

Co je nového u cytokinů – jak si žije IL-1 rodina a další příbuzní?

Ilja Stríž



Zámek Sychrov 27.4. 2018





Padouch nebo hrdina, my jsme jedna rodina!

Limonádový Joe



## Prozánětlivé

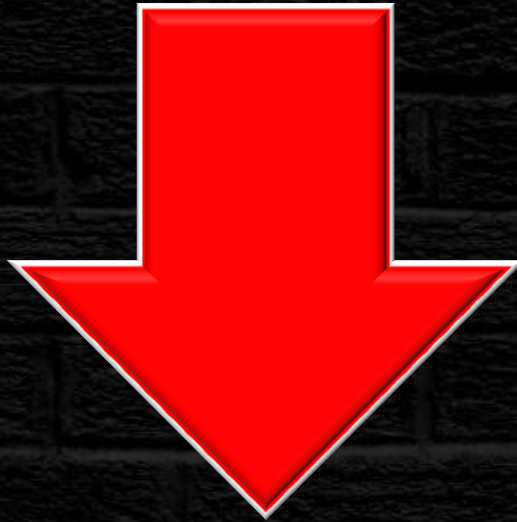
IL-1 $\alpha$

IL-1 $\beta$

IL-18

IL-33

IL-36  $\alpha$ ,  $\beta$ ,  $\gamma$



## Protizánětlivé

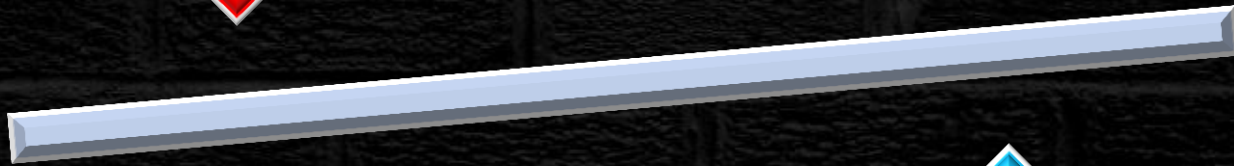
IL-1Ra

IL-18BP

IL-36Ra

IL-37

IL-38



# IL-1 rodina

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graph TD; A[IL-1 rodina] --- B[IL-1 podrodina]; A --- C[IL-18 podrodina]; A --- D[IL-36 podrodina]; B --- B1[IL-1α]; B --- B2[IL-1β]; B --- B3[IL-33]; C --- C1[IL-18]; C --- C2[IL-37]; D --- D1[IL-36α,β,γ]; D --- D2[IL-38];
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## IL-1 podrodina

IL-1 $\alpha$

IL-1 $\beta$

IL-33

## IL-18 podrodina

IL-18

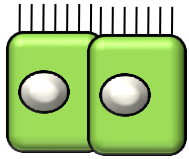
IL-37

## IL-36 podrodina

IL-36 $\alpha,\beta,\gamma$

IL-38

**epithelial cells**



adhesion molecules  
chemokines

**hepatocytes**



acute phase  
proteins

**fibroblasts**



proliferation  
migration  
collagen

**endothelial cells**



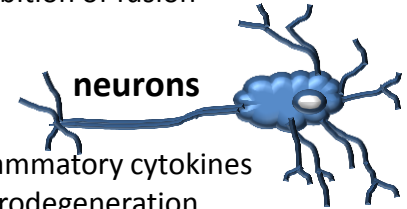
procoagulant activity  
adhesion molecules  
NO synthesis

**muscle cells**



apoptosis  
pro-inflammatory genes  
inhibition of fusion

**neurons**



pro-inflammatory cytokines  
neurodegeneration  
thermoregulation in hypothalamus

**neutrophils**



recruitment  
phagocytosis  
respiratory burst

**eosinophils**



activation?

**mast cells**



Th2 cytokines  
pro-inflammatory cytokines

**NK cells (ILC1)**



IFN $\gamma$  induction  
differentiation

**innate lymphoid cells**



activation of ILC2  
Inhibition of ILC3

**Th cells**



expansion  
Th17 and Th22  
differentiation

**Tc cells**



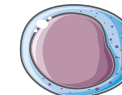
expansion  
granzyme B

**Treg**



Foxp3 inhibition

**B cells**

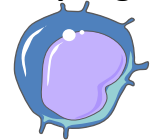


limited direct effects  
differentiation of B cell lines

**monocytes**



**macrophages**



pro-inflammatory cytokines  
chemokines  
differentiation  
phagocytosis  
antigen presentation

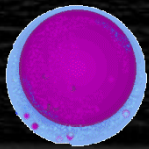
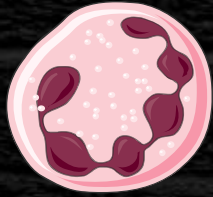
**dendritic cells**



# Interleukin -1



# Indukce chemokinových genů v renálním epitelu

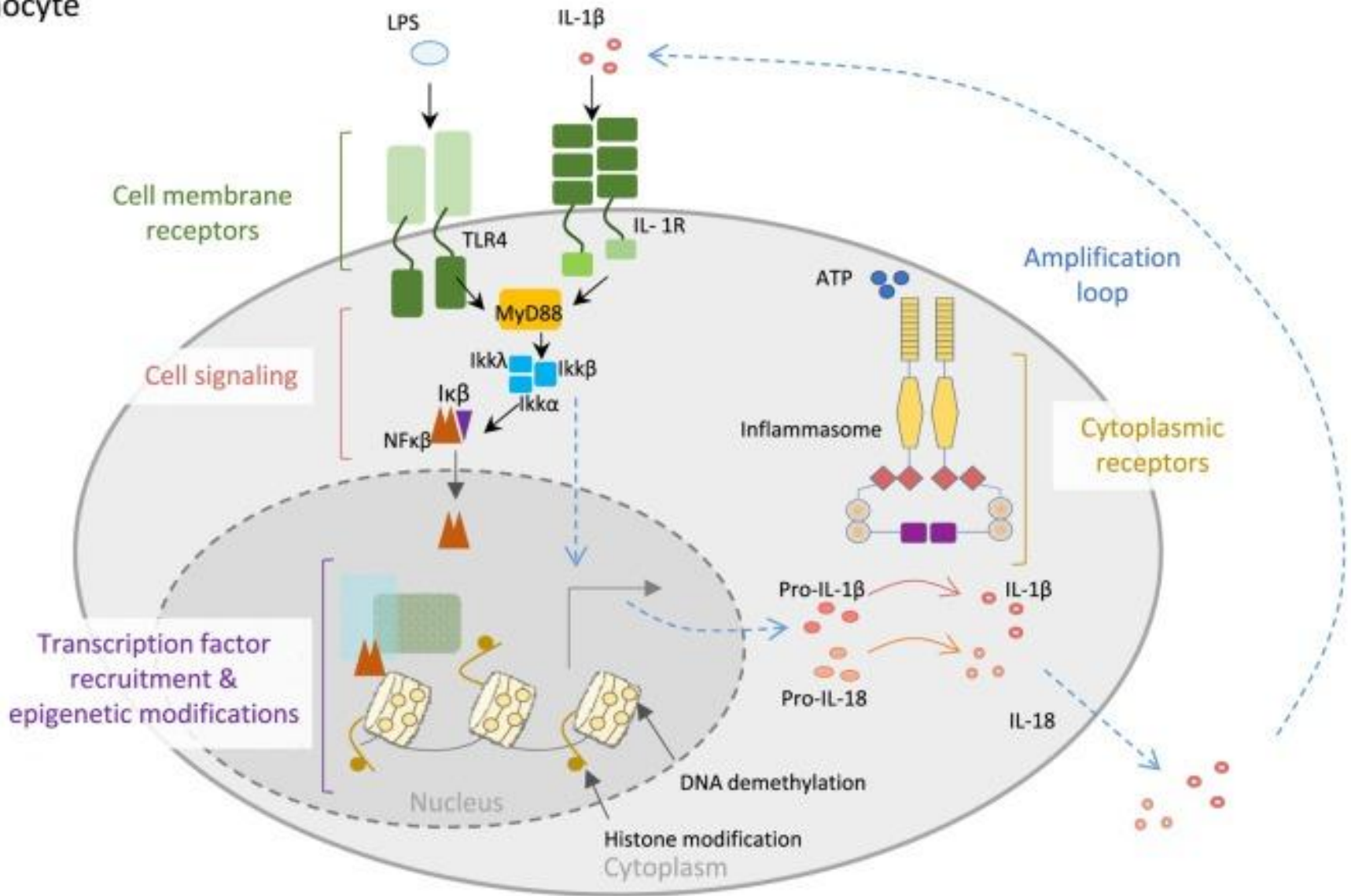


	Control	TNF- $\alpha$	IL-1 $\beta$
CXCL5 (ENA-78)	blue	red	red
CXCL6 (GCP-2)	blue	red	red
CXCL8 (IL-8)	blue	red	red
CXCL3 (GRO- $\gamma$ )	blue	blue	blue
CXCL2 (GRO- $\beta$ )	blue	red	red
CXCL1 (GRO- $\alpha$ )	blue	red	red
CCL20 (MIP-3 $\alpha$ )		blue	blue
CCL2 (MCP-1)		blue	blue
CCL5 (RANTES)		blue	blue
CCL4 (MIP-1 $\beta$ )			blue

moderate expression – blue  
strong expression - red



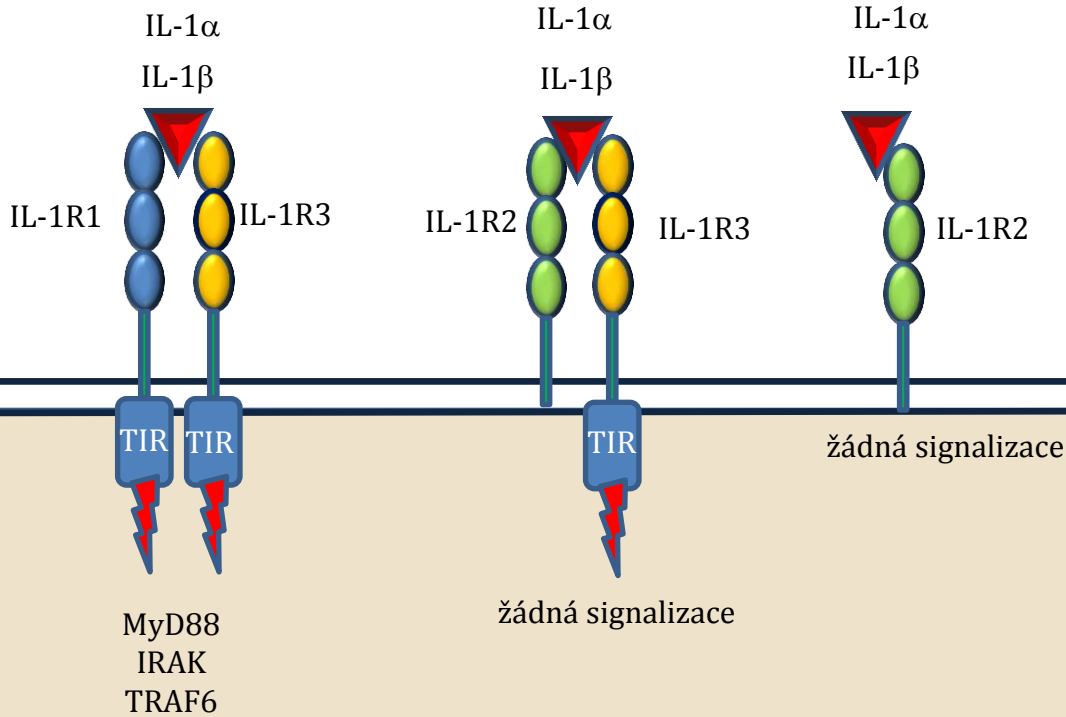
# Monocyte



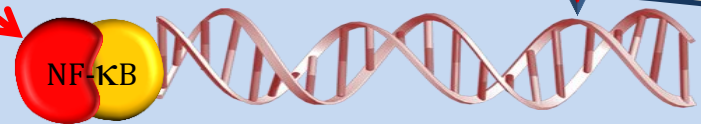


# IL-1 alfa a beta ... IL-1 receptorový antagonist

IL-Ra vazba k IL-1R1 nebo IL-1R2 = žádná signalizace



NFκB translokace



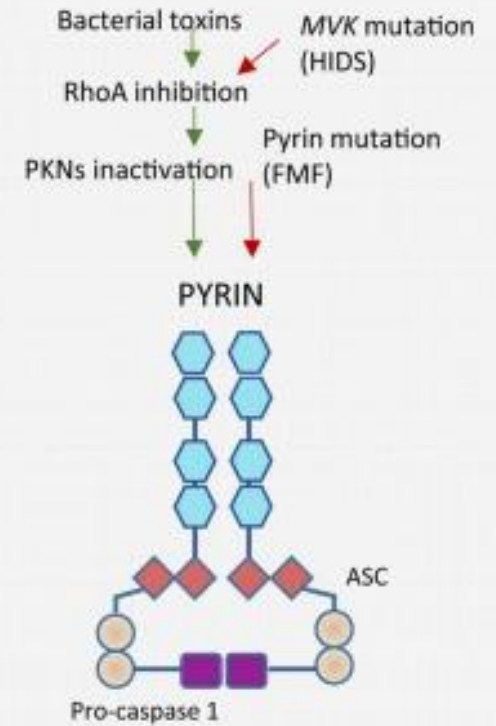
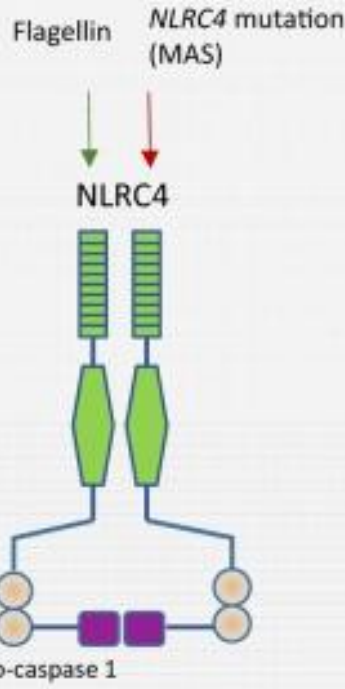
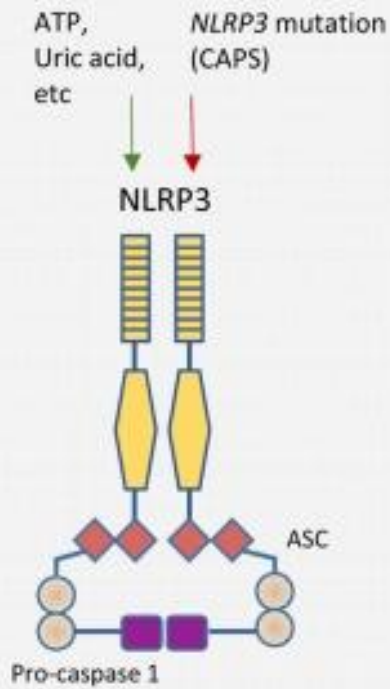
endogení

IL-1α

**Cryopyrin associated periodic syndromes (CAPS)**

**Macrophage activation syndrome (MAS)**

**Familial Mediterranean Fever (FMF) & hyper IgD syndrome (HIDS)**



Pro-IL-1 $\beta$

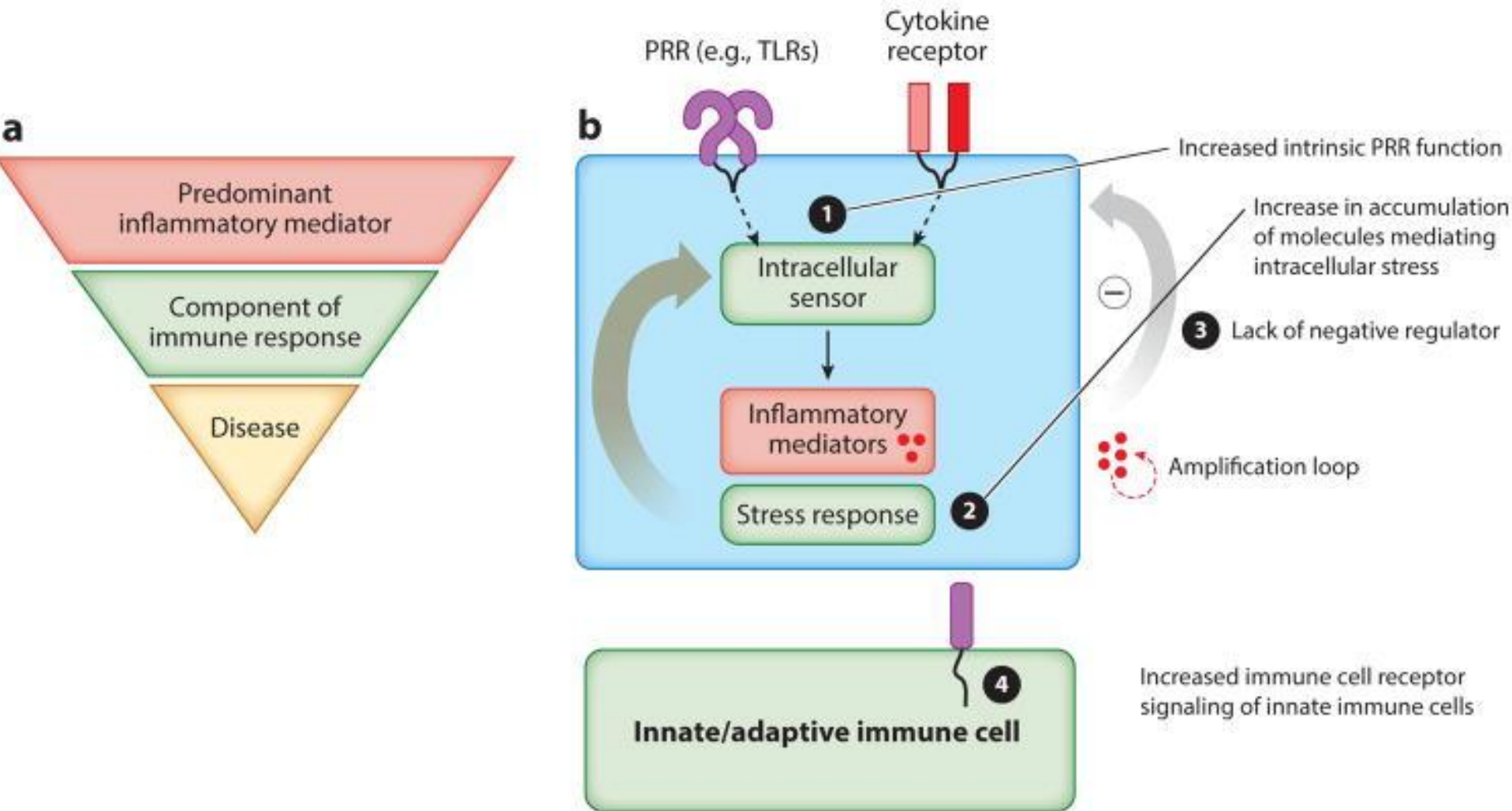
Pro-IL-18



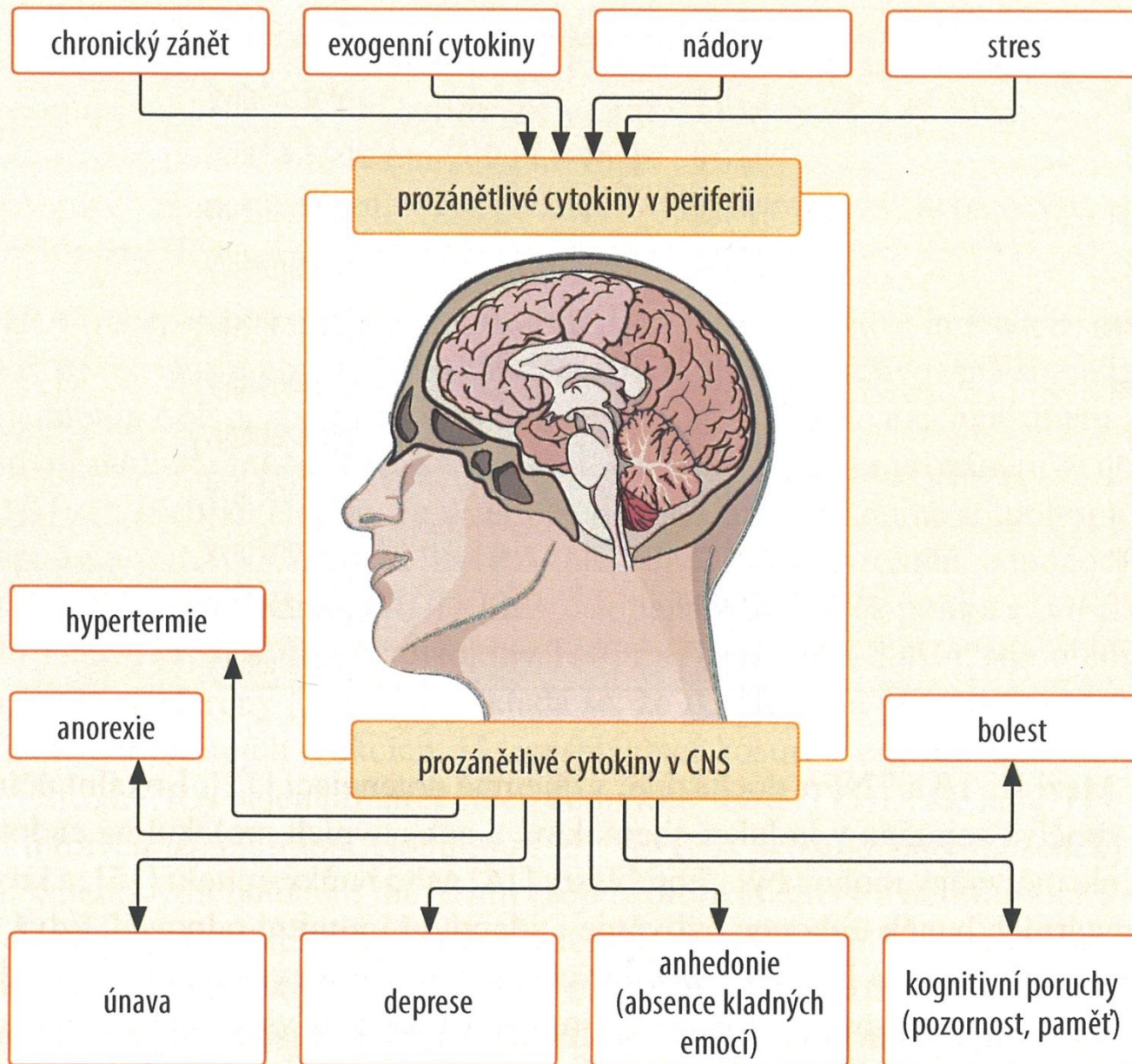
IL-1 $\beta$

IL-18

# Vznik autoinflamatorního onemocnění







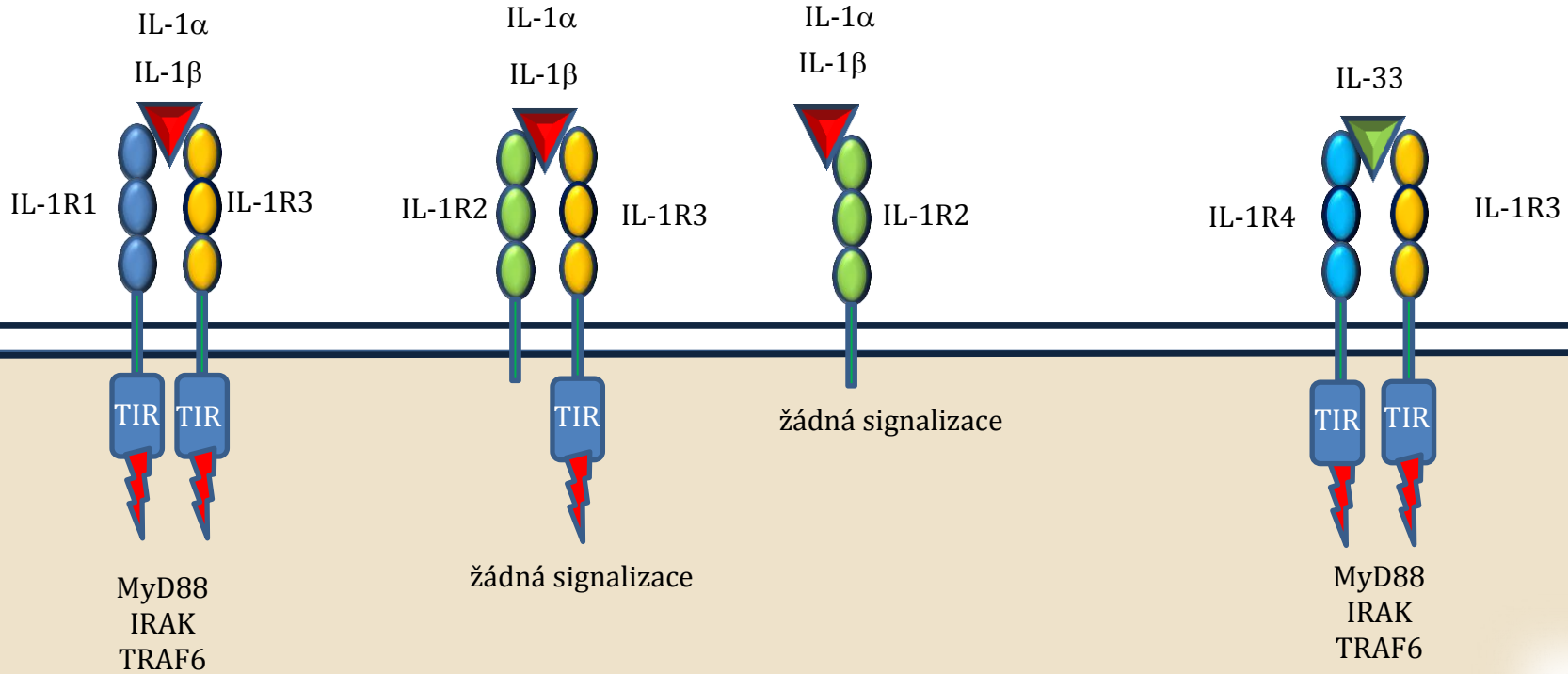
# Projevy autoinflamatorních onemocnění

Choroba	Gen	Protein	Dědičnost	Klinická manifestace
FMF	<i>MEFV</i>	Pyrin	AR/AD	Horečka, artralgie, exanthem na DK, záněty sliznic, amyloidóza
TRAPS	<i>TNFRSF1A</i>	TNFR1	AD	Horečka, myalgie, exanthem, artralgie, záněty sliznic, periorbitální edém
HIDS	<i>MVK</i>	Mevalonát kináza	AR	Horečka, exanthem, artralgie, bolest břicha, průjem, konjunktivitis, cervikální lymfadenopatie, splenomegalie
CAPS	<i>NLRP3</i>	Kryopyrin	AD	Horečka, urtika, intolerance chladu, konjunktivitis, artralgie, postižení sluchu

# IL-1podrodina

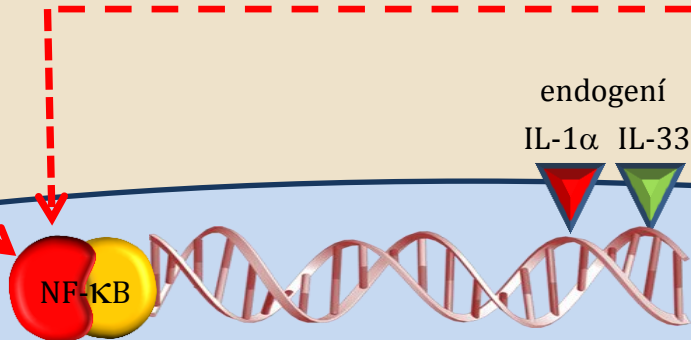


IL-Ra vazba k IL-1R1 nebo IL-1R2 = žádná signalizace



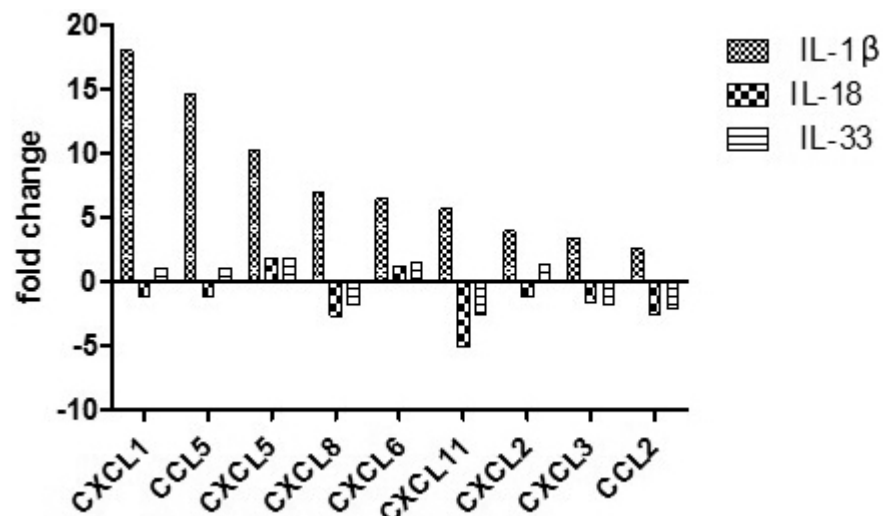
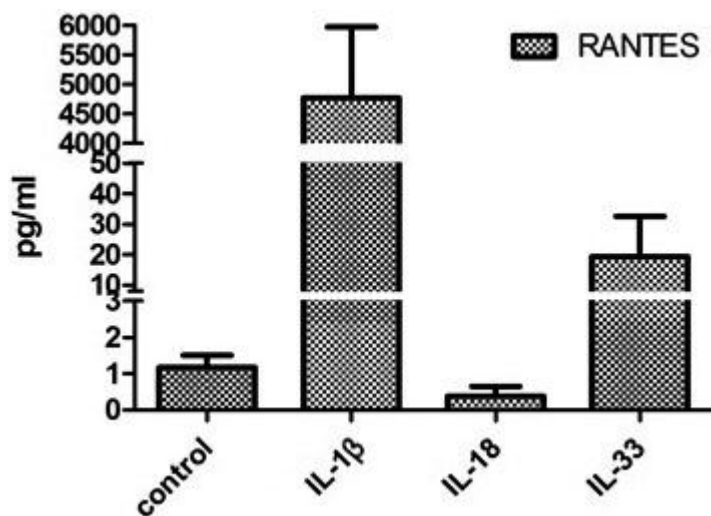
NFkB translokace

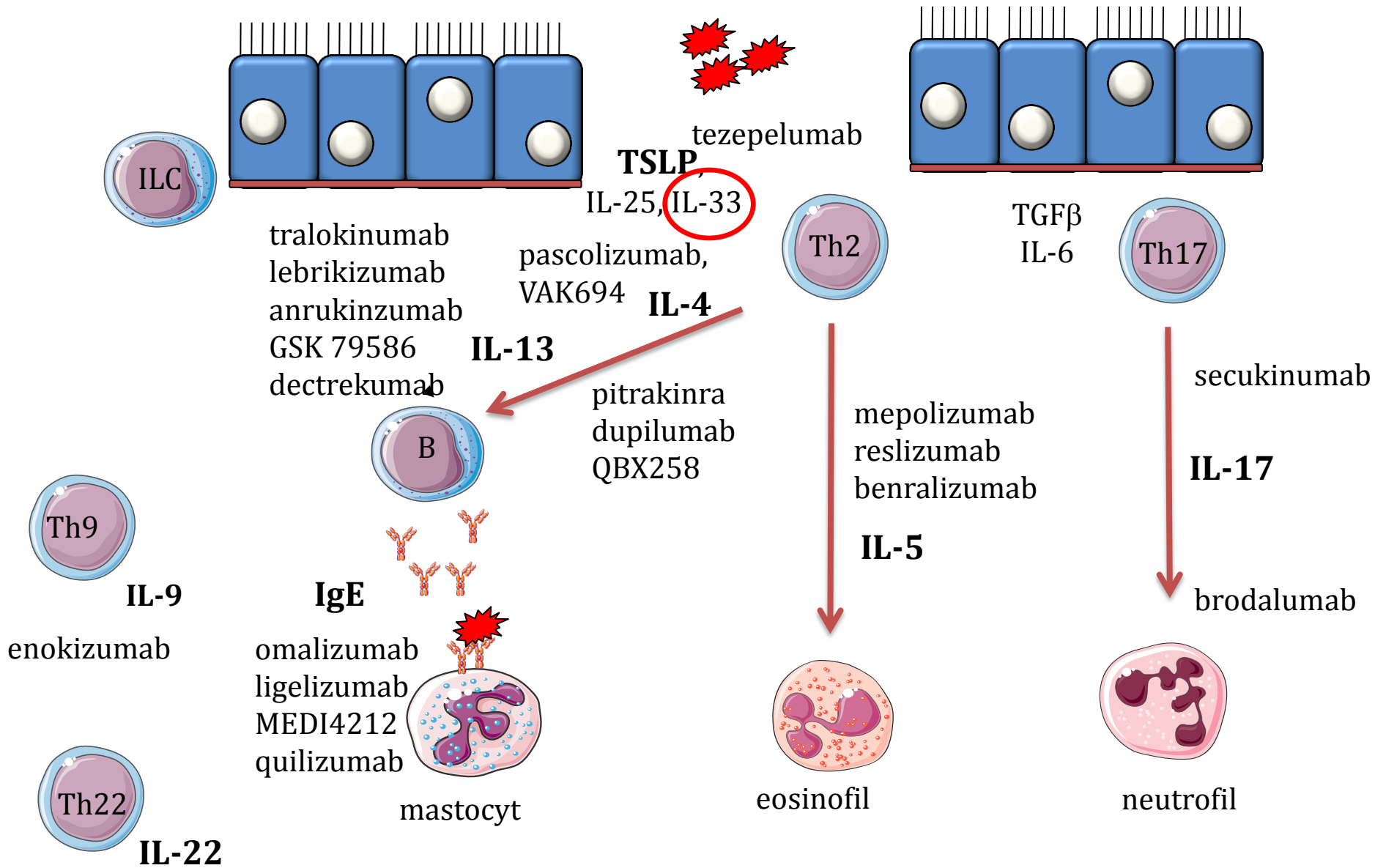
NFkB translokace





IL-33 má nižší schopnost indukovat tvorbu chemokinů oproti IL-1 $\beta$





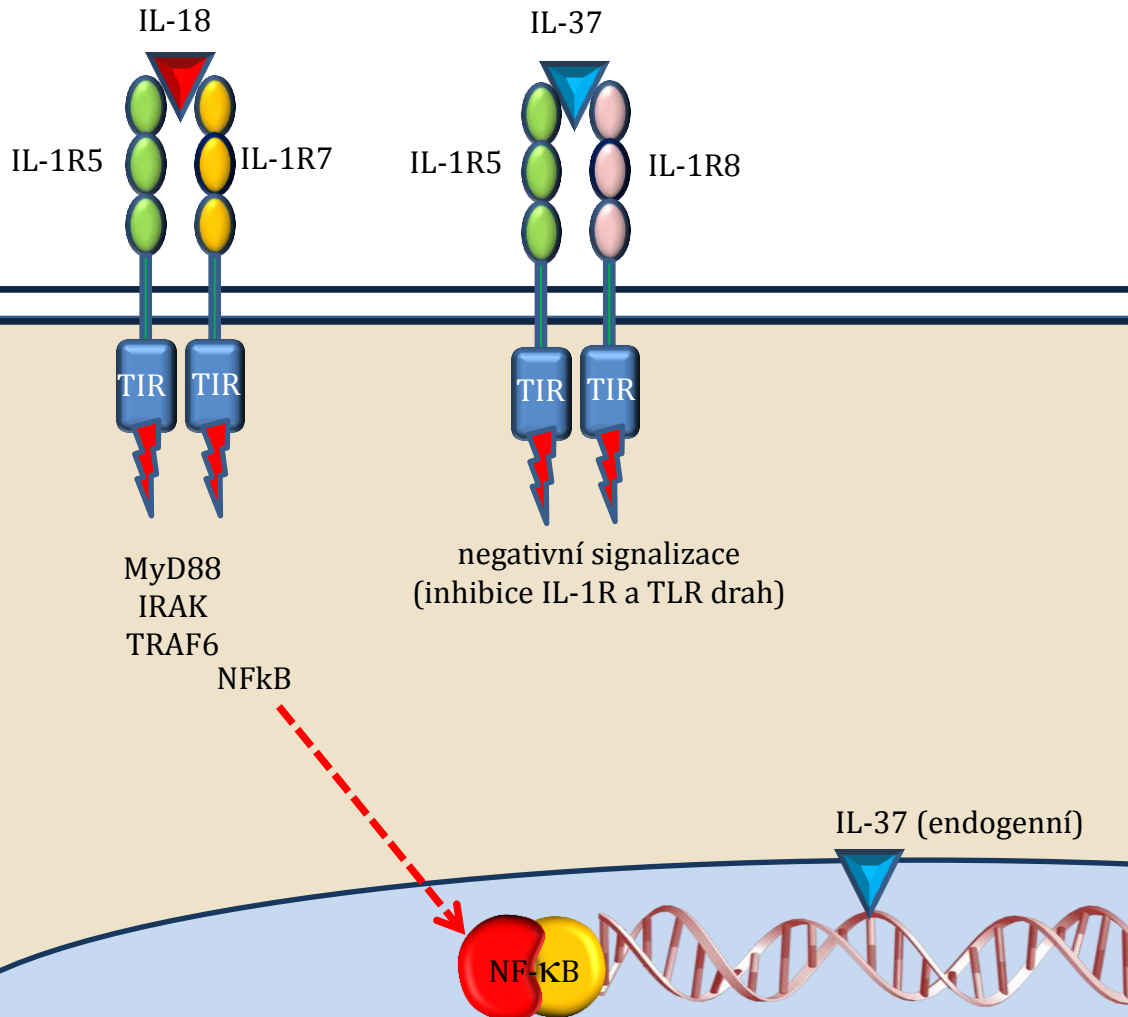
# alergický zánět



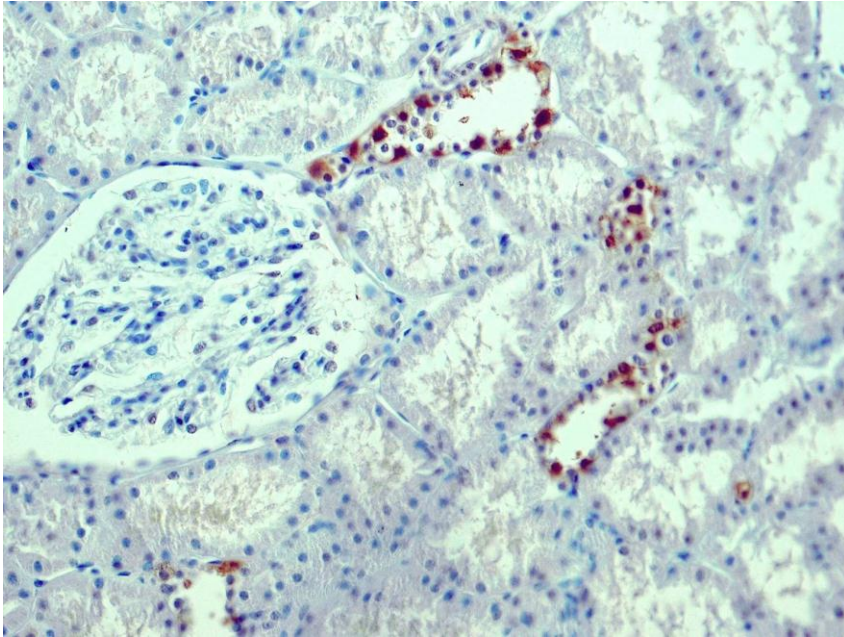


# IL-18 podrodina

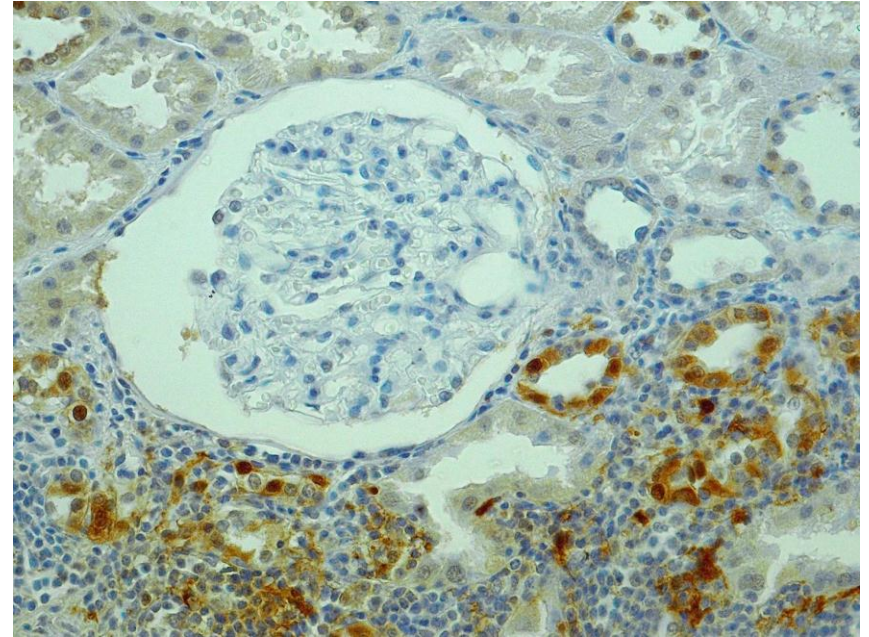
IL-18BP vyváže IL-18= žádná signalizace



# Renální epitel jako zdroj IL-18 v transplantované ledvině

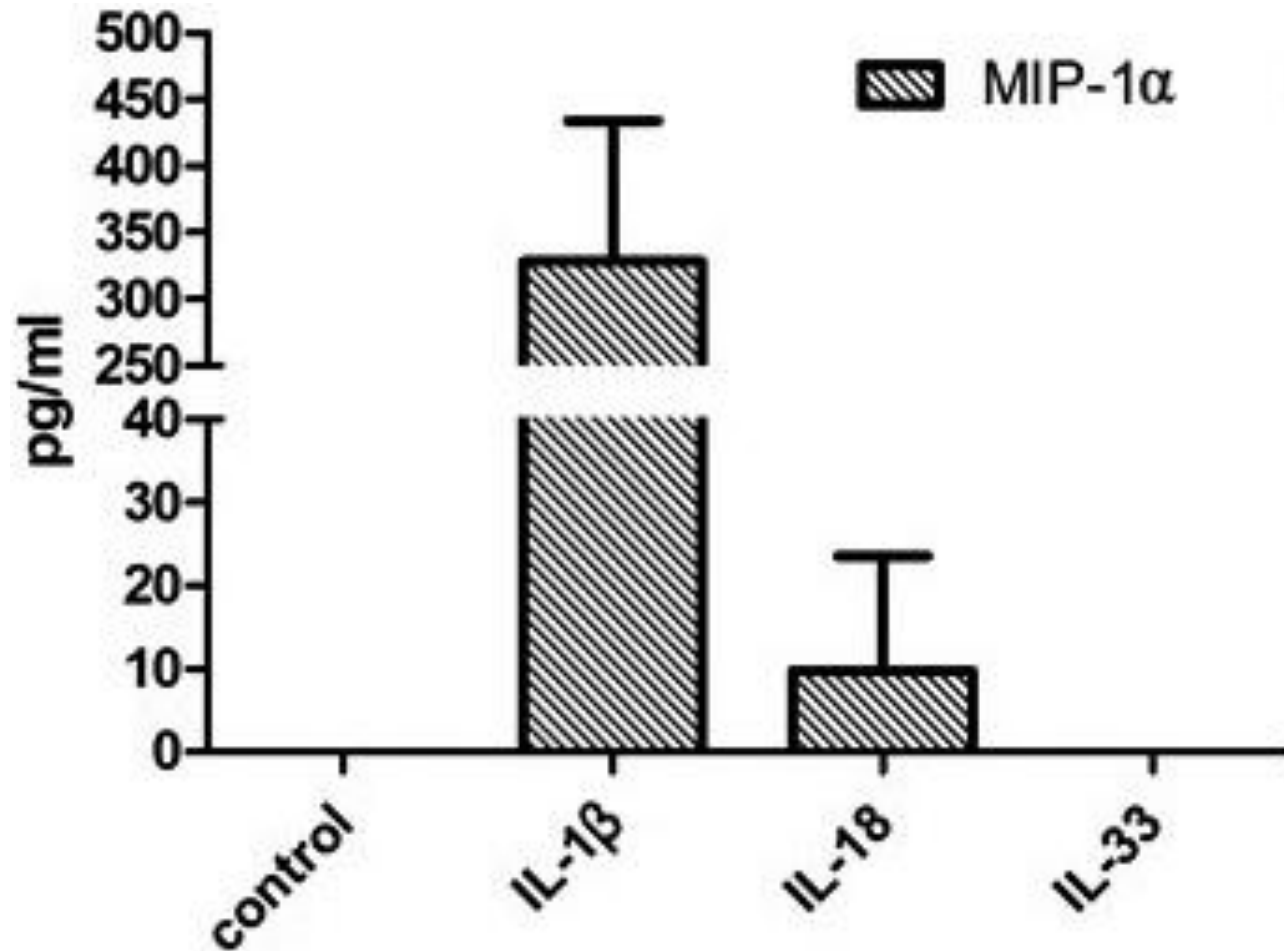


Biopsie pacienta bez rejekce

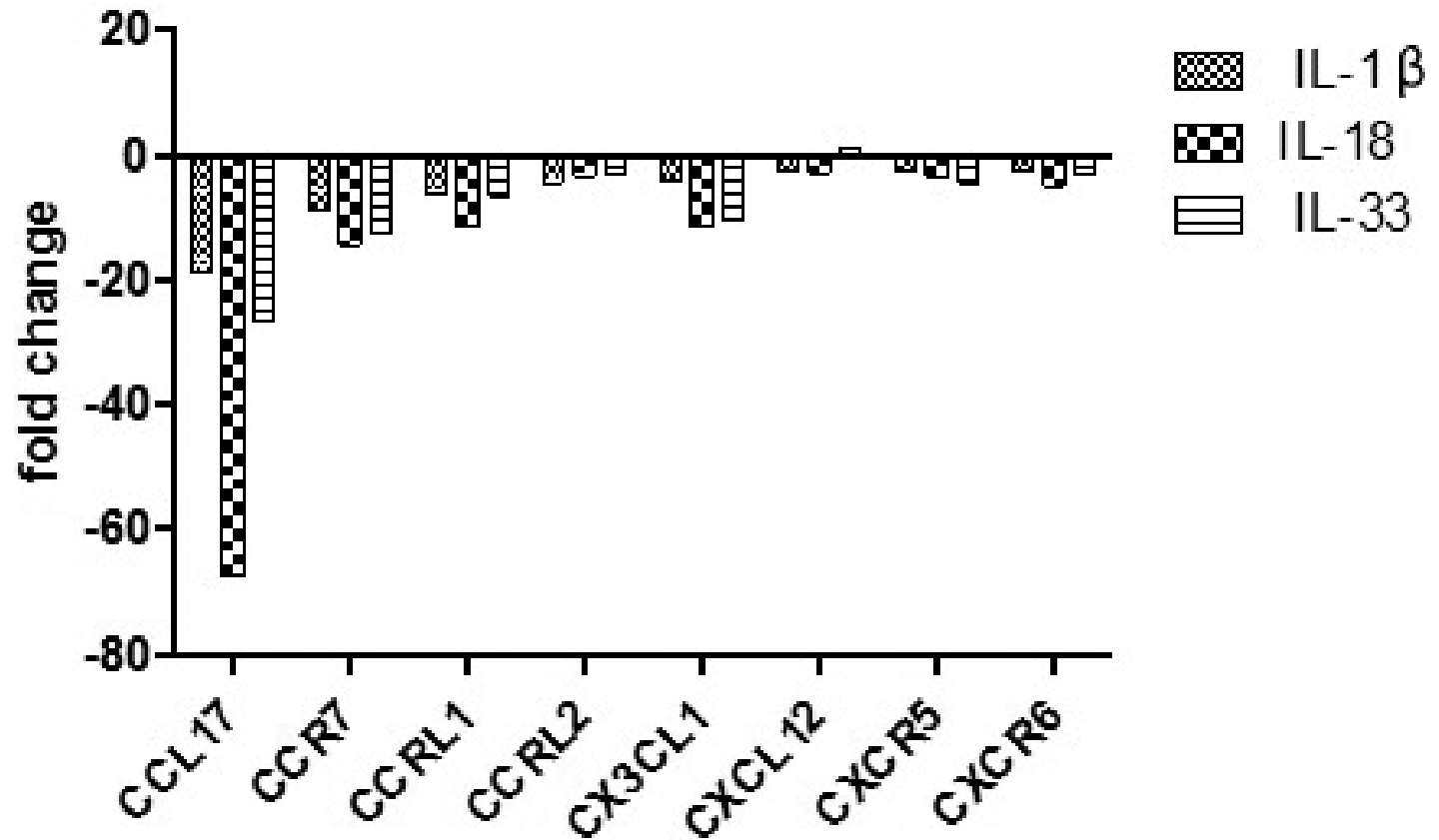


Biopsie pacienta s akutní rejekcí

IL-18 mírně indukuje tvorbu MIP-1 $\alpha$  (CCL3) v respiračním epitelu



# IL-18 inhibuje genovou expresi chemokinu CCL17 (TARC) v respiračním epitelu





# IL-1 rodina

```
graph TD; A[IL-1 rodina] --- B[IL-1 podrodina]; A --- C[IL-18 podrodina]; A --- D[IL-36 podrodina]; B --- B1[IL-1α]; B --- B2[IL-1β]; B --- B3[IL-33]; C --- C1[IL-18]; C --- C2[IL-37]; D --- D1[IL-36 α,β,γ]; D --- D2[IL-38];
```

## IL-1 podrodina

IL-1 $\alpha$

IL-1 $\beta$

IL-33

## IL-18 podrodina

IL-18

IL-37

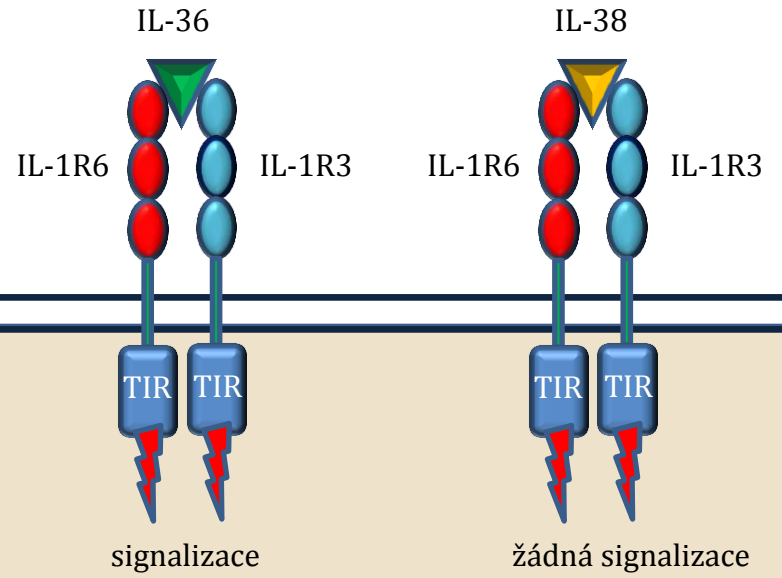
## IL-36 podrodina

IL-36  $\alpha,\beta,\gamma$

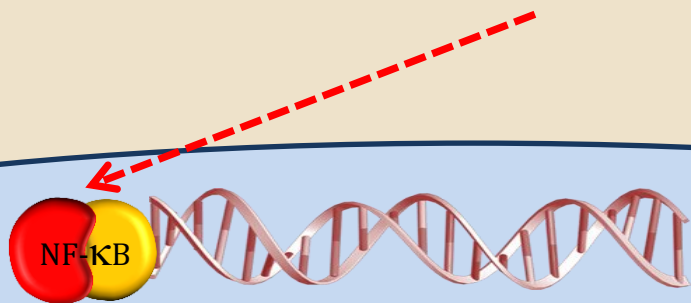
IL-38

# IL-36 podrodina

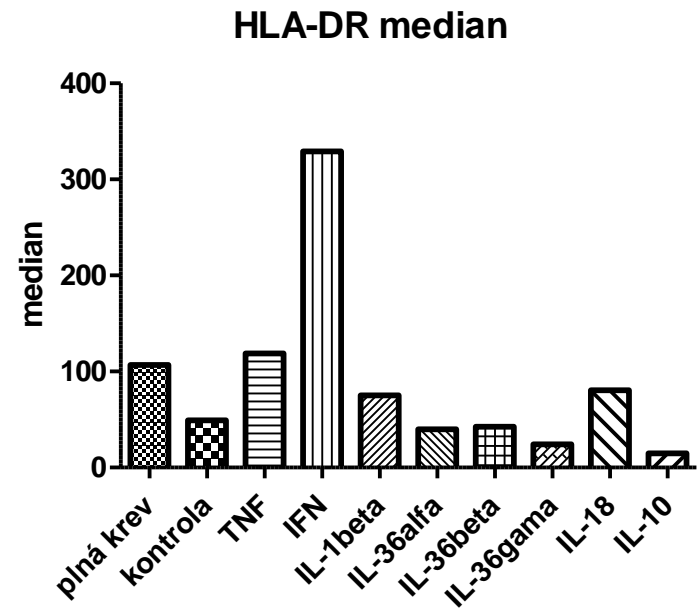
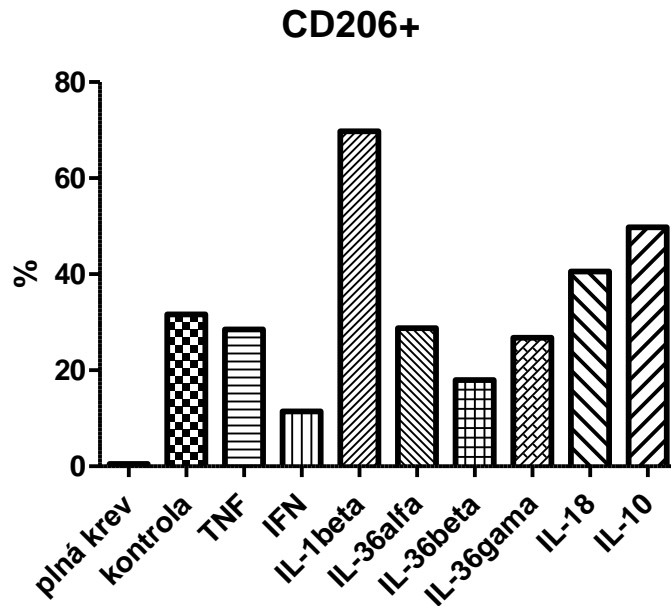
IL-36Ra se váže na IL-1R6 = žádná signalizace



MyD88  
IRAK  
TRAF6  
NFkB



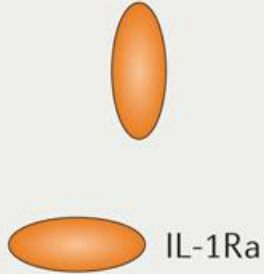
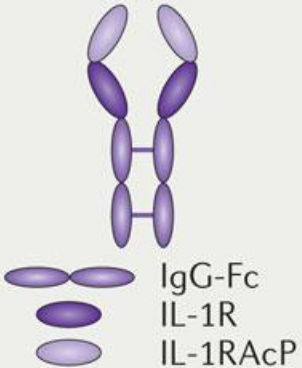
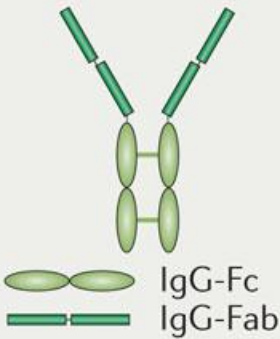
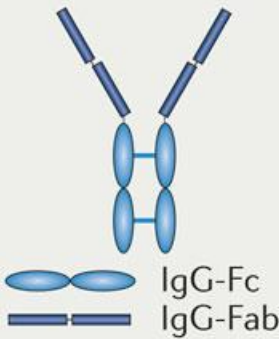
IL-36 $\beta$  spolu s IFN $\gamma$  snižuje expresi CD206 na periferních monocytech, ale nemá vliv expresi HLA-DR



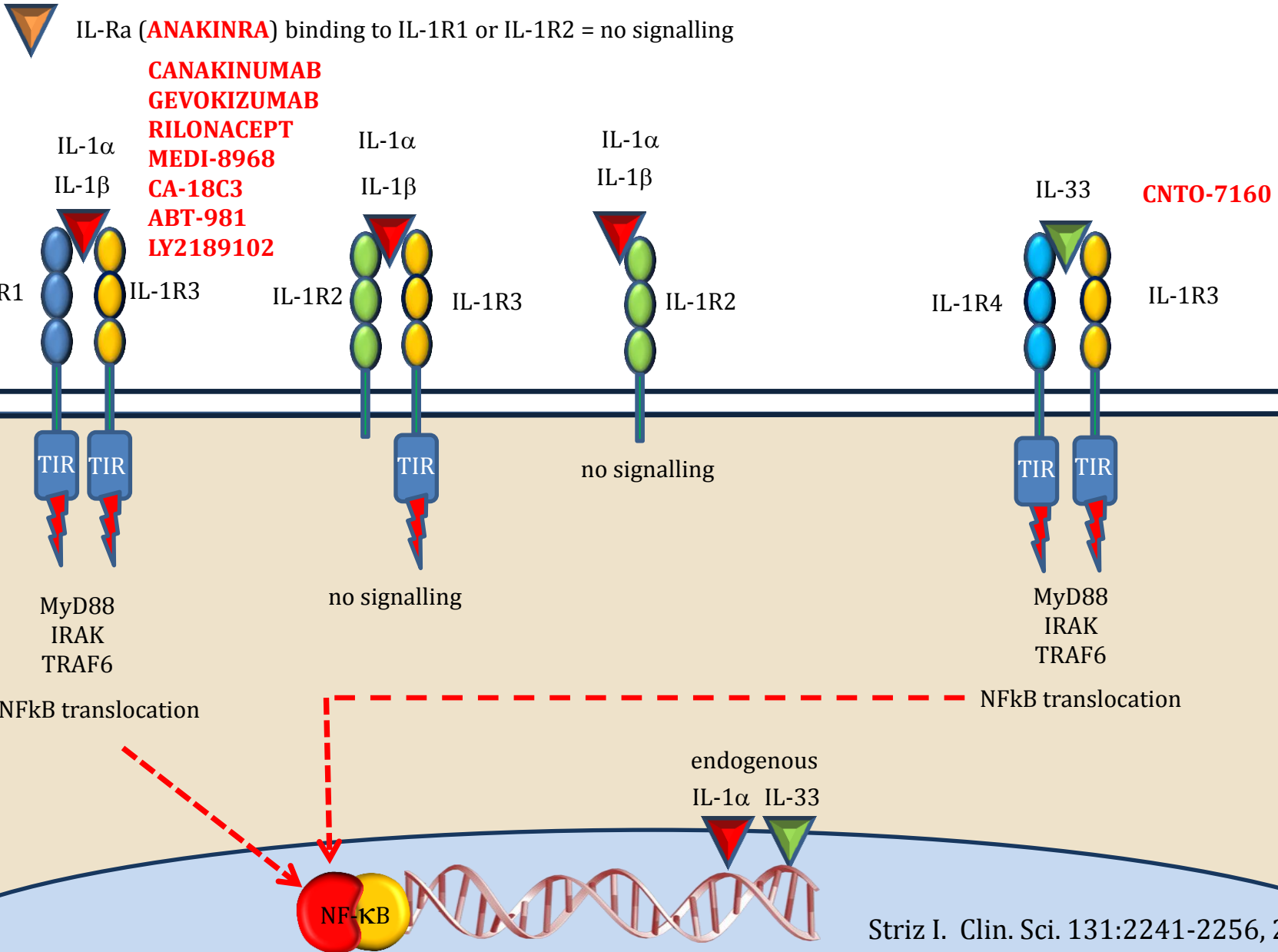
# Možnosti léčebného ovlivnění agresivních členů IL-1 rodinného klanu ?





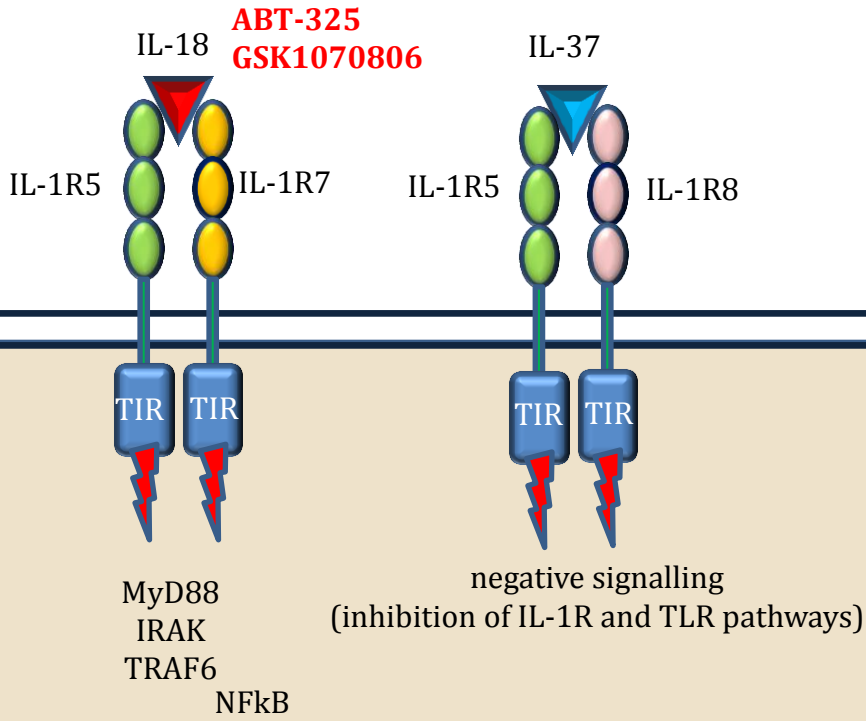
	Anakinra	Riloncept	Canakinumab	Gevokizumab
				
Parameter	IL-1Ra	IL-1R/IL-1RAcP-Fc	Anti-IL-1 $\beta$ antibody	Anti-IL-1 $\beta$ antibody
Structure	Recombinant protein	Fc fusion protein	IgG1 mAb	IgG2 mAb
Binding to IL-1 $\alpha$	Yes	Yes	No	No
Affinity to IL-1 $\beta$	None	0.5 pmol	23 pmol	300 fmol
Half 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

# IL-1 subfamily



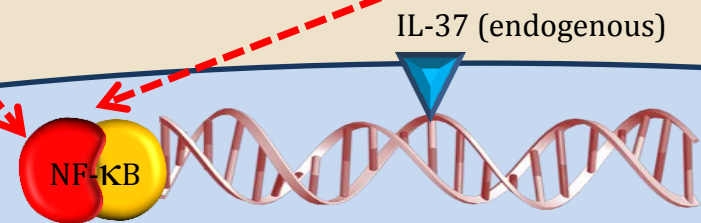
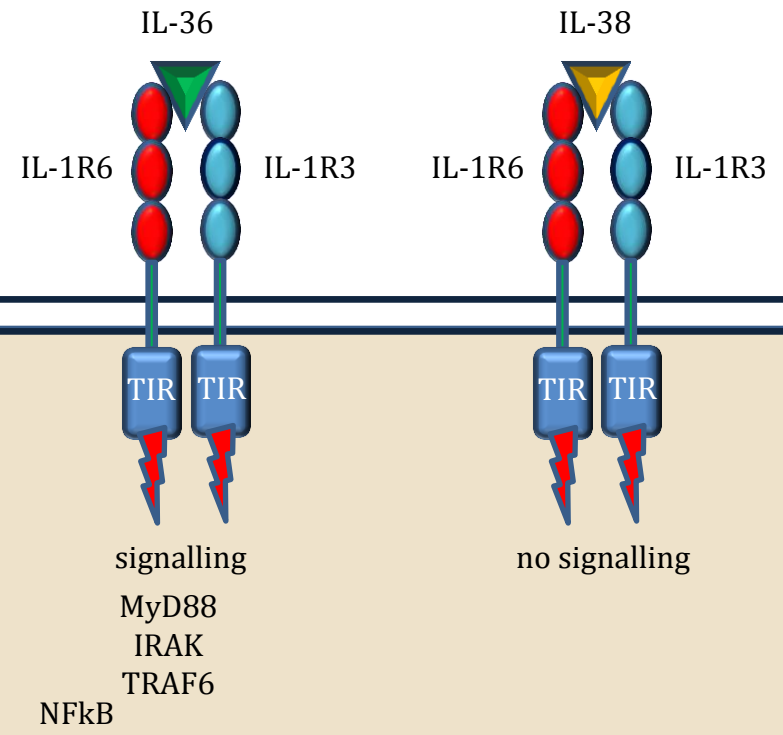
# IL-18 subfamily

IL-18BP (**TADEKINIG ALFA**) binding to IL-18= no signalling



# IL-36 subfamily

IL-36Ra binding to IL-1R6 = no signalling



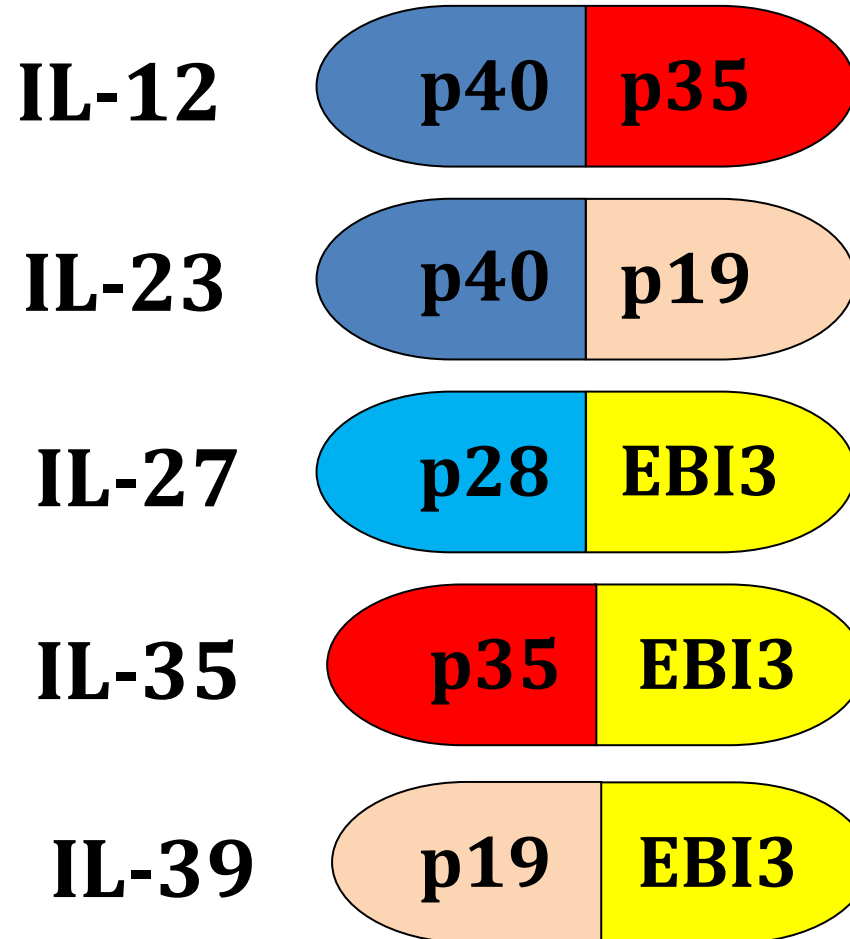
**IL-38 již není poslední !**

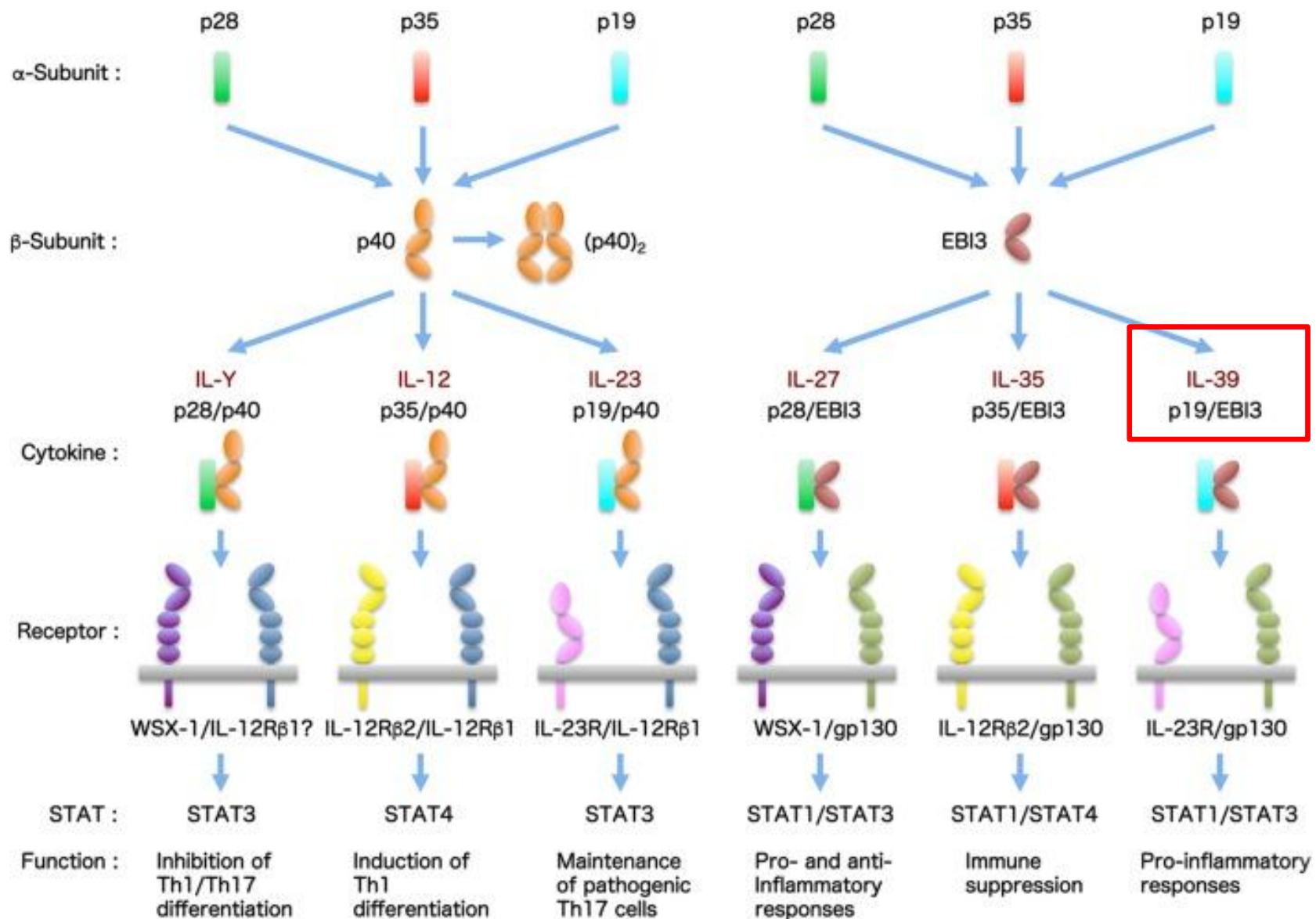


# Nový přírůstek do IL-12 rodiny



# IL-12 rodina





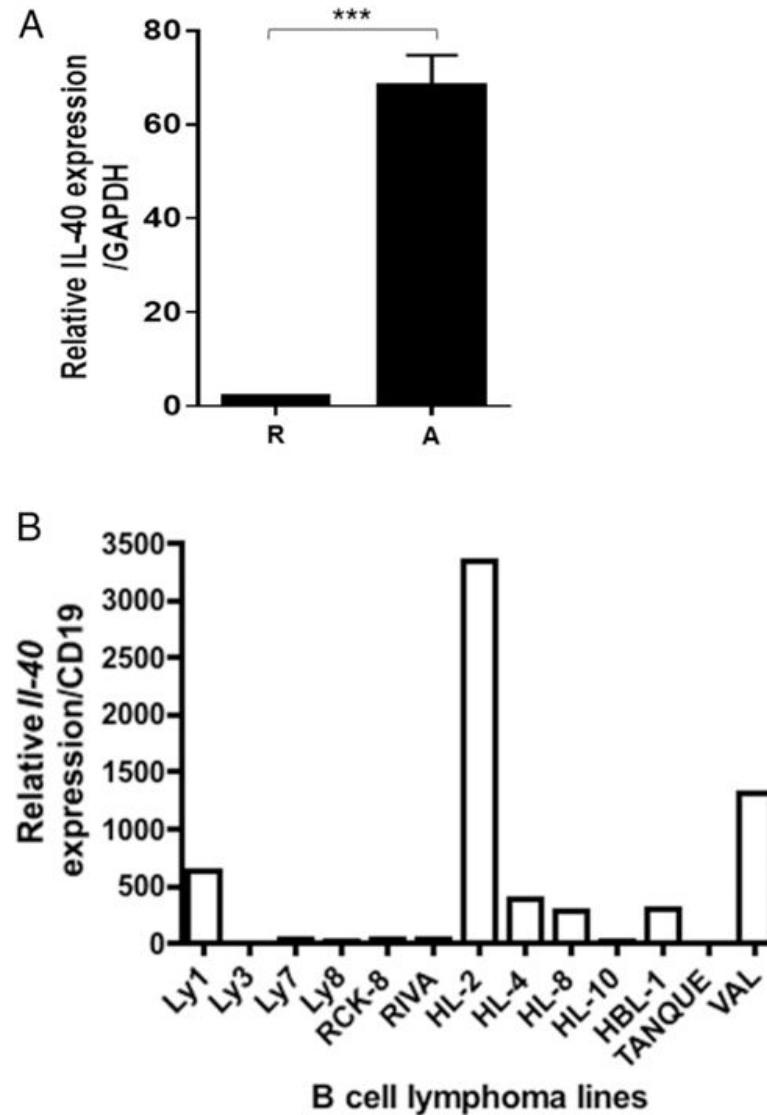
Luo Y et al. Elevated serum IL-39 in patients with ST-segment elevation myocardial infarction was related with left ventricular systolic dysfunction. *Biomarkers in Medicine* 11:6 2017

Scholz GM et al. MEK-ERK signaling diametrically controls the stimulation of IL-23p19 and EBI3 expression in epithelial cells by IL-36 $\gamma$ . *Immunol Cell Biol* 2018 (v tisku)





IL-40 mRNA je exprimována v aktivovaných B lymfocytech a některých liniích





A photograph of a dog standing on a dirt path in a misty forest. The dog is a medium-sized breed with a mottled coat, possibly a mix of breeds, and is looking towards the camera. The path is made of reddish-brown earth and leads into the distance, where the trees are shrouded in a thick mist. The forest is composed of tall, thin evergreen trees. The overall atmosphere is quiet and somewhat somber due to the fog.

**Děkuji za pozornost !**



