tissue-derived molecules are provided here. Abbreviations: 2-AG, 2-Arachidonoylglycerol; ASP, acylating simulation protein; BMPs, bone morphogenetic proteins; CTRPs, C1q/TNF-related proteins; FGF21, fibroblast growth factor 21; MCP-1, monocyte chemotactic protein-1; PAI-1, plasminogen activator inhibitor-1; RAS, renin angiotensin system; RBP4, retinol binding protein 4. Modified from [3,5,6].

# Mozek a zánět



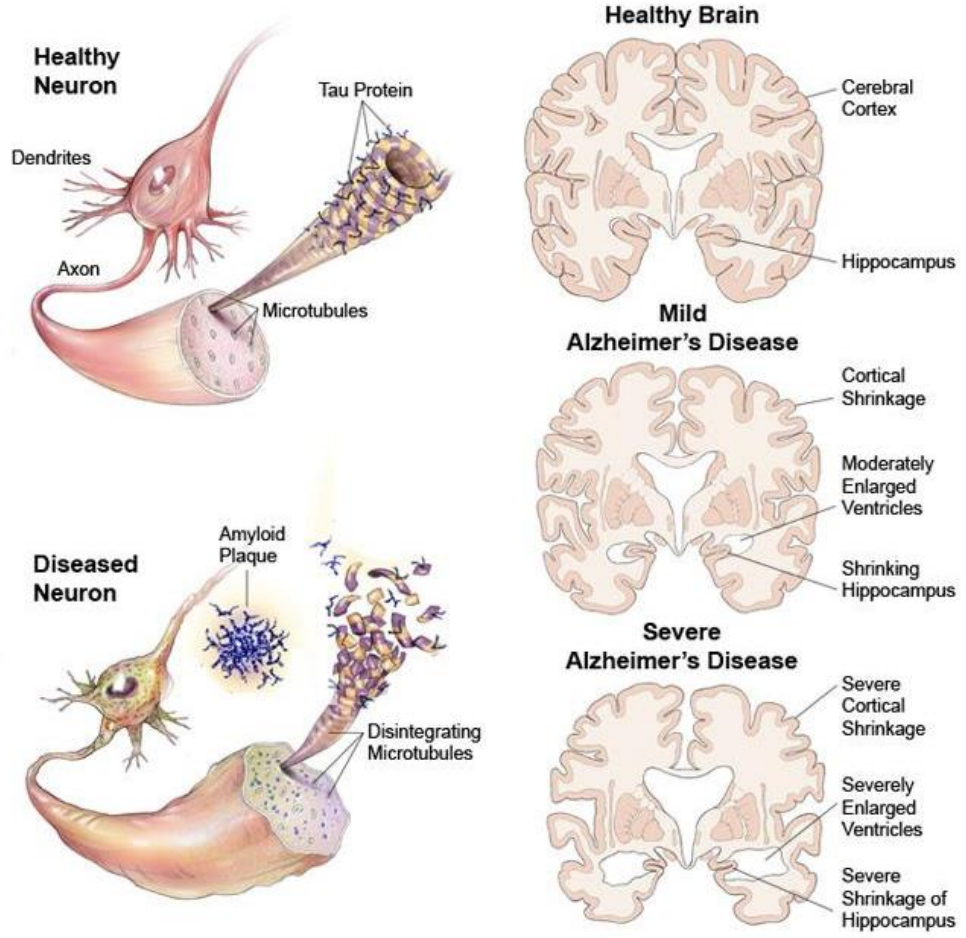
# Alzheimerova choroba

neurodegenerativní onemocnění mozku, **nejčastější příčina demence**, 90% případů se vyskytuje sporadicky, role polymorfismu ApoE ε4

u familiární formy mutace např. v PSEN1 a PSEN2 (podjednotky enzymu štěpící **amyloid precursor protein, APP**)

Molekulární mechanismus nejasný: pravděpodobná role produktů metabolismu APP a vznik **amyloidních plaků**, abnormální fosforylace proteinu Tau (**neurofibrilární klubíčka**), odumírání neuronů, výrazná imunitní složka

častý výskyt AD u Downova syndromu (trisomie 21. chromosomu => extra kopie APP)



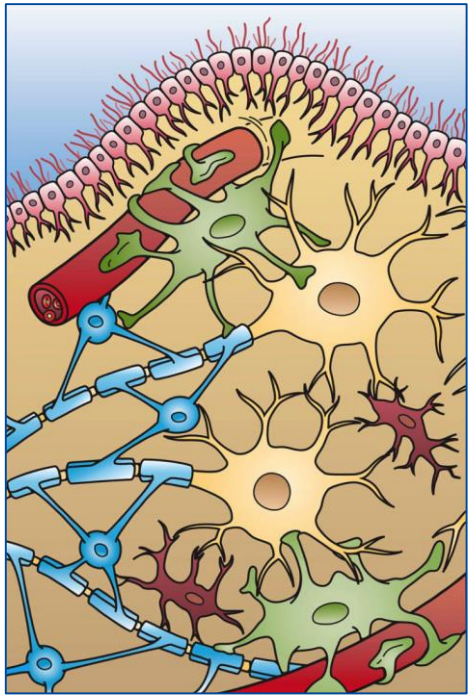

http://www.brightfocus.org/sites/default/files/styles/full_width/public/BFF_2015MedIllust_Progression_of_Alzheimers.jpg?itok=tDpL9sm9

# V hlavní roli glie?

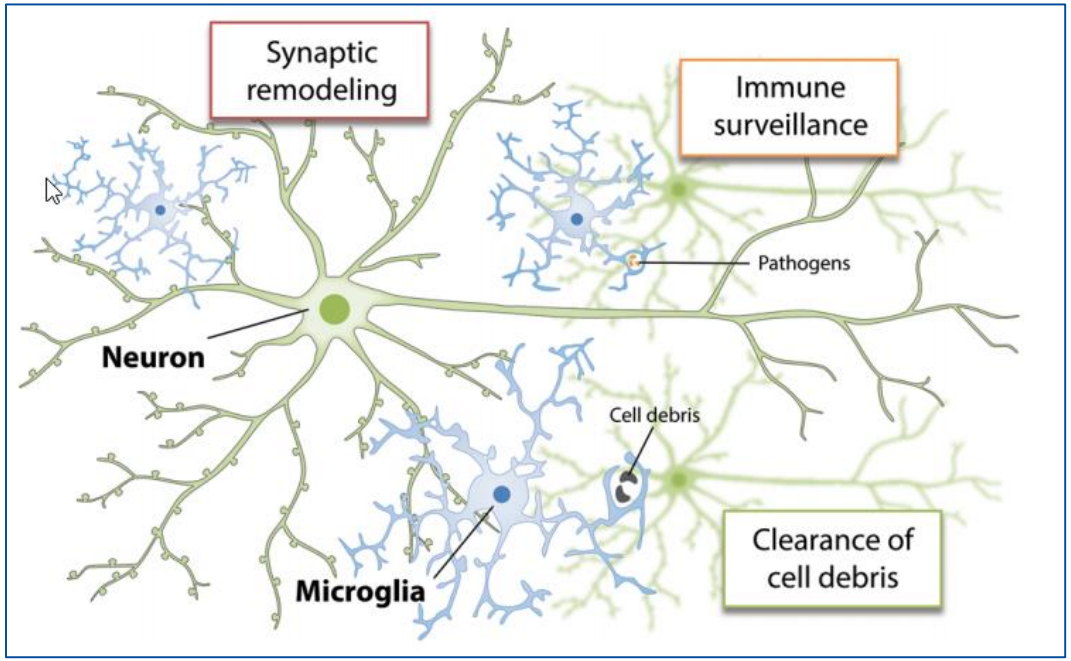
**Mikroglie** – rezidentní imunitní buňky v CNS, široké spektrum fenotypů, pohyblivost, fagocytóza a udržování homeostázy, produkce cytokinů (prozánětlivé cytokiny jsou součástí konsolidace paměti), aktivace je spojená s AD (ale je to špatně?), možná role receptoru TREM2 (Triggering receptor expressed on myeloid cells 2)

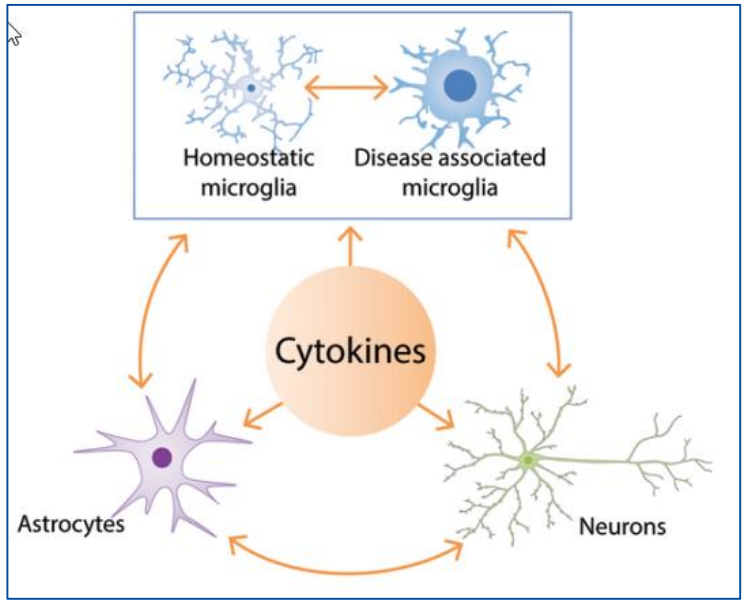
**Astrocyty** – protektivní úloha v CNS, tvorba gliální jizvy, regulace zánětu, produkce cytokinů, neurotransmiterů, změny tvaru i molekulárních funkcí po stimulaci

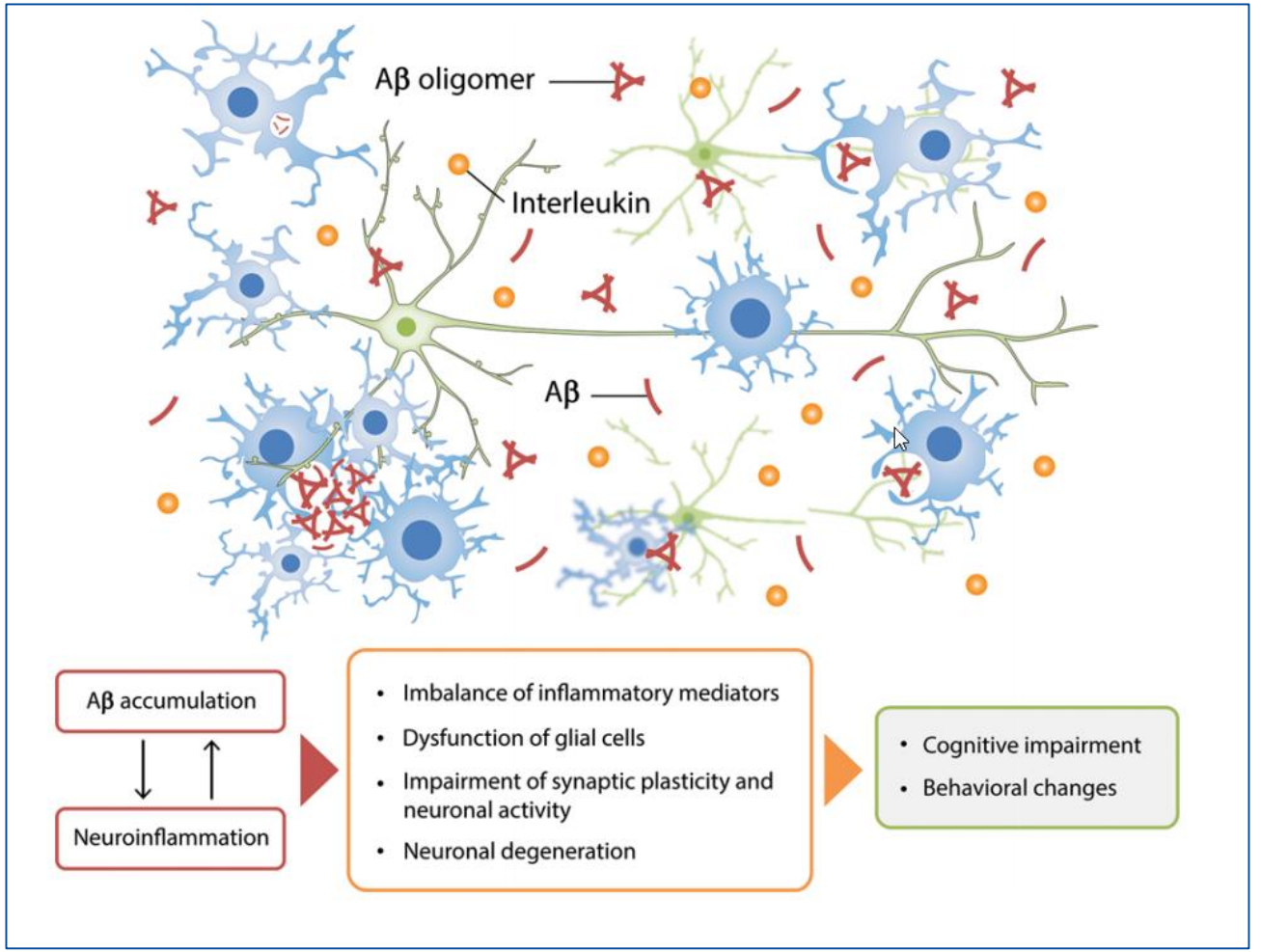
**Oligodendrocyty** – obklopují axony neuronů a vytvářejí na nich myelin, produkce trofických faktorů, přísun metabolitů

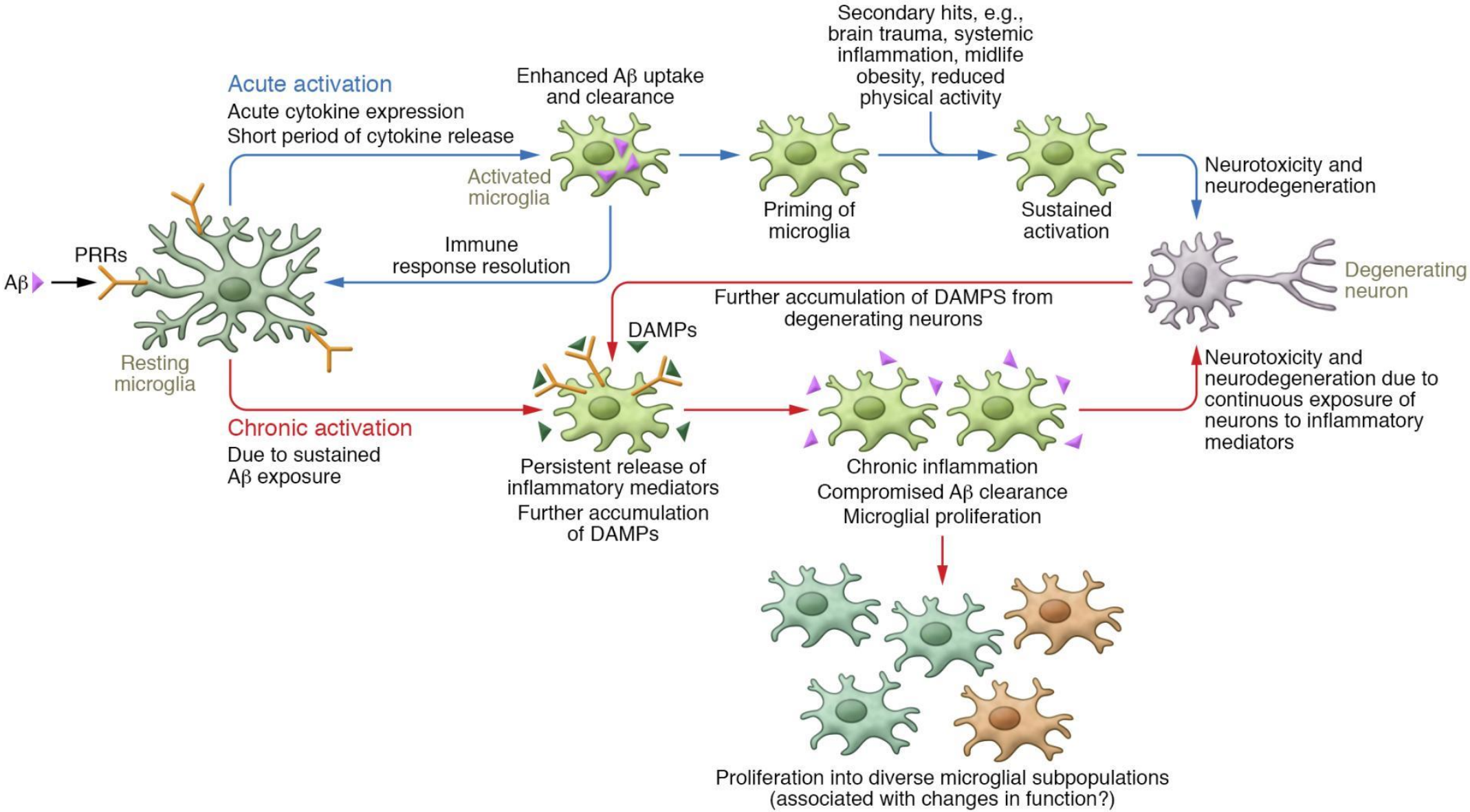


https://en.wikipedia.org/wiki/Glia#/media/File:Glial_Cell_Types.png

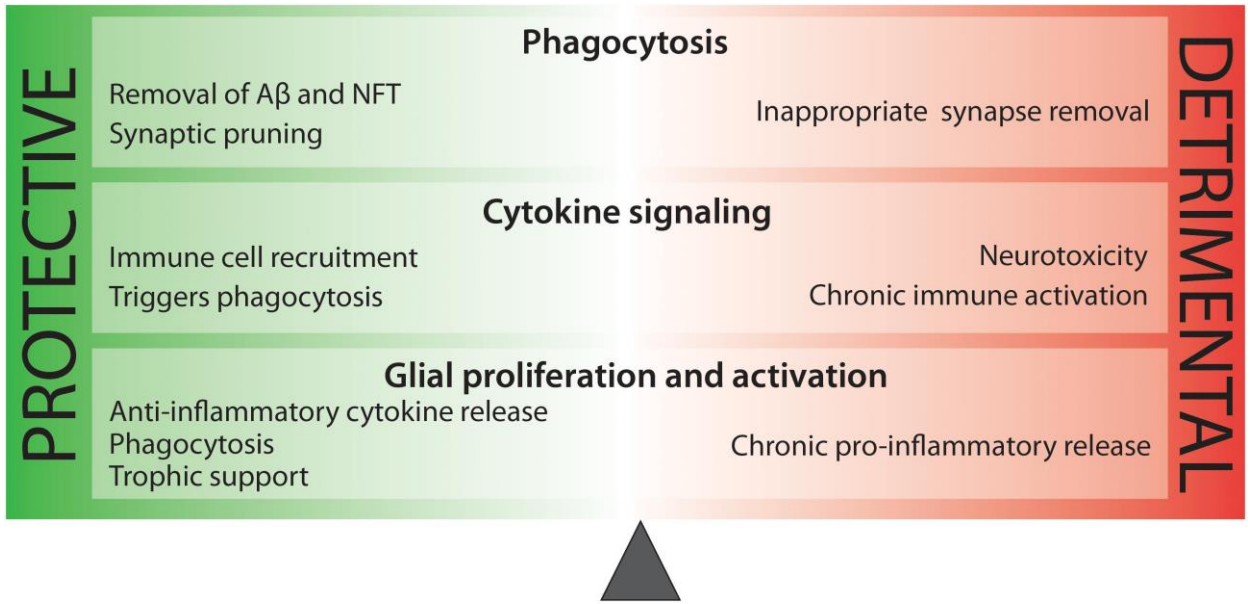


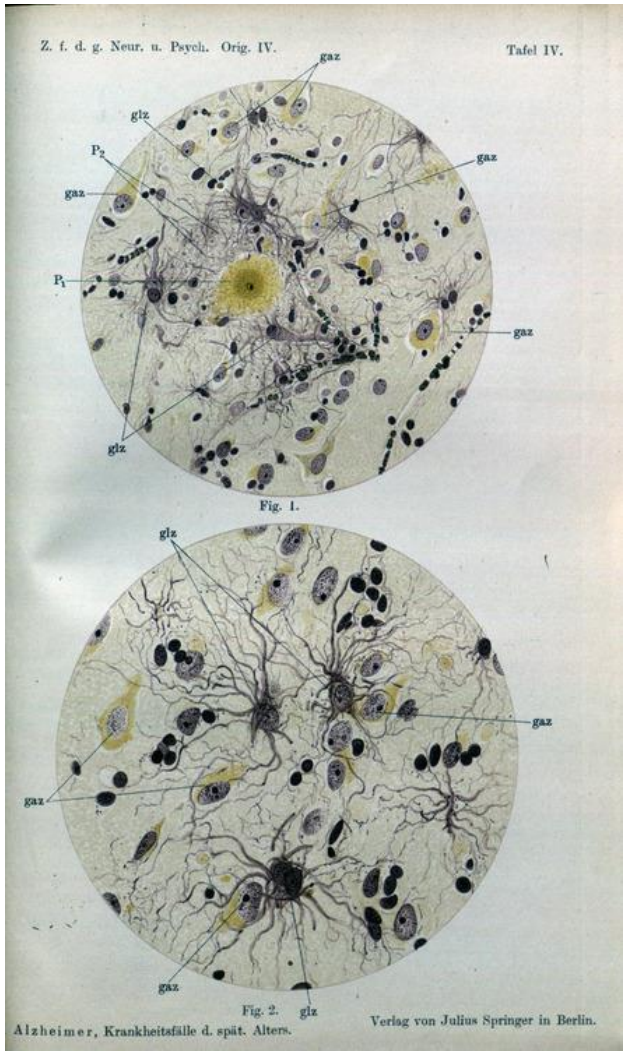



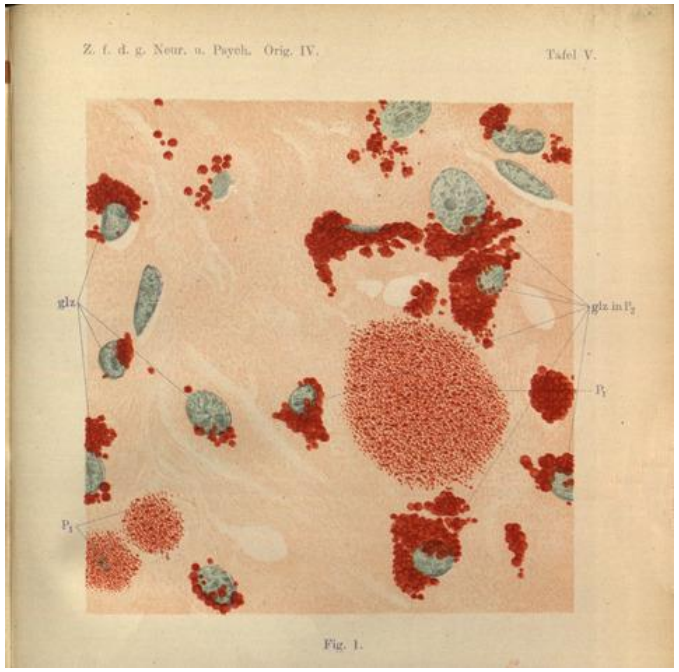



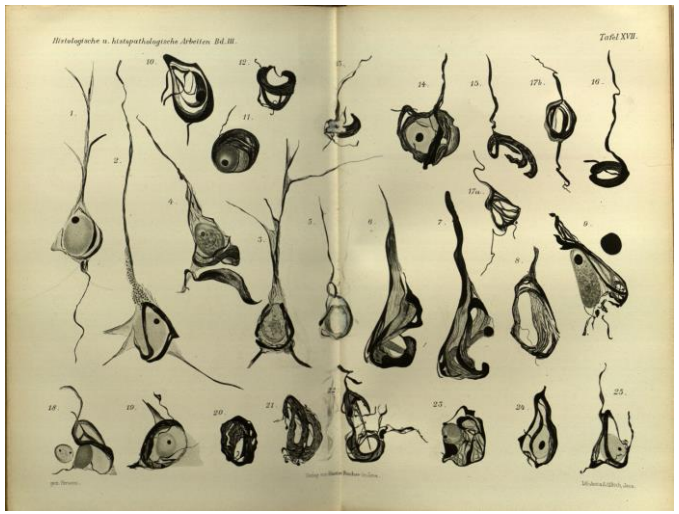


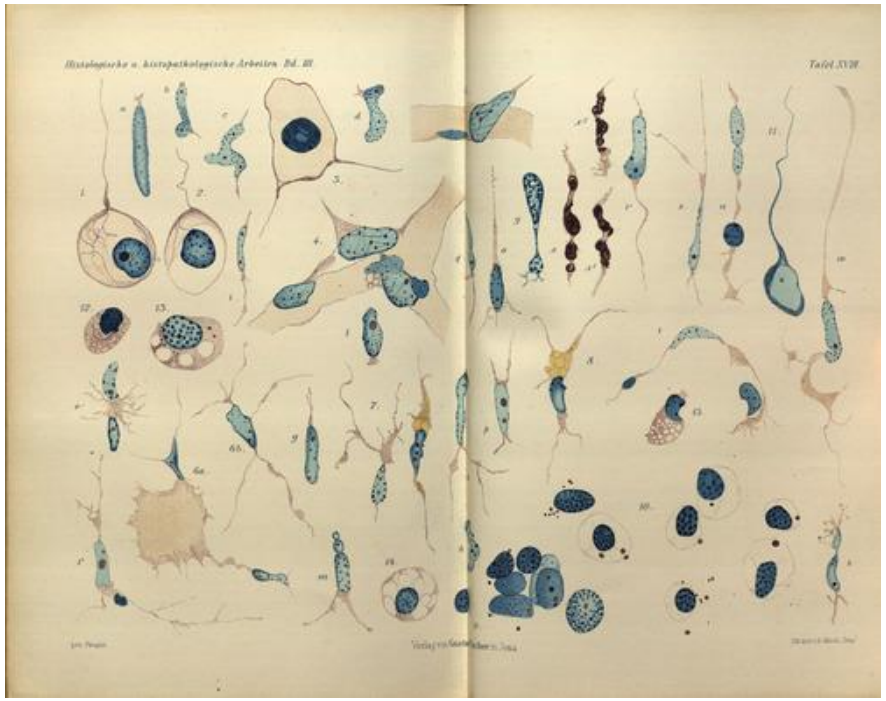
| Cytokine | Involvement in AD pathology |
|---|---|
| TNF-α | TNF-α is involved in inducing acute phase inflammation and is elevated in AD serum, cerebrospinal fluid (CSF) and cortex (Tarkowski et al., 1999, 2003). Anti-TNF-α treatment reduces Aβ deposition, behavioral impairments, and inflammation in AD animal models suggesting TNF-α is detrimental factor in AD (Russo et al., 2012; Tweedie et al., 2012; Detrait et al., 2014; Gabbita et al., 2015). However, one study suggests that TNF-α expression in APP transgenic mice at early stage induces glial uptake of Aβ (Chakrabarty et al., 2011). Additionally, neuronal TNF-α expression in 3xTg AD mice promotes neuronal death (Janelsins et al., 2008). |
| IL-1β | IL-1β is rapidly secreted in response to injury and is an important mediator of inflammatory response as well as cell proliferation, differentiation and apoptosis. IL-1β has been found at high levels near the sites of Aβ plaques (Griffin et al., 1989; Das and Potter, 1995; Licastro et al., 2000). Overexpression of IL-1β in APP/PS1 mice activates a phagocytic population of microglia and reduces Aβ plaques (Ghosh et al., 2013; Cherry et al., 2015). Furthermore, mice deficient in the receptor for IL-1β have lower recruitment of microglia to Aβ plaques, supporting the idea that IL-1β can mediate microglial chemotaxis (Kamphuis et al., 2012). |
| IL-6 | IL-6 may be both proinflammatory and anti-inflammatory and is elevated in the plasma, CSF, and brain of AD patients (Ershler and Keller, 2000; Licastro et al., 2000, 2003; Shibata et al., 2002; Baranowska-Bik et al., 2008; Galimberti et al., 2008). |
| IL-10 | IL-10, also known as cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine upregulated in AD patients (Guillot-Sestier et al., 2015). Overexpression of IL-10 in AD animal models reduces microglial phagocytosis of Aβ leading to cognitive impairment (Chakrabarty et al., 2015; Guillot-Sestier et al., 2015). |
| TGF-β | TGF-β is an immunosuppressive cytokine that protects neurons against damage. A genetic polymorphism in in TGFB1 is associated with the risk of developing AD (Luedecking et al., 2000). Post mortem AD brains contain increased levels, specifically in Aβ plaques (van der Wal et al., 1993; Chao et al., 1994). Long-term overexpression of TGF-β by astrocytes can increase Aβ clearance by microglia and improve cognitive impairment (Wyss-Coray et al., 2001; Chen et al., 2015). Conversely, TGF-β induces astrocyte aggregation and Aβ deposition near brain microvessels (Ueberham et al., 2005). |
| IFN-γ | IFN-γ is a proinflammatory regulatory cytokine that activates microglia. It is primarily produced by T cells and natural killer cells but can also be secreted by microglia and astrocytes (Fultz et al., 1993). IFN-γ is upregulated in the AD brain (Huberman et al., 1994) and a polymorphism is associated with fast progressing AD, suggesting it could play a detrimental role in the course of AD (Asselineau et al., 2015). |

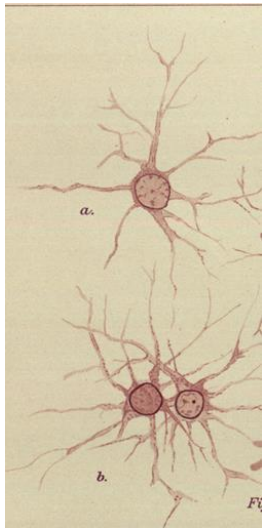




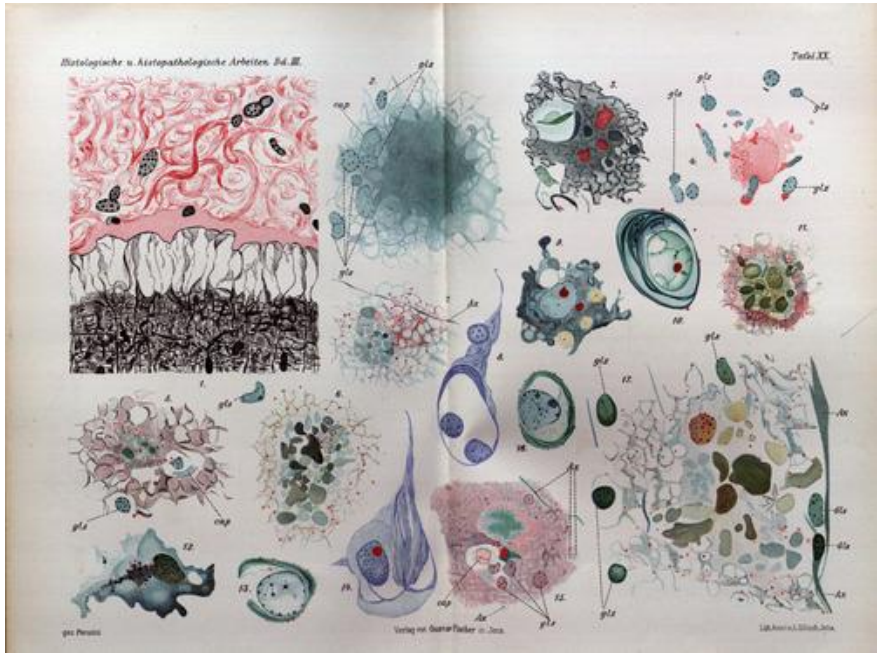



**Table 1 Specific characteristics of inflammation in various tissues and diseases**

| Disease/tissue | Main characteristics of inflammation | Main pathways/markers | Specific complications | Immunotherapy |
|---|---|---|---|---|
| Sepsis | • Exaggerated inflammation and inappropriate endothelial activation combined with immunoparalysis | • Increased cytokines/acute-phase proteins<br>• Activation of complement, coagulation and endothelial cells | • Septic shock<br>• Multiple-organ failure<br>• Opportunistic infections | • Personalized immunotherapy: in hyperinflammation, IL-1Ra, anti-C5a; in immunoparalysis, rIFN-γ, GM-CSF, anti-PD1, rIL7 |
| Inflammation of the gastrointestinal tract | • Permanent structural and functional alterations<br>• Ulcers, strictures, fistulas<br>• Disturbed motility and barrier function | • Increased circulating cytokines and acute-phase proteins<br>• Decreased neutrophil function | • Peptic ulcer disease<br>• Chronic pancreatitis<br>• Celiac disease<br>• Crohn's disease<br>• Ulcerative colitis | • Corticosteroids<br>• Antibodies to TNF, IL-12, IL-23 or integrin $\alpha_4\beta_7$ |
| Rheumatoid arthritis | • Autoantibodies/immune complexes<br>• Proinflammatory cytokines<br>• Macrophage influx<br>• Pathogenic T and B cells | • TNF, IL-1β, IL-6, IL-12, IL-18 and IL-23<br>• IFN-$\gamma^+$IL-17$^+$IL-22$^+$ $T_H$17 cells<br>• RANKL<br>• Anti–citrullinated peptides | • Joint inflammation<br>• Cartilage destruction | • Anti-TNF, IL-1Ra, Anti-IL-6R, Anti-IL-12p40, Anti-IL-17A<br>• JAK–STAT inhibitors |
| Atherosclerosis | • Dyslipidemia and cholesterol deposition<br>• Monocyte and lymphocyte influx in intima<br>• Activation of inflammasomes and cytokines | • Inflammasome and cytokines<br>• hsCRP | • Angina pectoris<br>• Acute myocardial infarction<br>• Stroke | • Statins, including methotrexate and anti-IL-1β (canakinumab) currently in trials |
| Neurodegenerative diseases | • Peripheral infection/inflammation–induced activation of microglial cells<br>• β-amyloid fibrils | • *TREM2*, *CD33*, *PLCG2*<br>• *LRRK2*, *C9orf72*, *TBK1*, *CHCHD10*<br>• Activation of inflammasomes and IL-1β | • Alzheimer's disease<br>• Parkinson's disease<br>• Amyotrophic lateral sclerosis | • Not yet available |
| Liver disease | • Acute liver failure<br>• Hepatic acute-phase response<br>• Steatosis<br>• Cholestasis, hypergamma-globulinemia, fibrosis | • IL-1α and other proinflammatory cytokines<br>• TGF-β for fibrosis | • Acute and chronic hepatitis<br>• Nonalcoholic fatty liver disease<br>• Cirrhosis | • Not yet available |

| | | | | |
|---|---|---|---|---|
| Diabetes | • Infiltration of pancreatic islets with innate and adaptive immune cells and beta-cell apoptosis in T1D<br>• Low-grade innate inflammation in adipose tissue, liver and islets; insulin resistance and beta-cell apoptosis in T2D | • Proinflammatory cytokines IL-1β and TNF<br>• In T1D, also T cell–mediated beta-cell killing | •Macrovascular complications (myocardial infarction, stroke, claudication)<br>•Microvascular complications (kidney, ocular, neuronal) | • Anti-IL-1 (anakinra, canakinumab)<br>• Anti-TNF |
| Lung disease | • Inflammation and hyper-reactivity<br>• Fibrosis | • $T_H2$ and IL-4/IL-5/IL-13 allergic responses (asthma)<br>•Polymorphonuclear leukocyte and macrophage infiltrate, cytokines (COPD)<br>• TGF, integrin $a_v\beta_6$, platelet-derived growth factor β (idiopathic pulmonary fibrosis) | • Asthma<br>• COPD<br>• Idiopathic pulmonary fibrosis | • Corticosteroids<br>• Anti-IL5 |
| Chronic kidney disease | • Low-grade inflammation | • NLRP3 inflammasome, IL1β, IL-6, PGE2, TGF-β | • Kidney insufficiency | • IL-1Ra (anakinra)<br>• IL-1 soluble receptor (rilonacept) |
| Inflammatory skin diseases | • Inflammation with exaggerated $T_H2$ (Alzheimer's disease) or $T_H17$ (psoriasis)<br>• Inflammation in apocrine glands (HS) | • $T_H17$, $T_H2$, antimicrobial peptides<br>• $T_H2$, filaggrin<br>• IL-1β and TNF (HS) | • Psoriasis<br>• Atopic dermatitis<br>• HS | • Antibodies to TNF, IL-17, IL-17R, IL-23 (psoriasis)<br>• Anti-TNF and anti-IL-1 (HS) |
| Autoinflammatory syndromes (e.g., deficiency of IL-1Ra, FMF, HIDS, cryopyrin-associated periodic syndrome) | • Sterile inflammation in joints and peritoneum, fever, systemic inflammation | • Inflammasome/IL-1β pathway<br>IL-1/IL-1Ra balance<br>• NF-κB perturbations<br>• Type I IFN production | • Amyloid deposition (FMF) | • Anti-IL-1 therapies (anakinra, canakinumab, gevokizumab, rilonacept)<br>• TNF inhibitors<br>• JAK–STAT inhibitors |
| Cancer-related inflammation | • Infiltration of tumor-associated macrophages with strong immunosuppressive activity | • M2 macrophage phenotype<br>• Checkpoint proteins PD-1, PD-L1 and CTLA-4<br>• IL-1β, IL-6, TNF, IL-4, IL-10 and TGF-b<br>• Pentraxin-3 | • T cell exhaustion and anergy<br>• Tumor progression | • Checkpoint blockade: antibodies to PD-1, PD-L1 and CTLA-4<br>• Immunostimulatory: BCG, muramyl dipeptide (mifamurtide), β-glucan |

FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D and periodic fever syndrome; HS, hidradenitis suppurativa; hsCRP, high-sensitivity C-reactive protein; T1D, type I diabetes; COPD, chronic obstructive pulmonary disease; BCG, *Mycobacterium bovis* bacillus Calmette–Guerin; GM-CSF, granulocyte-macrophage colony-stimulating factor; r, recombinant.

# Chronický zánět asociovaný s rakovinou

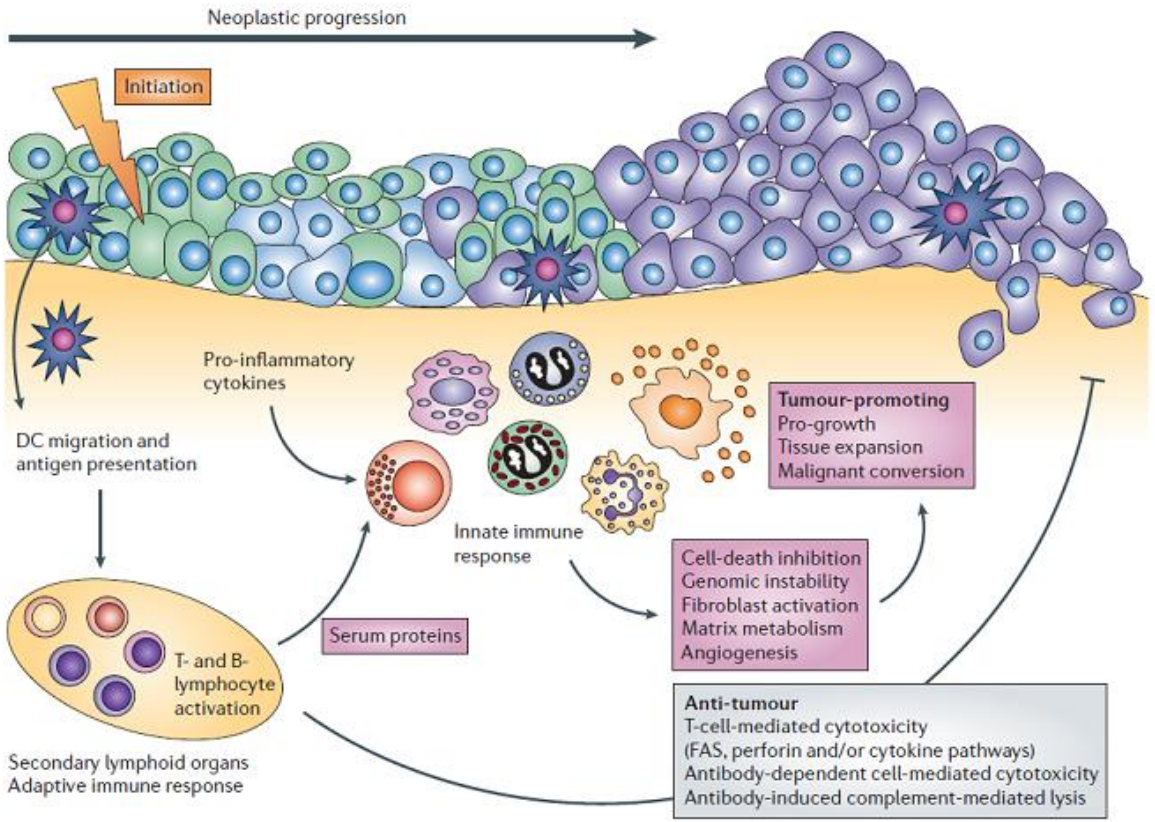



Table 1 **Chronic inflammatory conditions associated with neoplasms**

| Pathologic condition | Associated neoplasm(s) | Aetiologic agent |
|---|---|---|
| Asbestosis, silicosis | Mesothelioma, lung carcinoma | Asbestos fibres, silica particles |
| Bronchitis | Lung carcinoma | Silica, asbestos, smoking (nitrosamines, peroxides) |
| Cystitis, bladder inflammation | Bladder carcinoma | Chronic indwelling, urinary catheters |
| Gingivitis, lichen planus | Oral squamous cell carcinoma | |
| Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis | Colorectal carcinoma | |
| Lichen sclerosus | Vulvar squamous cell carcinoma | |
| Chronic pancreatitis, hereditary pancreatitis | Pancreatic carcinoma | Alcholism, mutation in trypsinogen gene on Ch. 7 |
| Reflux oesophagitis, Barrett's oesophagus | Oesophageal carcinoma | Gastric acids |
| Sialadenitis | Salivary gland carcinoma | |
| Sjögren syndrome, Hashimoto's thyroiditis | MALT lymphoma | |
| Skin inflammation | Melanoma | Ultraviolet light |
| **Cancers associated with infectious agents** | | |
| *Opisthorchis, Cholangitis* | Cholangiosarcoma, colon carcnoma | Liver flukes (*Opisthorchis viverrini*), bile acids |
| Chronic cholecystitis | Gall bladder cancer | Bacteria, gall bladder stones |
| Gastritis/ulcers | Gastric adenocarcinoma, MALT | *Helicobacter pylori* |
| Hepatitis | Hepatocellular carcinoma | Hepatitis B and/or C virus |
| Mononucleosis | B-cell non-Hodgkin's lymphoma, Burkitts lymphoma, | Epstein-Barr Virus |
| AIDS | Non-Hodgkin's lymphoma, squamous cell carcinomas, Kaposi's sarcoma | Human immunodeficiency virus, human herpesvirus type 8 |
| Osteomyelitis | Skin carcinoma in draining sinuses | Bacterial infection |
| Pelvic inflammatory disease, chronic cervicitis | Ovarian carcinoma, cervical/anal carcinoma | Gonnorrhoea, chlamydia, human papillomavirus |
| Chronic cystitis | Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen | Schistosomiasis |

https://www.nature.com/articles/nature01322
https://www.astro.org/Patient-Care-and-Research/Research/Professional-Development/Research-Primers/Tumor-Immune-Interactions