Adhézió – angiogenezis - chemokinek

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DEÁOK Reumatológiai Tanszék

www.rheumatology.hu

DEBRECENI EGYETEM

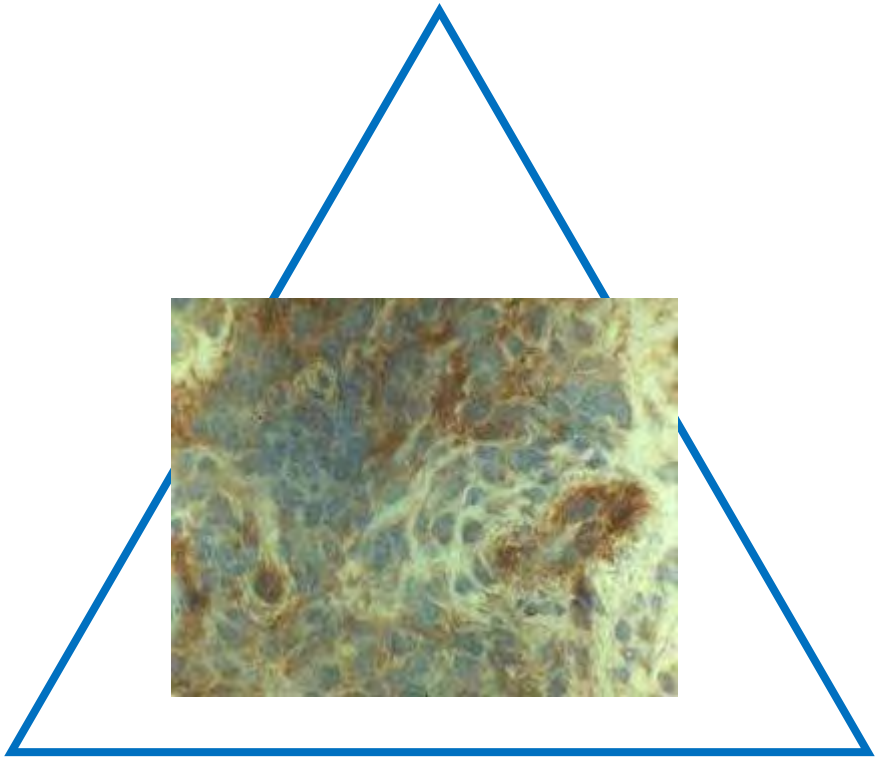
Tematika

- Bevezetés
- Sejtadhézió – migráció – homing
- Chemokinek
- Angiogenezis
- Célzott terápiás lehetőségek

Bevezetés

Az igazi Bermuda-háromszög

Adhézió-migráció



chemokinek

angiogenesis

RA patogenezise: jó példa

INICIÁCIÓS SZAKASZ

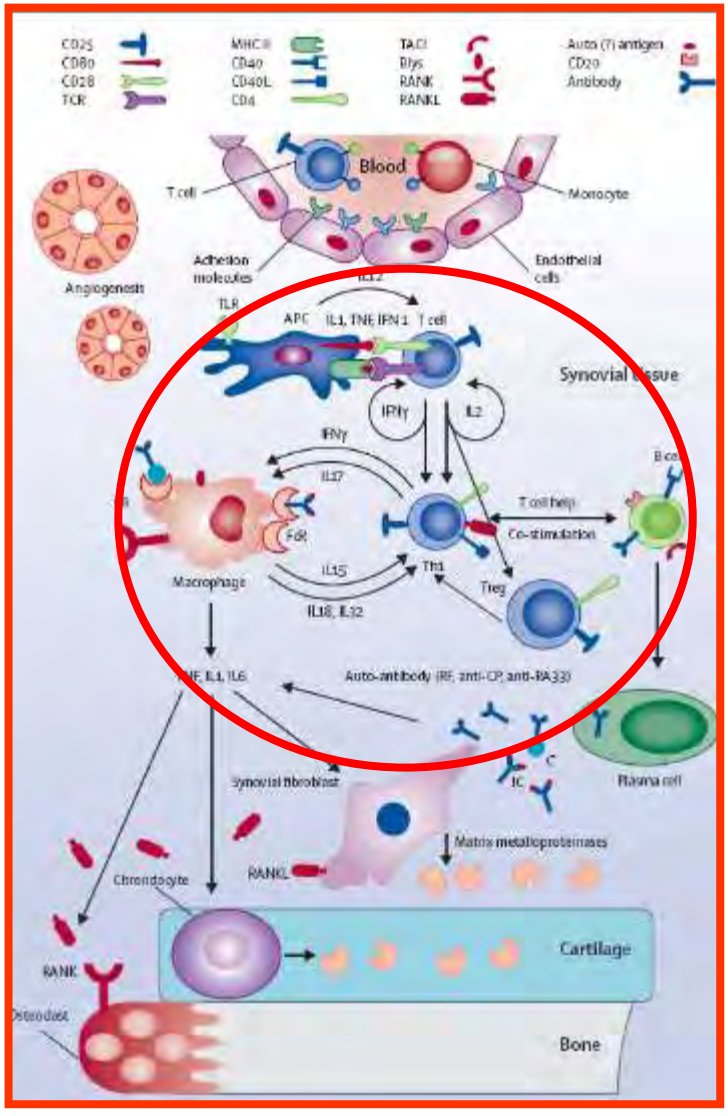
GENETIKA

GYULLADÁS

KÖRNYEZET

AUTOIMMUNITÁS

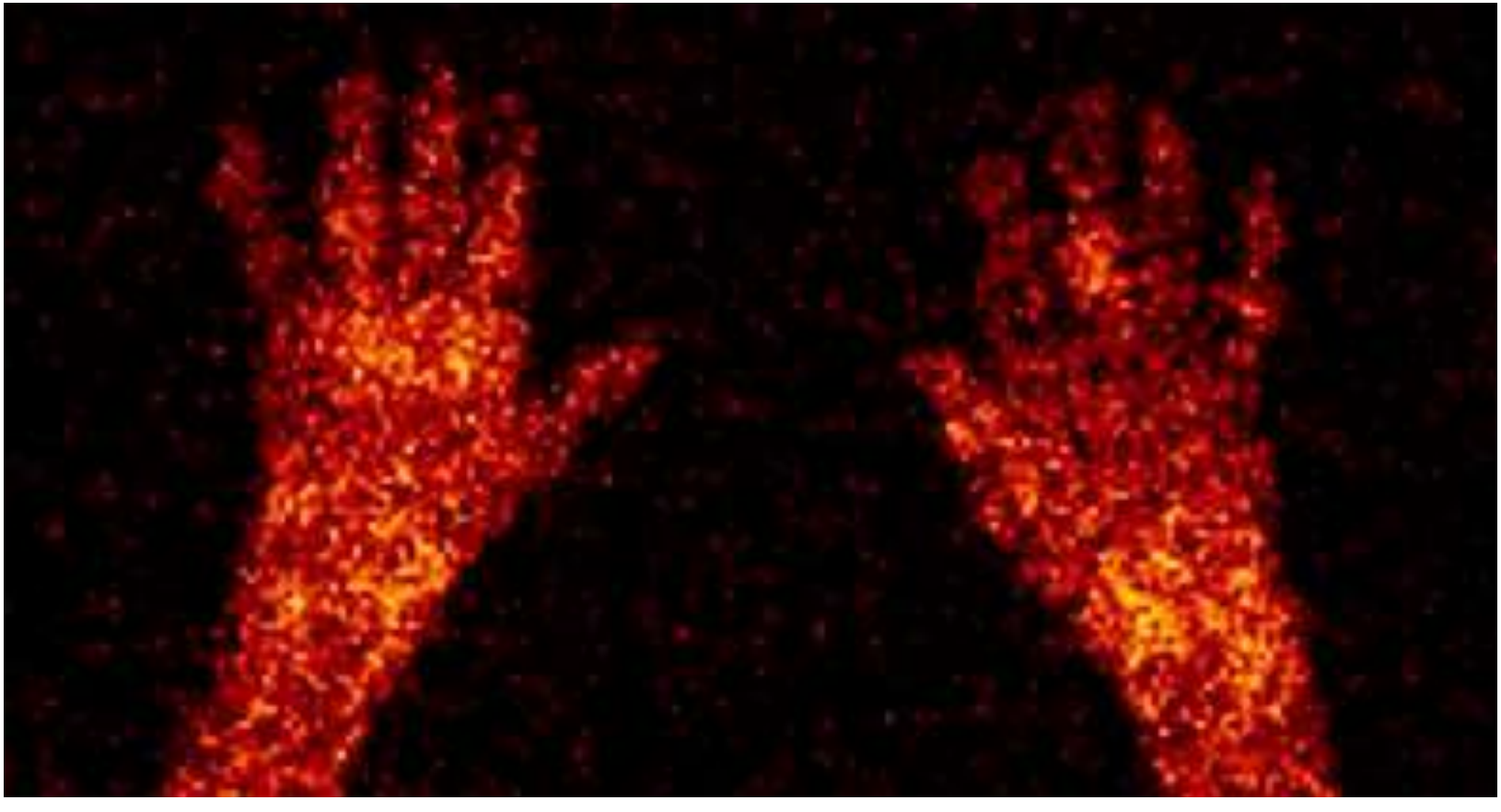
EFFEKTOR SZAKASZ



Smolen & Steiner, Nature Rev. Drug Disc.2003

Sejtadhézió, migráció, homing

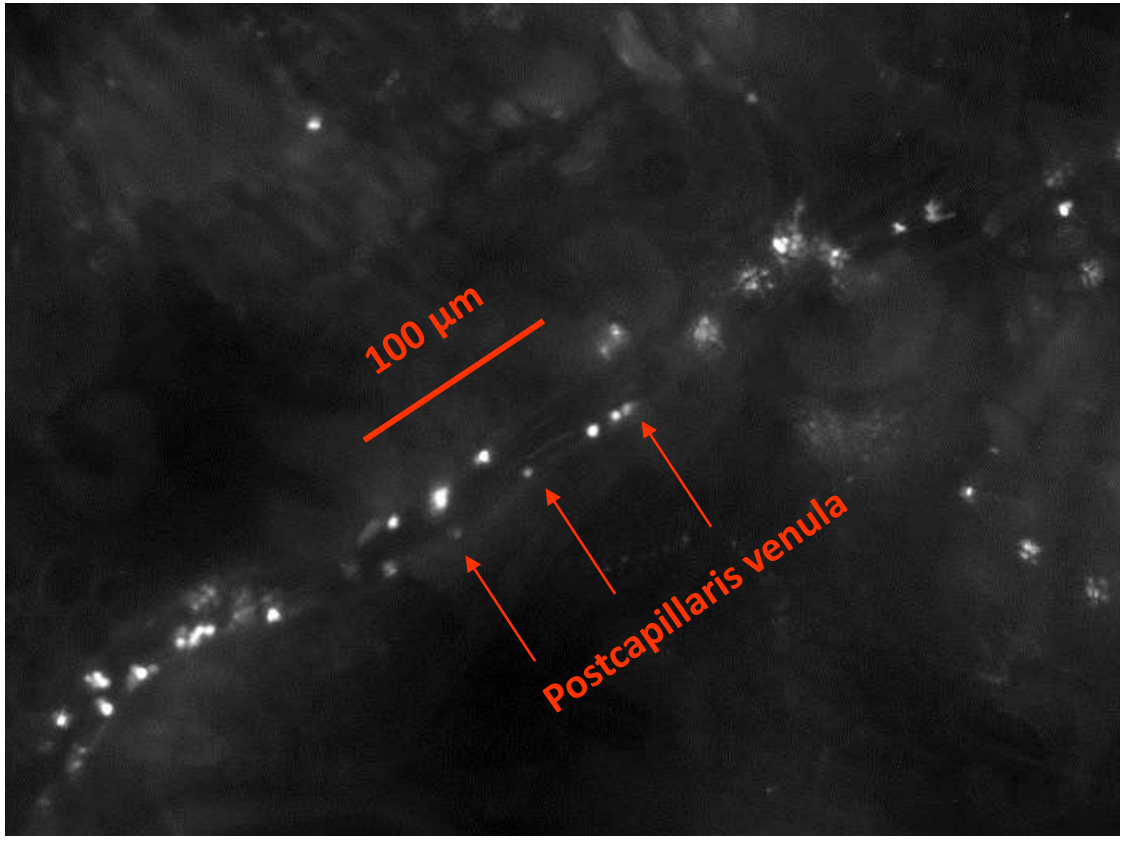
Jelzett monocyták a gyulladt ízületben



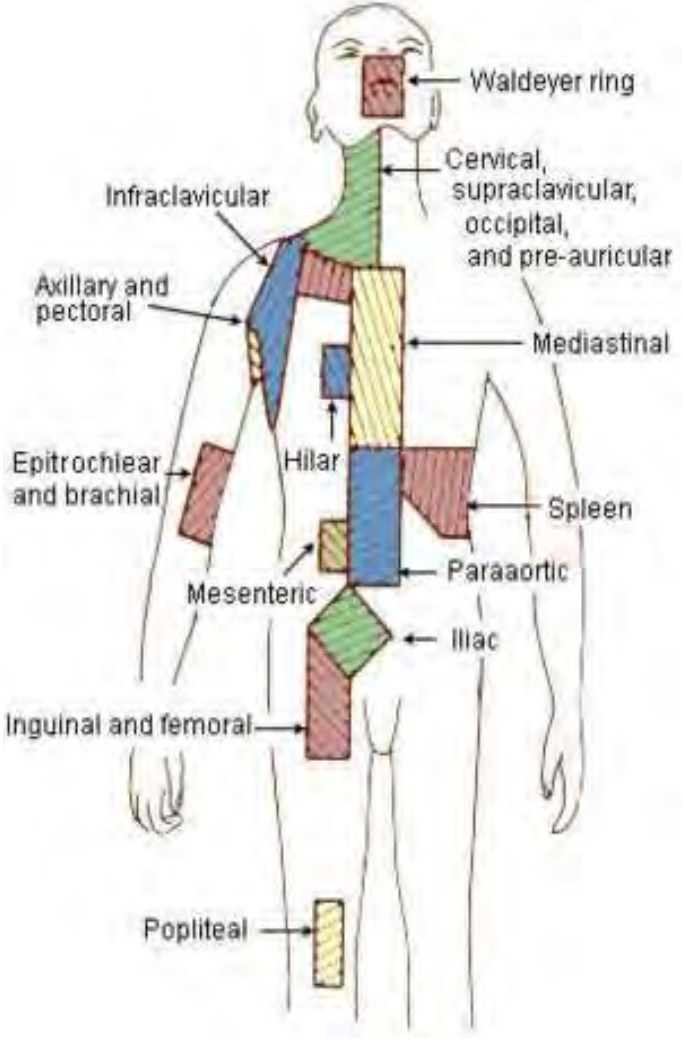
Thurlings et al. PLoS One 2009;4:e7865

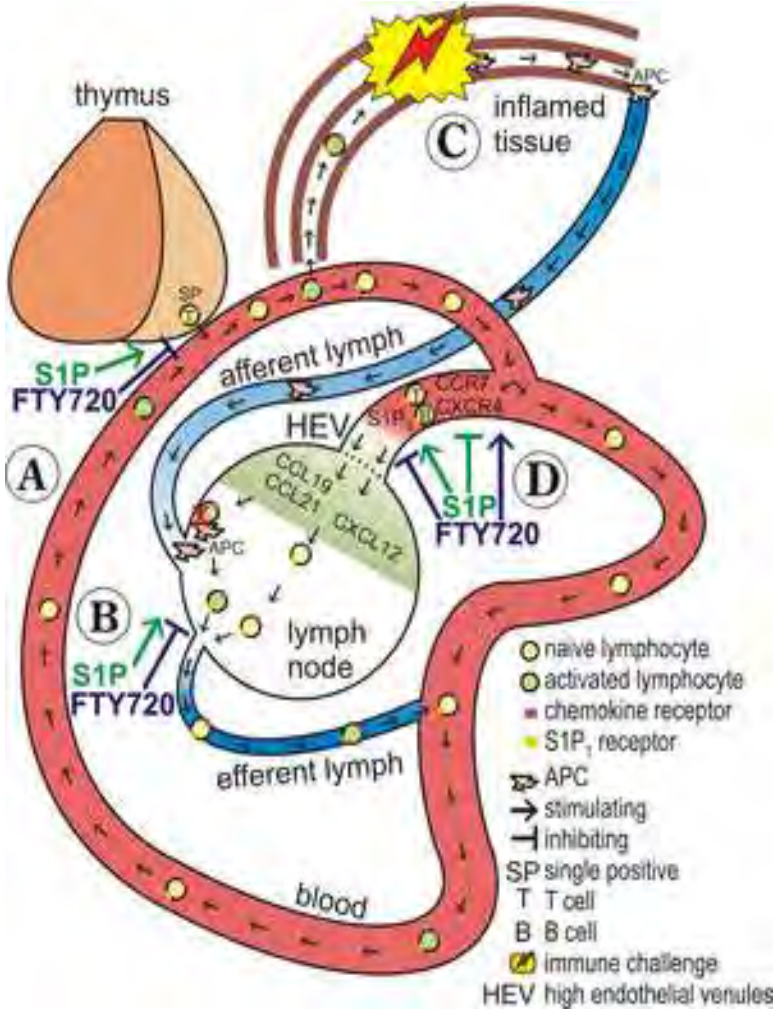
Mikrocirkuláció

In vivo videomicroscop (fluorescence)(Mikecz et al)

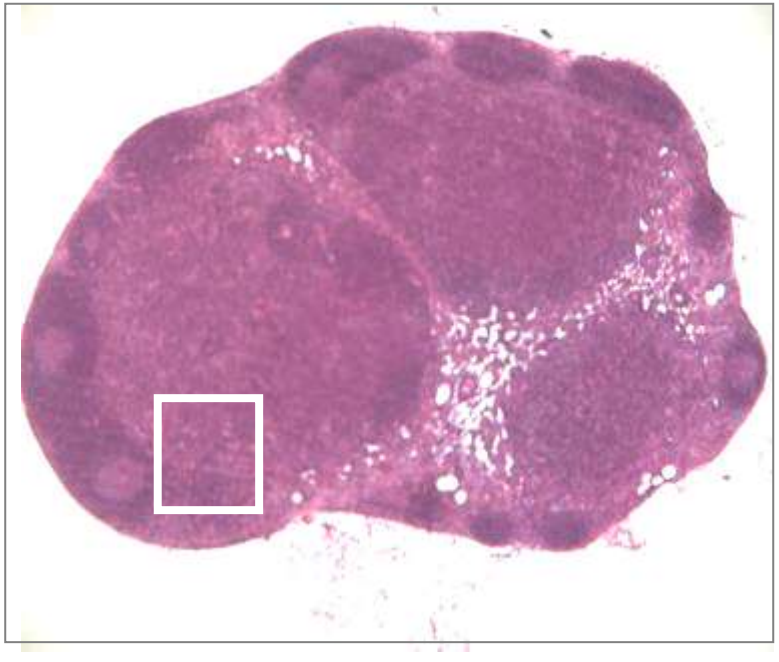


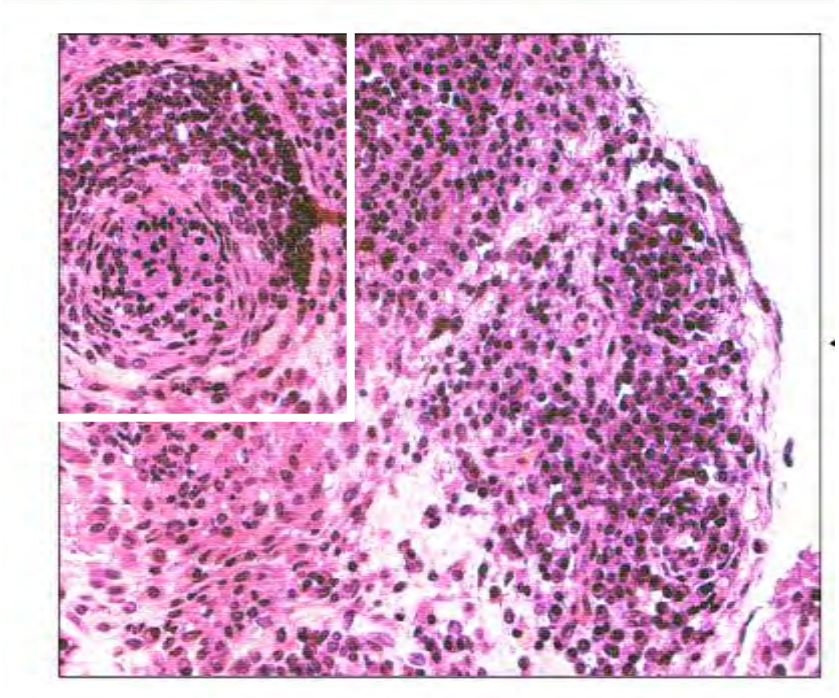
Homing


Waldeyer ring
Cervical, supraclavicular, occipital, and pre-auricular
Infraclavicular
Axillary and pectoral
Mediastinal
Epitrochlear and brachial
Hilar
Spleen
Paraaortic
Mesenteric
Iliac
Inguinal and femoral
Popliteal


thymus
inflamed tissue
C
APC
SP
S1P
FTY720
afferent lymph
HEV
CCR7
CXCR4
S1P
A
CCL19
CCL21
CXCL17
D
S1P
FTY720
APC
B
S1P
FTY720
lymph node
efferent lymph
blood
naive lymphocyte
activated lymphocyte
chemokine receptor
S1P1 receptor
APC
stimulating
inhibiting
SP single positive
T T cell
B B cell
immune challenge
HEV high endothelial venules

Nyirokcsomó vs arthritises synovium (lymphoid neogenesis, tercier strukturák)



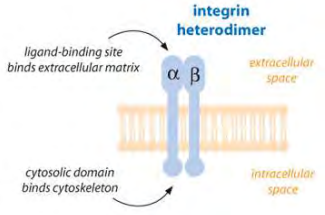


Sejtadhézió

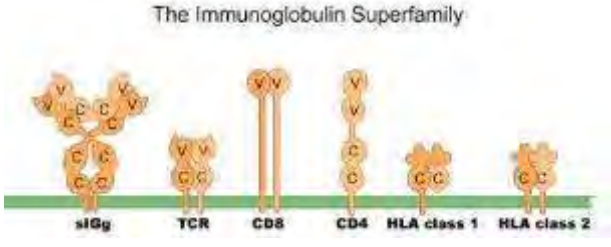
- **Élettani**
  - szövetfejlődés
  - sebgyógyulás
  - véralvadás
  - immunitás
  - lymphocyta recirculatio (homing)
  - angiogenesis
- **Pathologiás**
  - gyulladás
  - fertőzések - kórokozó receptor
  - thrombosis
  - tumormetastasis
  - „pathologiás” angiogenesis

Sejtadhéziós molekula (CAM) szupercsaládok

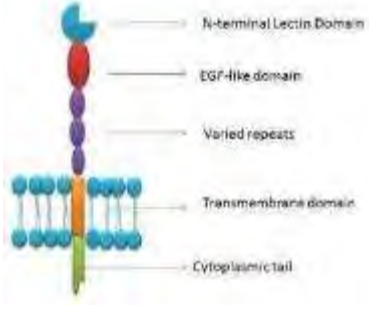
- Integrinek



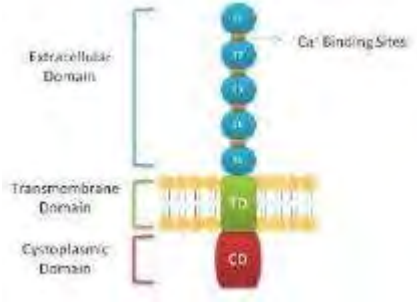
- Immunglobulin szupercsalád



- Szelektinek



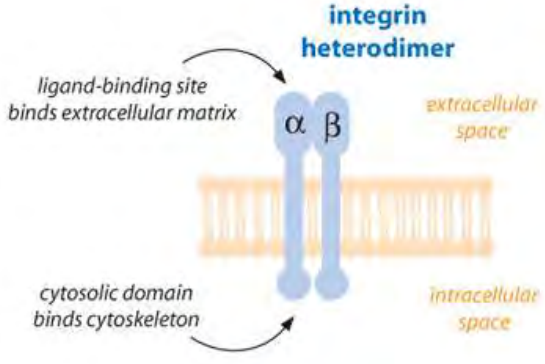
- Cadherinek



- Egyebek (pl. CD44, VAP-1)

Integrinek

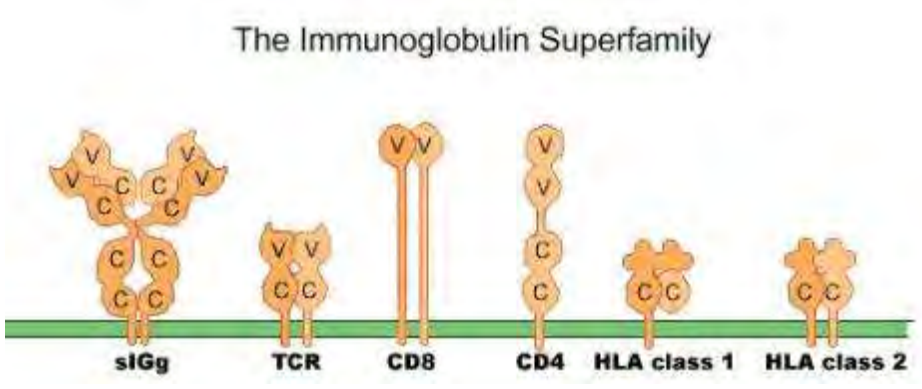
- αβ heterodimerek
- közös β (1-8) és specifikus α (1-11) alegység
- sejt-ECM interakciók
- Szignáltranszdukció



- α(1-11)β1 VLA antigének, matrix ligand
- α(L,M,X)β2 leukocyta integrinek, másik CAM
- α(V,IIb)β3 matrix ligand (thr aggregatio)
- α6β4 laminin
- αVβ5 VN, FN
- αVβ6 VN
- α4β7 VCAM-1 (homing, Peyer plakk)
- αVβ8 VN

Immunglobulin szupercsalád

- Ig-domainek
- integrin-ligandok
- széles expresszió

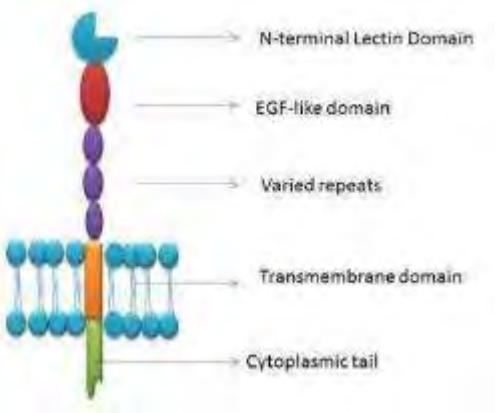


ICAM-1	LFA-1, Mac-1	sok sejt
ICAM-2	LFA-1	nyugvó end.
ICAM-3	LFA-1	szignál
VCAM-1	α4β1/VLA-4	sok sejt
CD31/PECAM	homológ	endothel
CD2	LFA-3	leukocyta
LFA-3	CD2	endothel

Szelektinek

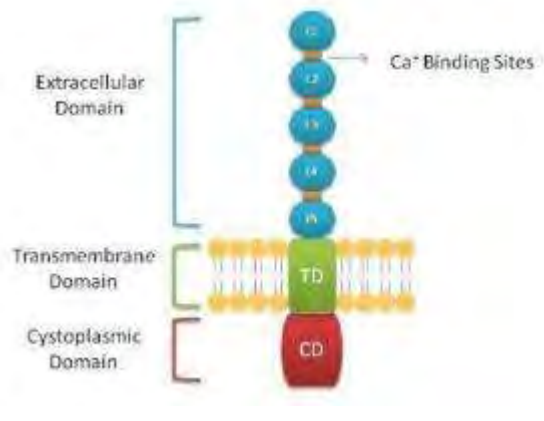
- **Lektin-EGF domainek**

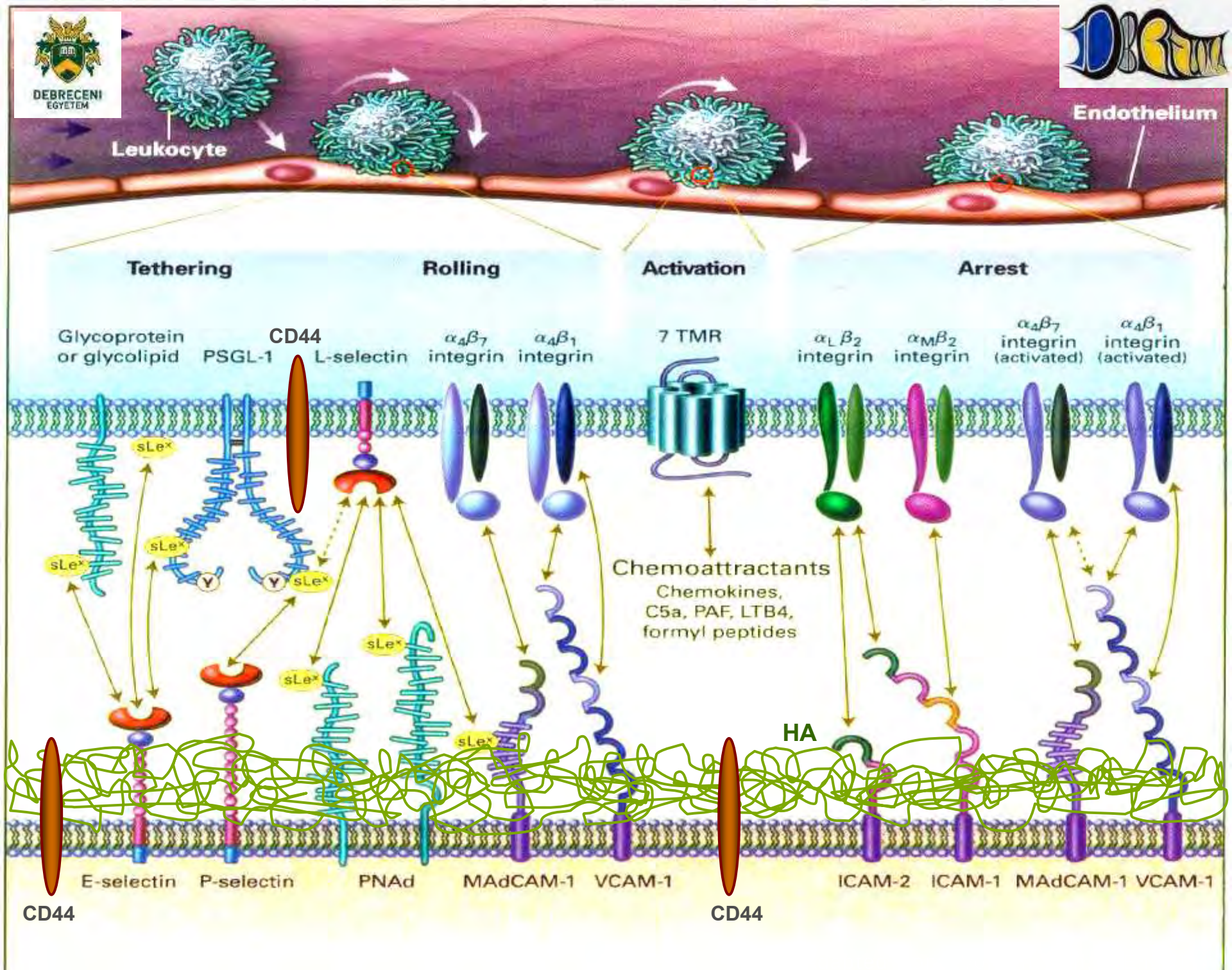
L-szelektin (LEU)	**sialyl-Lewis-X**
E-szelektin (END)	**ESGL-1, sLx**
P-szelektin (END)	**PSGL-1, sLx**



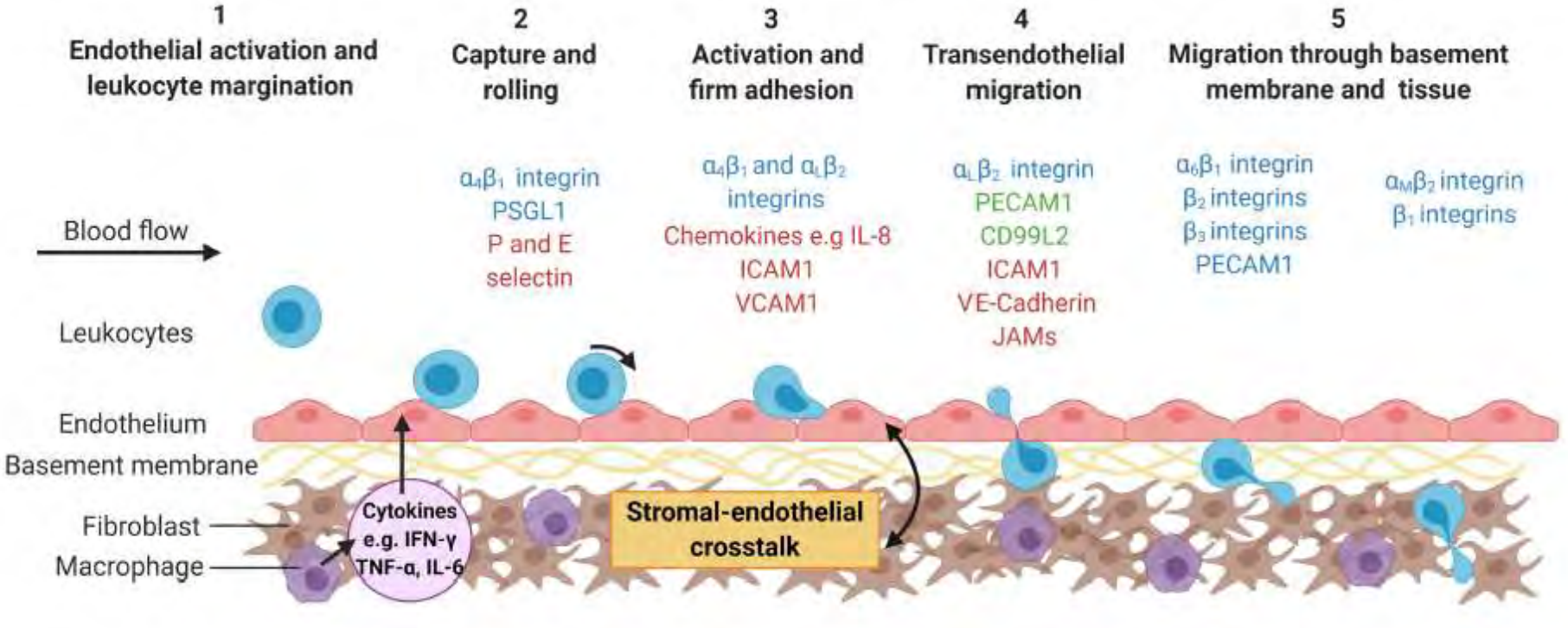
Cadherinek

- **E-cadherin (endothel)**
- **P-cadherin (platelet)**
- **N-cadherin (neuralis)**
- **Cadherin-11**



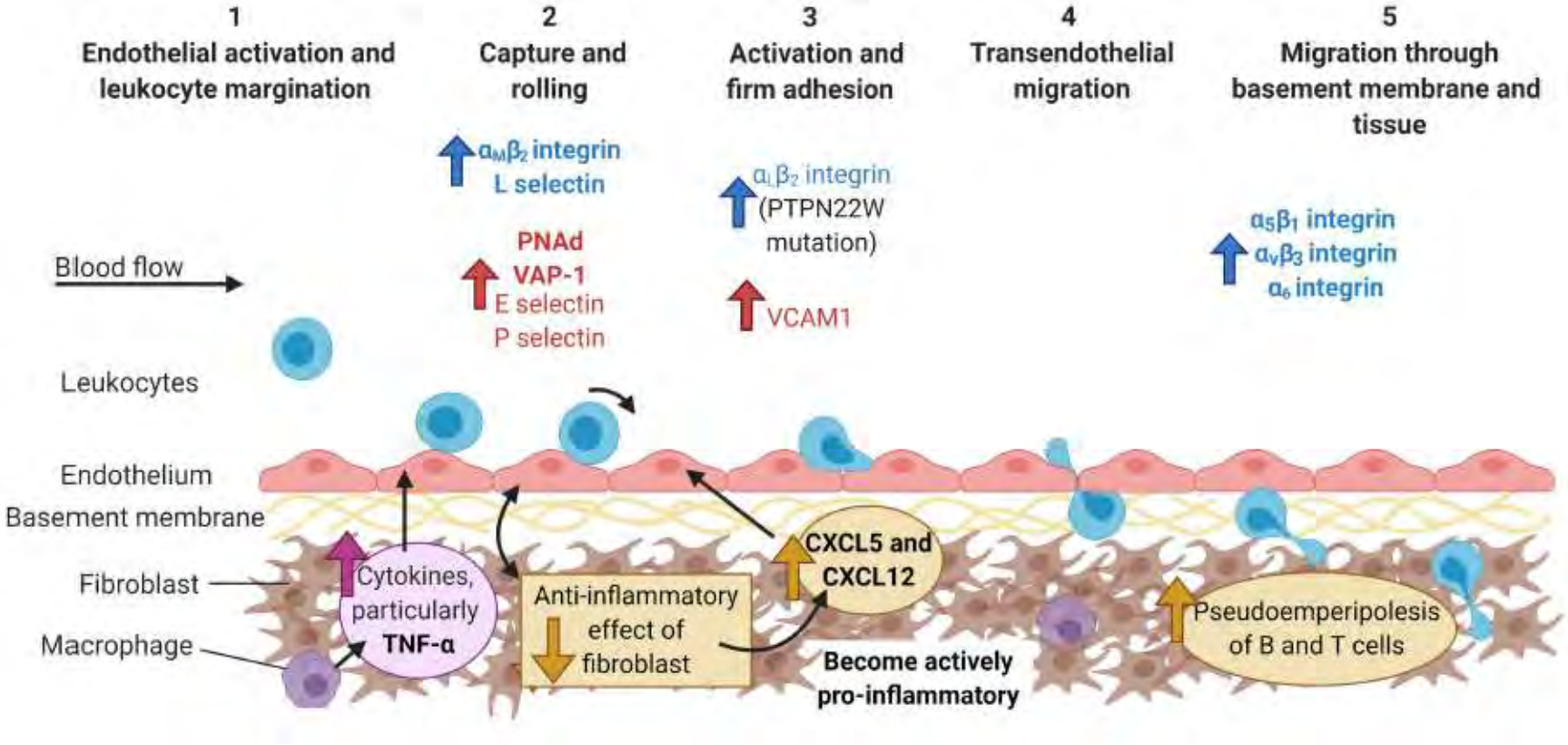

Leukocyte
Endothelium
Tethering
Rolling
Activation
Arrest
Glycoprotein or glycolipid
PSGL-1
CD44
L-selectin
$\alpha_4\beta_7$ integrin
$\alpha_4\beta_1$ integrin
7 TMR
$\alpha_L\beta_2$ integrin
$\alpha_M\beta_2$ integrin
$\alpha_4\beta_7$ integrin (activated)
$\alpha_4\beta_1$ integrin (activated)
sLe^x
Chemoattractants
Chemokines, C5a, PAF, LTB4, formyl peptides
HA
E-selectin
P-selectin
PNAd
MAdCAM-1
VCAM-1
ICAM-2
ICAM-1
MAdCAM-1
VCAM-1
CD44
CD44

Fiziológiás leukocyta migráció



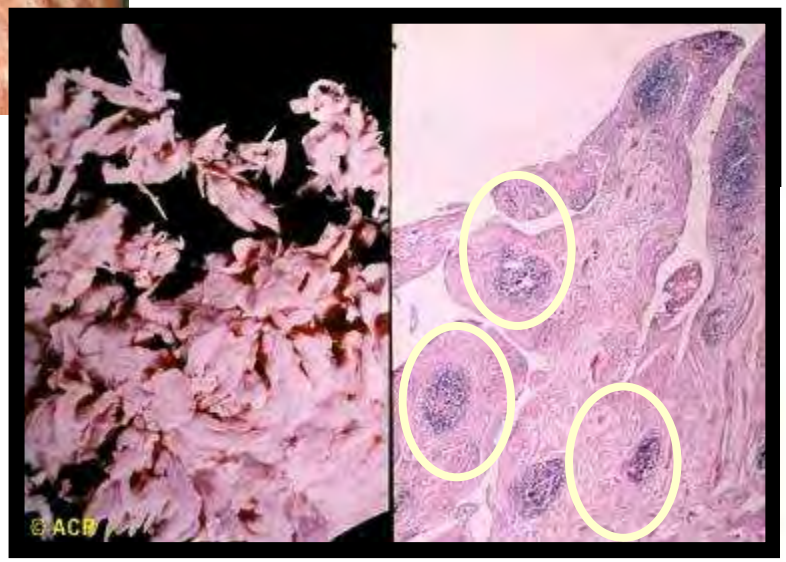
Manning et al, Front Cell Dev Biol 2021

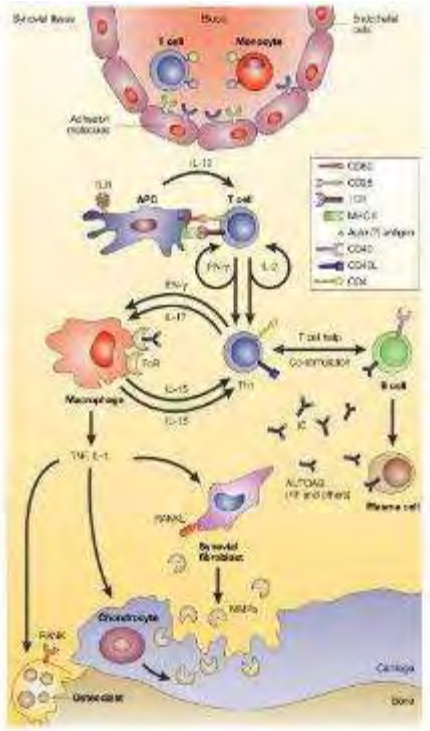
Patológiás (gyulladásos) leukocyta migráció



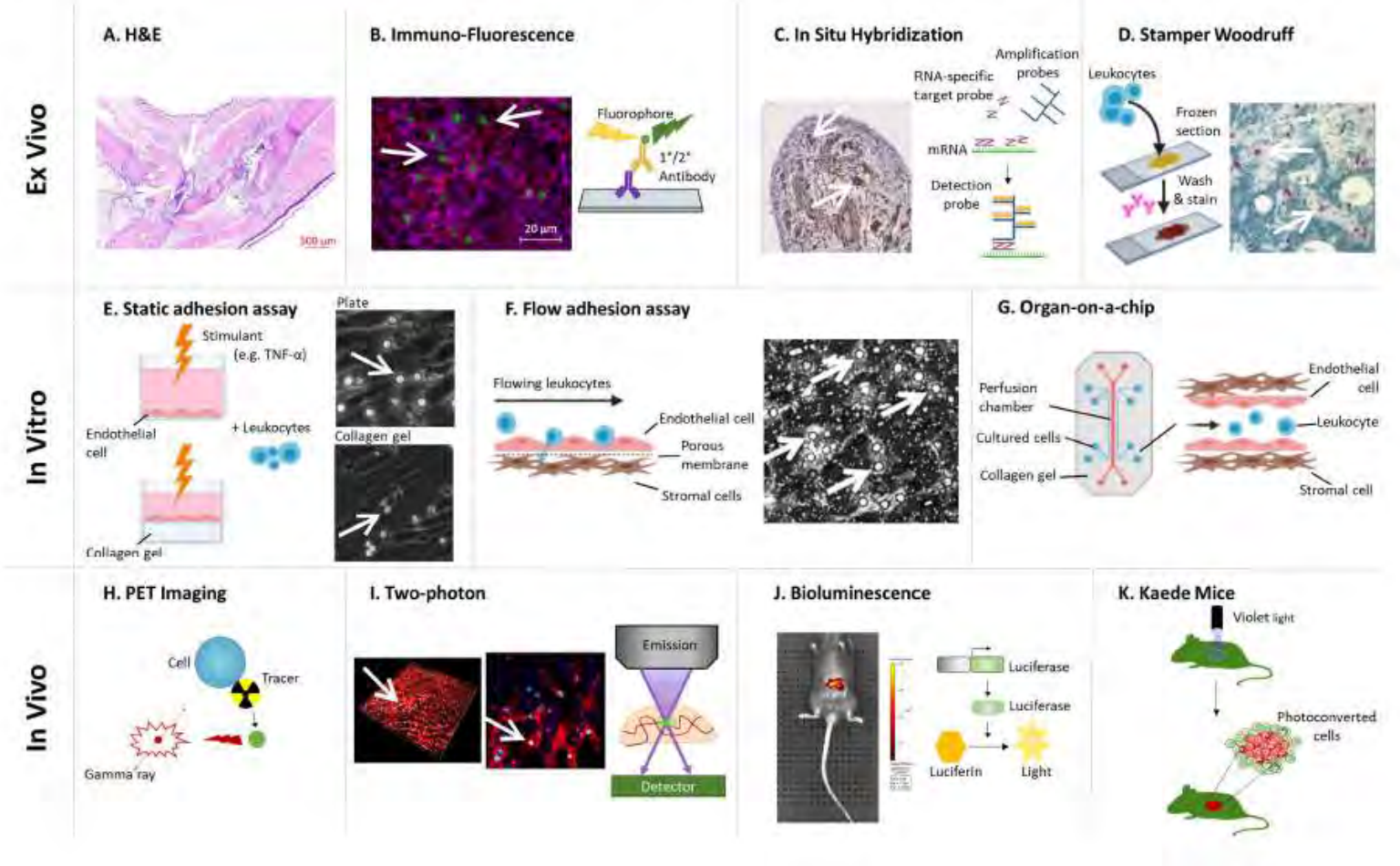
Manning et al, Front Cell Dev Biol 2021

A gyulladás példája: RA





Módszerek



Manning et al, Front Cell Dev Biol 2021

Adhéziós molekulák RA-ban
(immunhisztokémia)

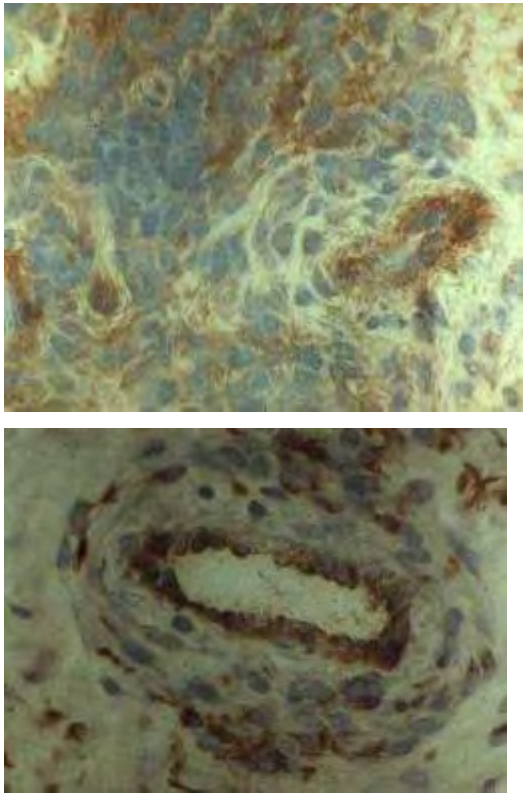
	Synovialis membrán			Synovialis folyadék
SAM	Leukocyta	Endothelsejt	Fibroblast	Lymphocyta
Integrinek				
β1 integrinek	+	+	-	+
αLβ2 (LFA-1)	+	-	-	+
αMβ2 (Mac-1)	+	-	-	-
αXβ2 (p150,95)	+	-	-	-
β3 integrinek	+	+	+	-
α4β7 integrin	+	-	-	+
Immunoglobulin szupercsalád				
ICAM-1	+	+	+	+
ICAM-2	-	+	-	?
ICAM-3	+	±	-	?
VCAM-1	±	+	-	+
CD2	+	-	-	+
LFA-3	+	+	+	+
CD31 (PECAM-1)	±	+	-	?
CD66	±	-	-	+
Szelektinek				
E-szelektin	-	+	-	?
L-szelektin	+	-	-	+
P-szelektin	-	+	-	?
Egyéb molekulák				
CD44	+	+	+	+
VAP-1	-	+	-	?
Endoglin	±	+	-	?

Magyarázat: +, expresszálódik; -, nem expresszálódik; +, bizonyos leukocytákon megjelenik; ?, nem ismert. A rövidítések magyarázatát lásd a szövegben.

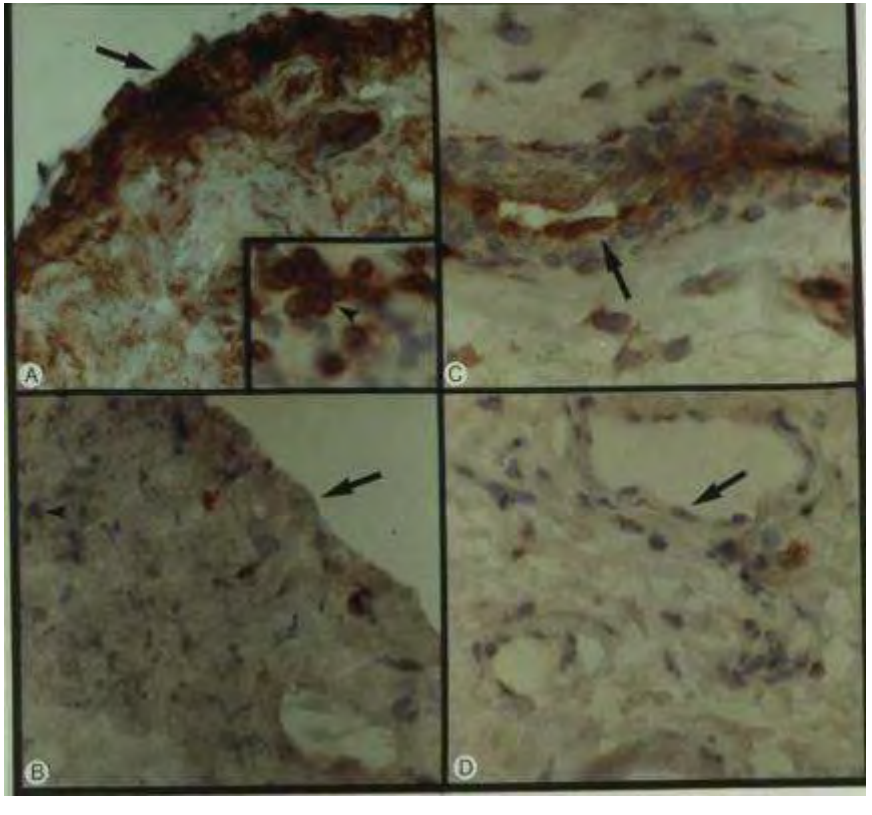
Szekanecz, In: Klinikai immunológia (szerkesztés alatt)

Adhéziós receptorok RA-ben

ICAM-1

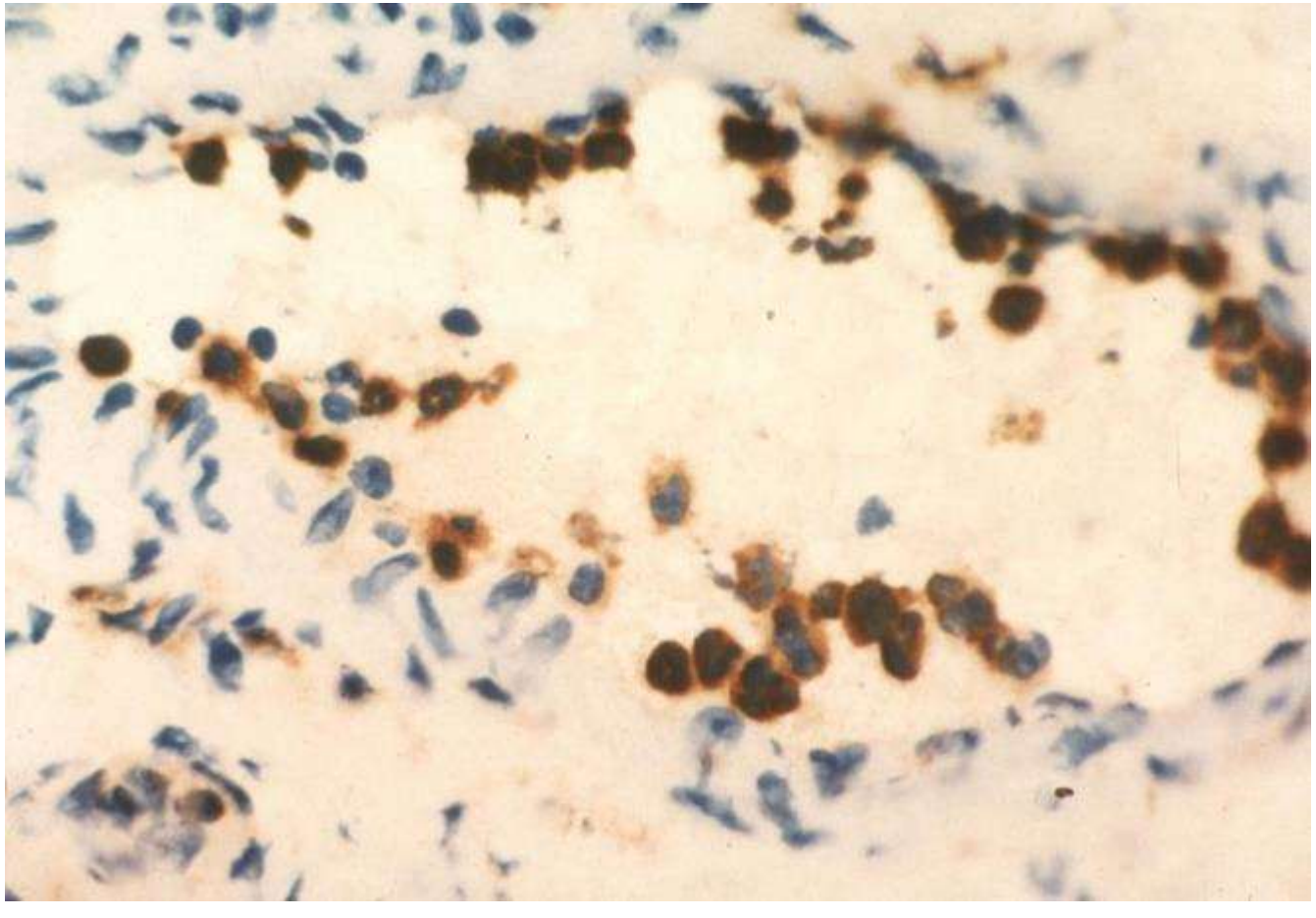


ICAM-1 ICAM-3



Szekanecz et al. Arthritis Rheum. 1994;37:221–31.

Patkány AIA - β2 integrinek



IBD: bél leukocyták – synovium

Az enteropathiás arthritis modellje

Stamper-Woodruff assay

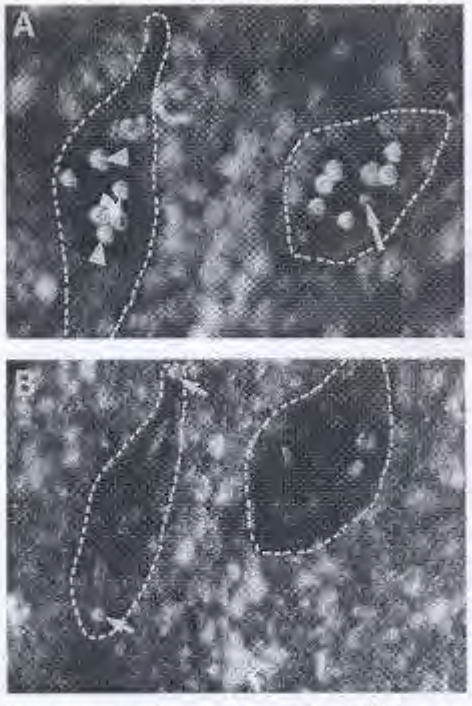


FIGURE 1. Mucosal leukocytes from IBD gut bind to synovium. *A*, Binding of small lymphocytes (arrow), immunoblasts (larger cells with a clear cytoplasm; curved arrow), and macrophages (large, ruffled, white cells; arrowheads) to synovial high endothelial venule-like vessels (basement membranes outlined by a dashed white line) in the presence of a negative control mAb is shown. The focus of the picture is a compromise between the plane of the tissue section and the bound cells on top of it. *B*, After blocking P-selectin with mAb WAPS12.2 on an adjacent section, the binding of macrophages to the same vessels is practically abolished, whereas adherence of small lymphocytes is not affected. Original magnification, ×200.

Salmi et al, 2001

Chemokinek

Chemokin és chemokin receptor családok

- CXC chemokinek — CXCL - CXCR
- CC chemokinek — CCL - CCR
- C chemokinek — CL - CR
- CX3C chemokinek — CX3CL – CX3CR

C = cystein, X = egyéb aminosav

Chemokin funkciók

- Leukocyta chemotaxis
  - CXC: neutrophil
  - CC: mononuclearis
- Angiogenesis
  - ELR+ CXC: angiogén
  - ELR- CXC: angiosztatikus
- Adhéziós molekula capping

CXC, CX3C és C chemokinek

Chemokine	Other names	Receptor
CXCL1	GROα, MGSA, mouse KC	CXCR2, ACKR1
CXCL2	GROβ, MIP-2α, mouse MIP2	CXCR2, ACKR1
CXCL3	GROγ, MIP-2β	CXCR2, ACKR1
CXCL4	PF4	Unknown
CXCL4L1	PF4V1	Unknown
CXCL5	ENA-78, mouse LIX'	CXCR2, ACKR1
CXCL6	GCP-2 (human only)	CXCR1, CXCR2, ACKR1
CXCL7	NAP-2	CXCR2, ACKR1
CXCL8	IL-8 (human only)	CXCR1, CXCR2, ACKR1
CXCL9	Mig	CXCR3
CXCL10	IP-10	CXCR3
CXCL11	I-TAC	CXCR3, ACKR1, ACKR3
CXCL12	SDF-1	CXCR4, ACKR3
CXCL13	BLC, BCA-1	CXCR5, ACKR1, ACKR4
CXCL14	BRAK	Unknown
CXCL15	Lungkine (mouse only)	Unknown
CXCL16		CXCR6

XCL1	Lymphotactin α, SCM-1α	XCR1
XCL2	Lymphotactin β, SCM-1β	XCR1
CX_3CL1	Fractalkine	CX_3CR1

Miyabe et al, JMA Journal 2020

CC chemokinek

CCL1	I-309, mouse TCA3	CCR8
CCL2	MCP-1, mouse JE	CCR2, ACKR1, ACKR2
CCL3*	MIP-1α, LD78α	CCR1, CCR5, ACKR2
CCL3L1	LD78β	CCR1, CCR3, CCR5, ACKR2
CCL4	MIP-1β	CCR5, ACKR2
CCL4L1	LAG-1	CCR5
CCL5	RANTES	CCR1, CCR3, CCR5, ACKR2
CCL6	C-10, MRP-1 (mouse only)	Unknown
CCL7	MCP-3, mouse Fic or MARC	CCR2, CCR3, ACKR1, ACKR2
CCL8	MCP-2	Human: CCR1, CCR2, CCR3, CCR5, ACKR1, ACKR2; mouse: CCR8, ACKR1, ACKR2
CCL9/10	MIP-1γ, MRP-2 (mouse only)	Unknown
CCL11	Eotaxin-1	CCR3, ACKR2
CCL12	MCP-5 (mouse only)	CCR2
CCL13	MCP-4 (human only)	CCR2, CCR3, CCR5, ACKR1, ACKR2
CCL14	HCC-1 (human only)	CCR1, ACKR1, ACKR2
CCL15	Leukotactin-1, HCC-2, MIP-5 (human only)	CCR1, CCR3
CCL16	HCC-4, NCC-4, LEC (human only)	CCR1, CCR2, CCR5, ACKR1
CCL17	TARC	CCR4, ACKR1, ACKR2
CCL18	PARC, DC-CK1 (human only)	CCR8
CCL19	MIP-3β, ELC	CCR7, ACKR4
CCL20	MIP-3α, LARC	CCR6
CCL21	SLC, 6CKine	CCR6, CCR7, ACKR4
CCL22	MDC	CCR4, ACKR1, ACKR2
CCL23	MPIF-1, MMP-3 (human only)	Unknown
CCL24	Eotaxin-2, MPIF-2	CCR3
CCL25	TECK	CCR9, ACKR4
CCL26	Eotaxin-3	CCR3, CX3CR1
CCL27	CTAK	CCR10
CCL28	MEC	CCR3, CCR10

Miyabe et al, JMA Journal 2020

Chemokinek és receptoraik

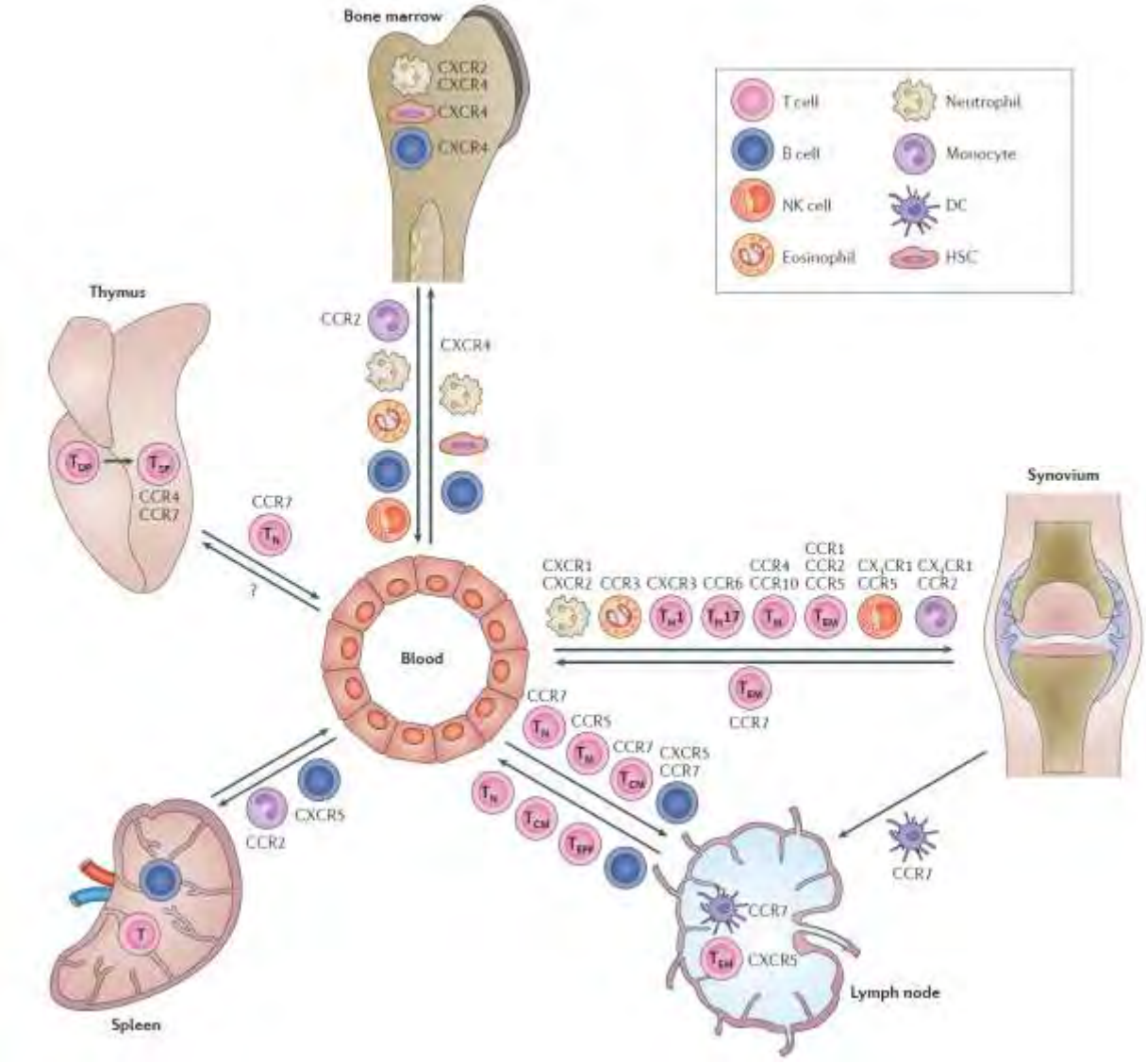
Chemokine ligand (alternative name)	Chemokine receptor: Conventional												Atypical		
	CCR1	CCR2	CCR3	CCR4	CCR5	CCR6	CCR7	CCR8	CCR9	CCR10	CCR11	CCR12	ACKR1	ACKR2	ACKR4
CC-chemokines															
CCL1 (I-309)								●							
CCL2 (MCP1)		●		●									●	●	
CCL3 (MIP1α)	●			●	●									●	
CCL3L1 (LD78)					●									●	
CCL4 (MIP1β)	●				●			●						●	
CCL5 (RANTES)	●	●	●	●	●								●	●	
Mouse CCL6 (C10)	●														
CCL7 (MCP3)	●	●	●		●								●	●	
CCL8 (MCP2)	●	●			●						●			●	
CCL9 (MIP1γ)	●														
CCL11 (Eotaxin)			●										●	●	
CCL12 (MCP5)		●												●	
CCL13 (MCP4)	●	●	●								●		●	●	
CCL14 (HCC1)	●				●								●	●	
CCL15 (HCC2)	●		●												
CCL16 (HCC4)	●	●			●										
CCL17 (TARC)				●				●					●	●	
CCL18 (PARC)								●							
CCL19 (MIP3β)							●								●
CCL20 (MIP3α)						●									
CCL21 (SLC)							●								●
CCL22 (MDC)				●										●	
CCL23 (MPIF1)	●											●			
CCL24 (Eotaxin 2)			●												
CCL25 (TECK)									●						●
CCL26 (Eotaxin 3)			●												
CCL27 (CTACK)										●					
CCL28 (MEC)			●							●					

Chemokine ligand (alternative name)	Chemokine receptor: Conventional									Atypical	
	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6	CXCR8	XCR1	CX_3CR1	ACKR1	ACKR3
CXC-chemokines											
CXCL1 (GROα)		●								●	
CXCL2 (GROβ)		●								●	
CXCL3 (GROγ)		●								●	
CXCL4 (PF4)			●								
CXCL5 (ENA78)		●								●	
CXCL6 (GCP2)	●	●								●	
CXCL7 (NAP2)		●								●	
CXCL8 (IL-8)	●	●								●	
CXCL9 (MIG)			●								
CXCL10 (IP10)			●								
CXCL11 (I-TAC)			●							●	●
CXCL12 (SDF1)				●							●
CXCL13 (BCA1)					●						
CXCL14 (BRAK)											
Mouse CXCL15 (Lungkine)											
CXCL16 (SR-PSOX)						●					
CXCL17 (DMC)							●				
C-chemokines											
XCL1 (Lymphotactin)								●			
XCL2 (SCM1α)								●			
CX_3C-chemokine											
CX_3CL1 (Fractalkine)									●		

Oda-vissza redundancia!!!

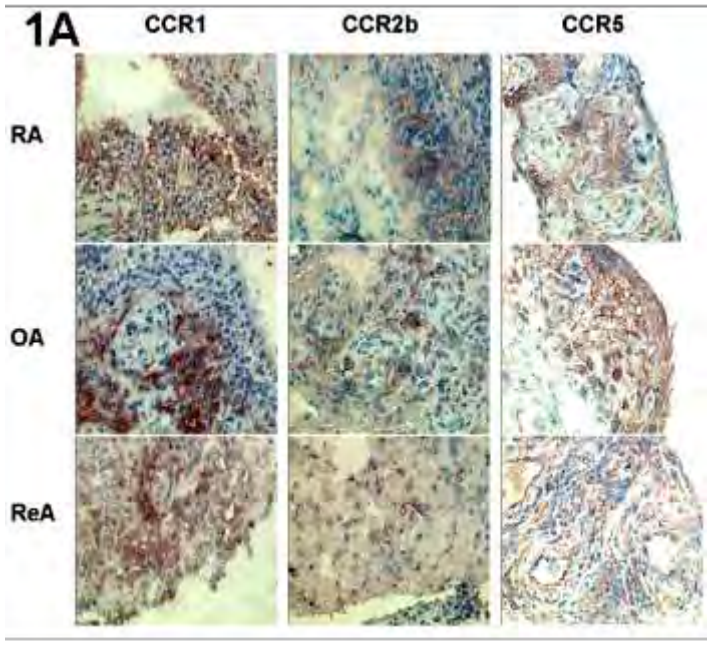
Szekanecz & Koch. Nat Rev Rheumatol. 2016;12:5–13.

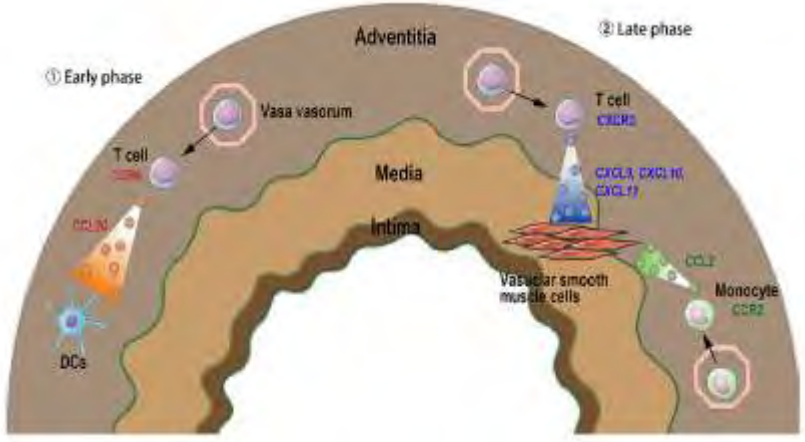
Chemokinek rheumatoid arthritisben

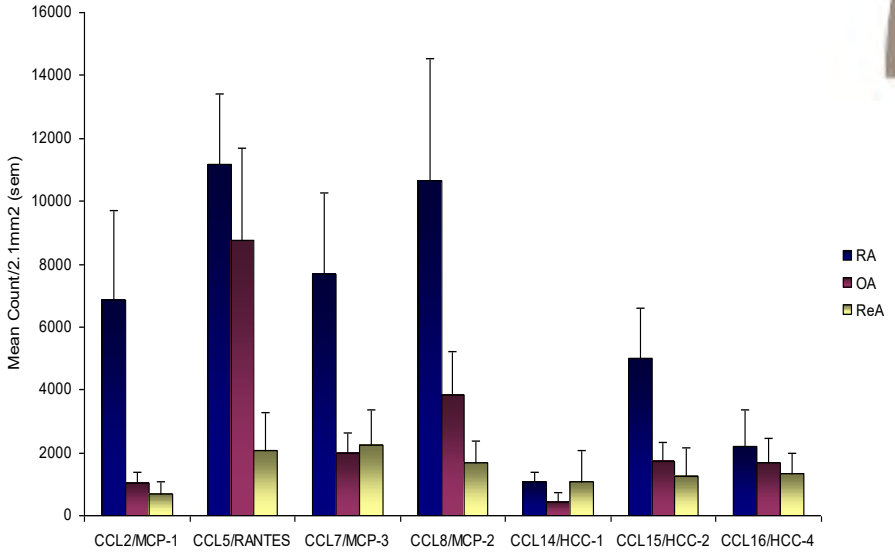


Szekanecz & Koch. Nat Rev Rheumatol. 2016;12:5–13.

Chemokinek RA-ban és GCA-ban

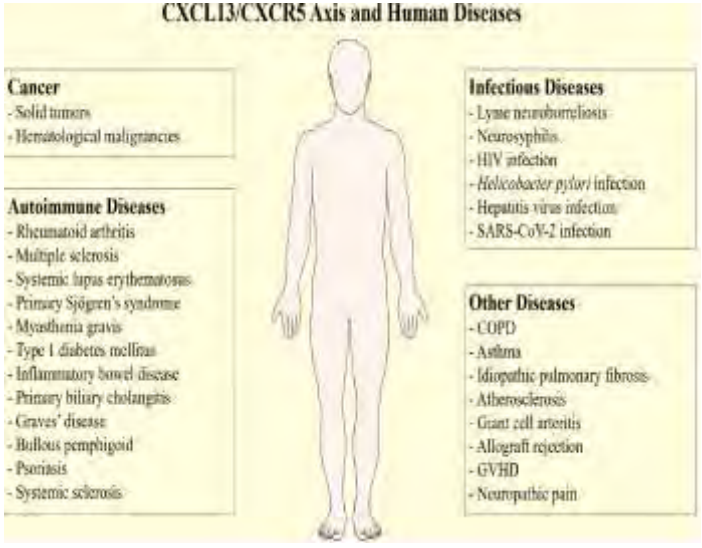


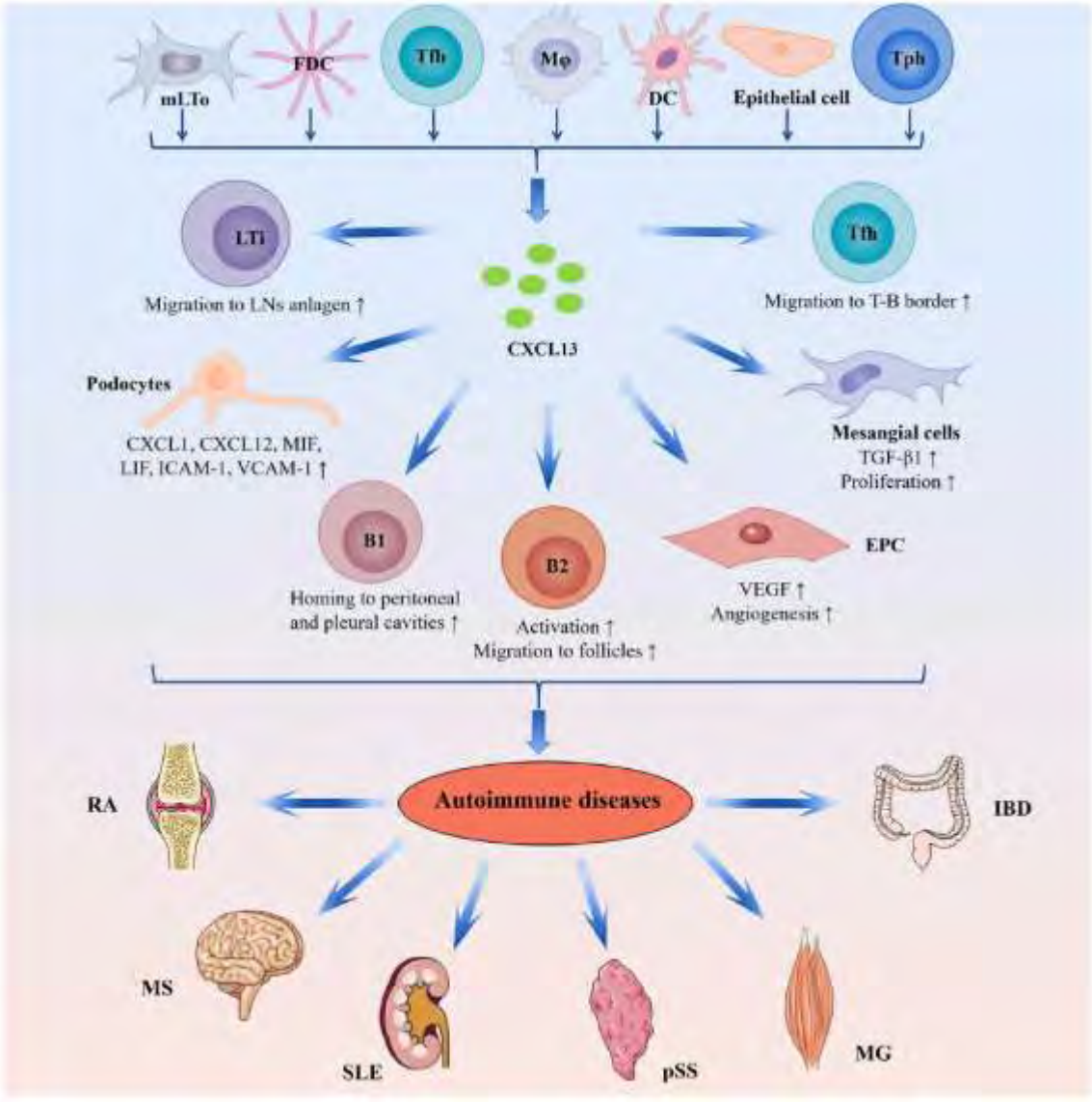




Haringman et al. Ann Rheum Dis 2006
Miyabe et al, JMA Journal 2020

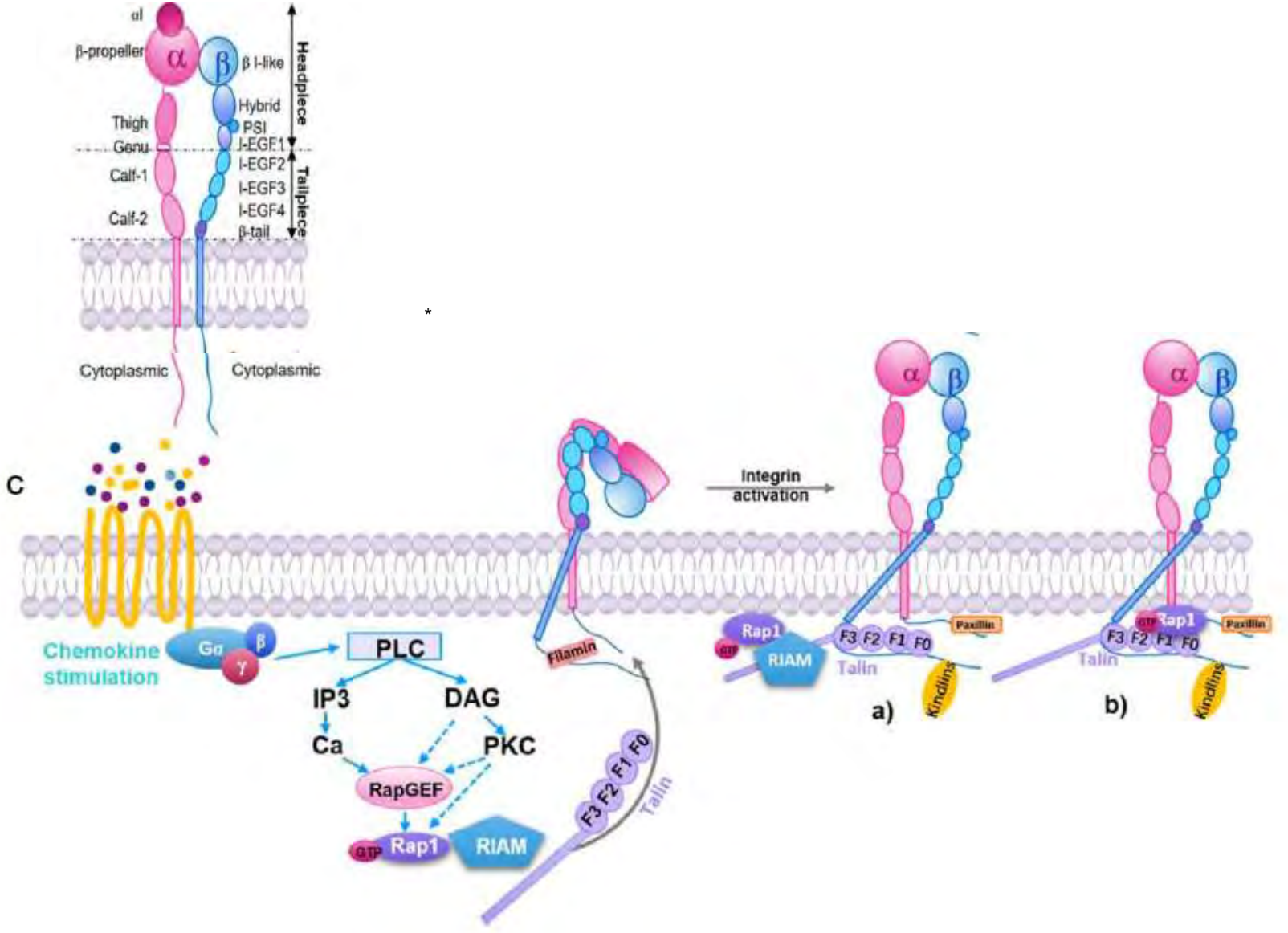
CXCL13/CXCR5 – „szuper”-chemokin





Pan et al, Front Immunol 2022

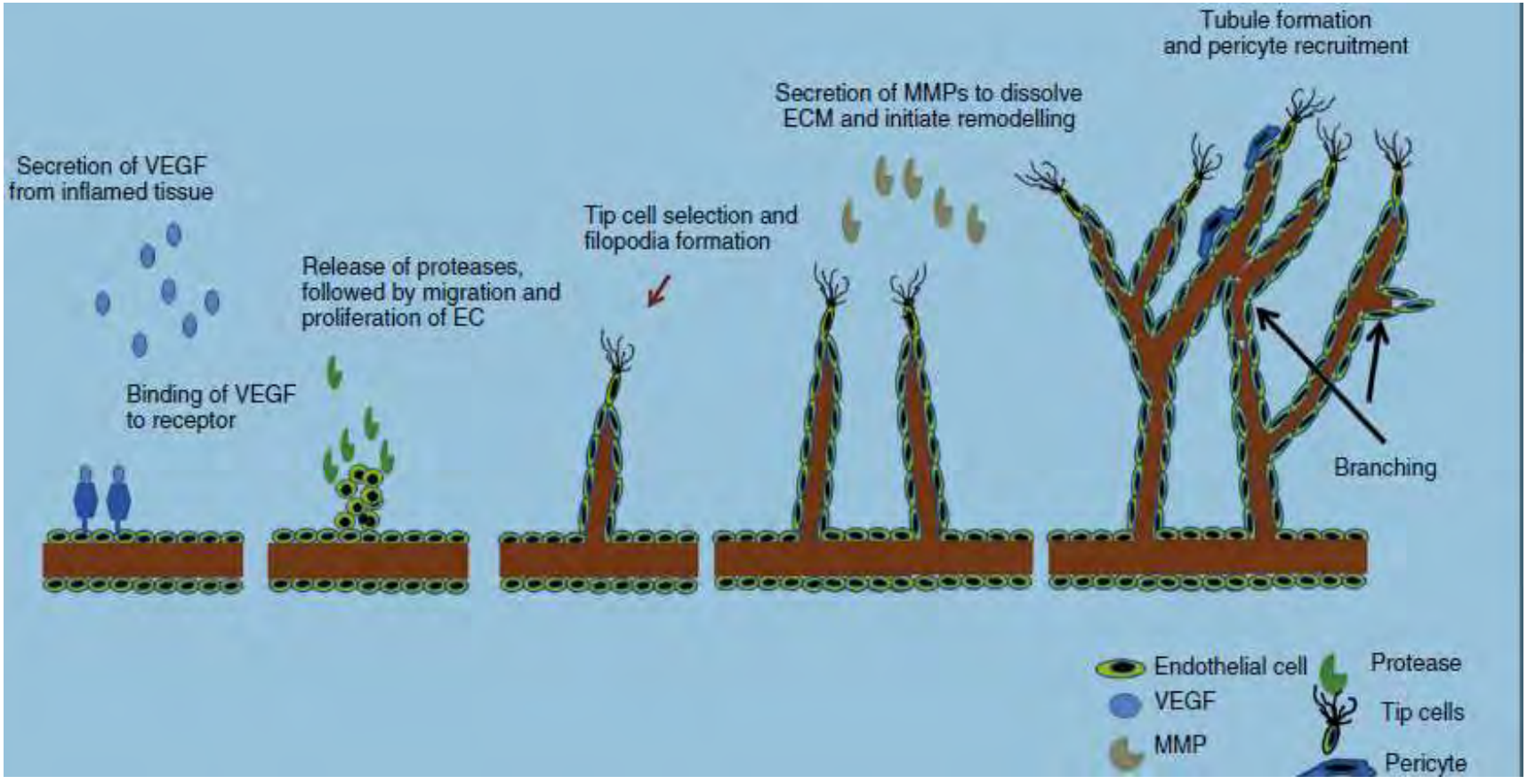
Chemokin-CAM szabályozás



Sun et al, Front Immunol 2021

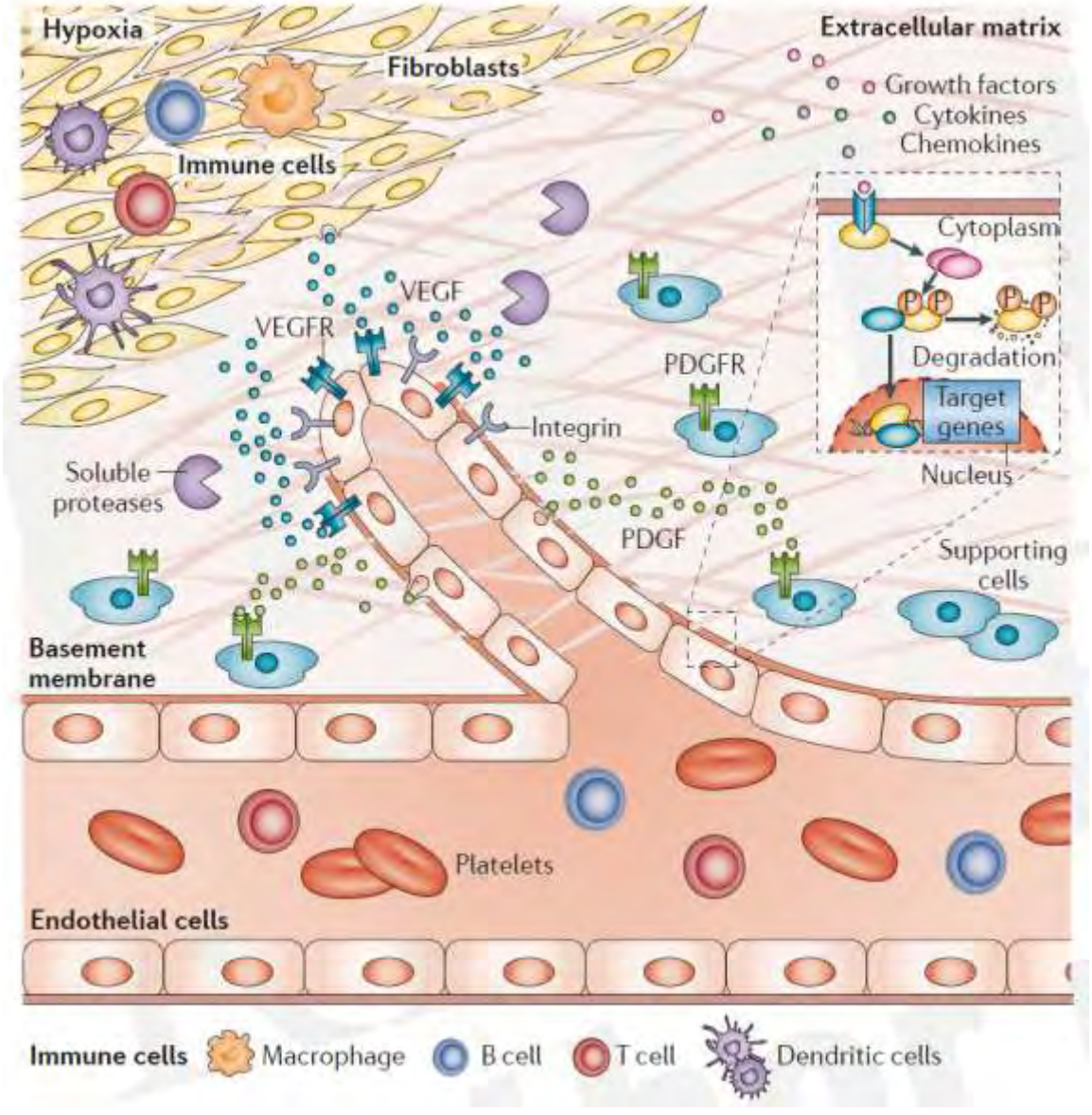
Angiogenesis

Az angiogenezis folyamata



Fearon, Szekanecz, Veale, In: Kelleys Textbook of Rheumatology, 2019

Az angiogenezis szereplői



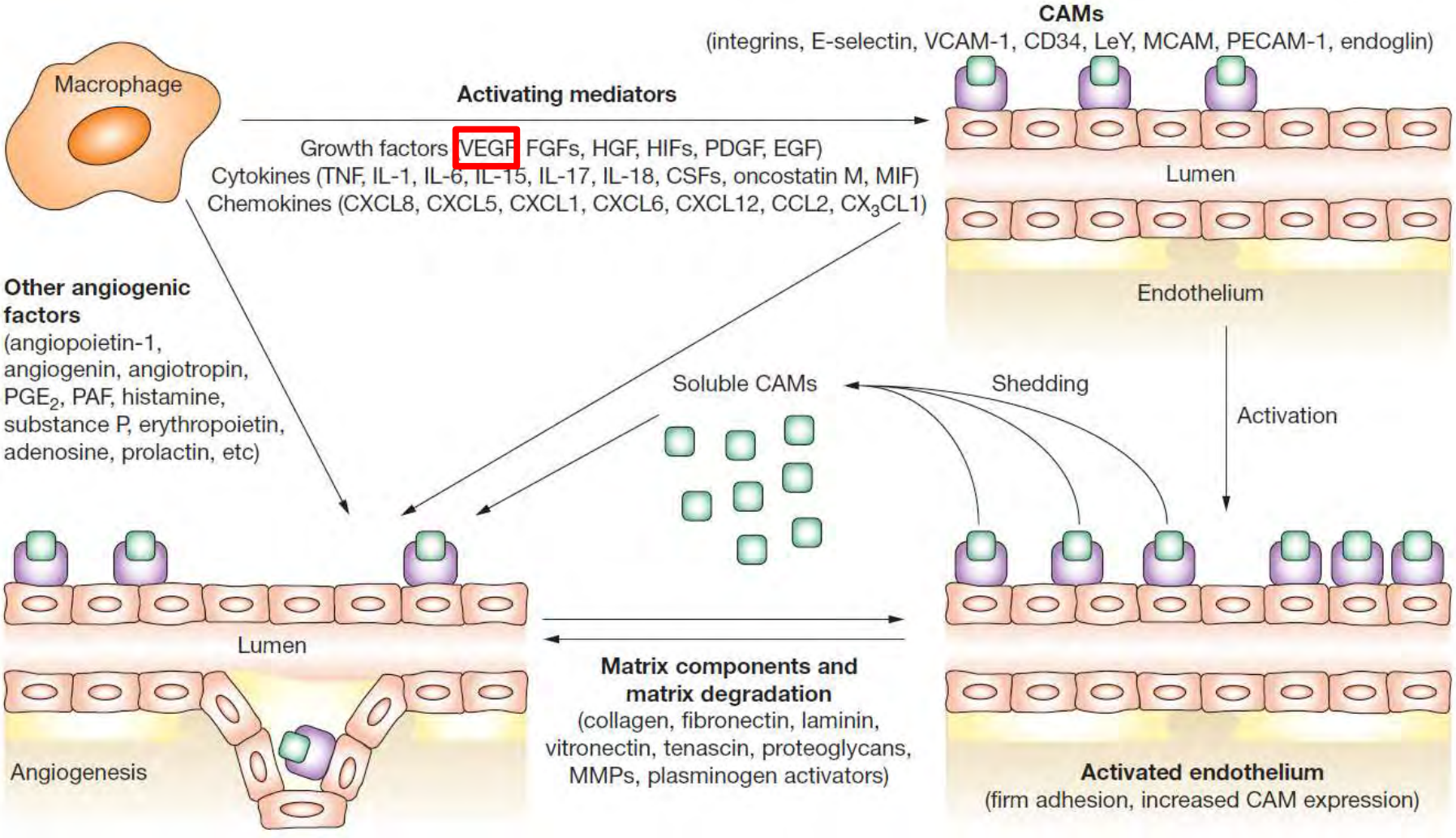
Tas, Szekanecz et al, Nat Rev Rheumatol 2016

Angiogén mediátorok és gátlók - redundancia

	Mediátorok	Inhibitorok
Chemokinek	CXCL1, CXCL5, CXCL7, CXCL8, CXCL12, CCL2, CCL21, CCL23, CX3CL1	CXCL4, CXCL9, CXCL10, CCL21
Extracelluláris mátrix makromolekulák	I. típusú kollagén, fibronectin, laminin, heparin, heparán szulfát	Thrombospondin 1, RGD peptid
Sejtadhéziós molekulák	β1 és β3 integrinek, E-selectin, P-selectin, VCAM-1, endoglin, CD31 (PECAM-1), VE-cadherin, Le^y/H és más szialilált szelektin ligandok	RGD peptid (integrin ligand)
Növekedési faktorok	VEGF, bFGF, aFGF, PDGF, EGF, IGF-I, HIF-1, TGF-β**	TGF-β**
Cytokinek	TNF-α, IL-1, IL-6, IL-15, IL-17, IL-18	IL-4, IL-35, IFN-α, IFN-γ
Proteázok	MMP-k, plazminogén aktivátorok (tPA, uPA), ADAMTS	TIMP, plazminogén aktivátor inhibitorok
Egyéb	Angiogenin, substance P, prolaktin	kortikoszteroidok, csDMARD-ok, bDMARD-ok, angiostatin, endostatin

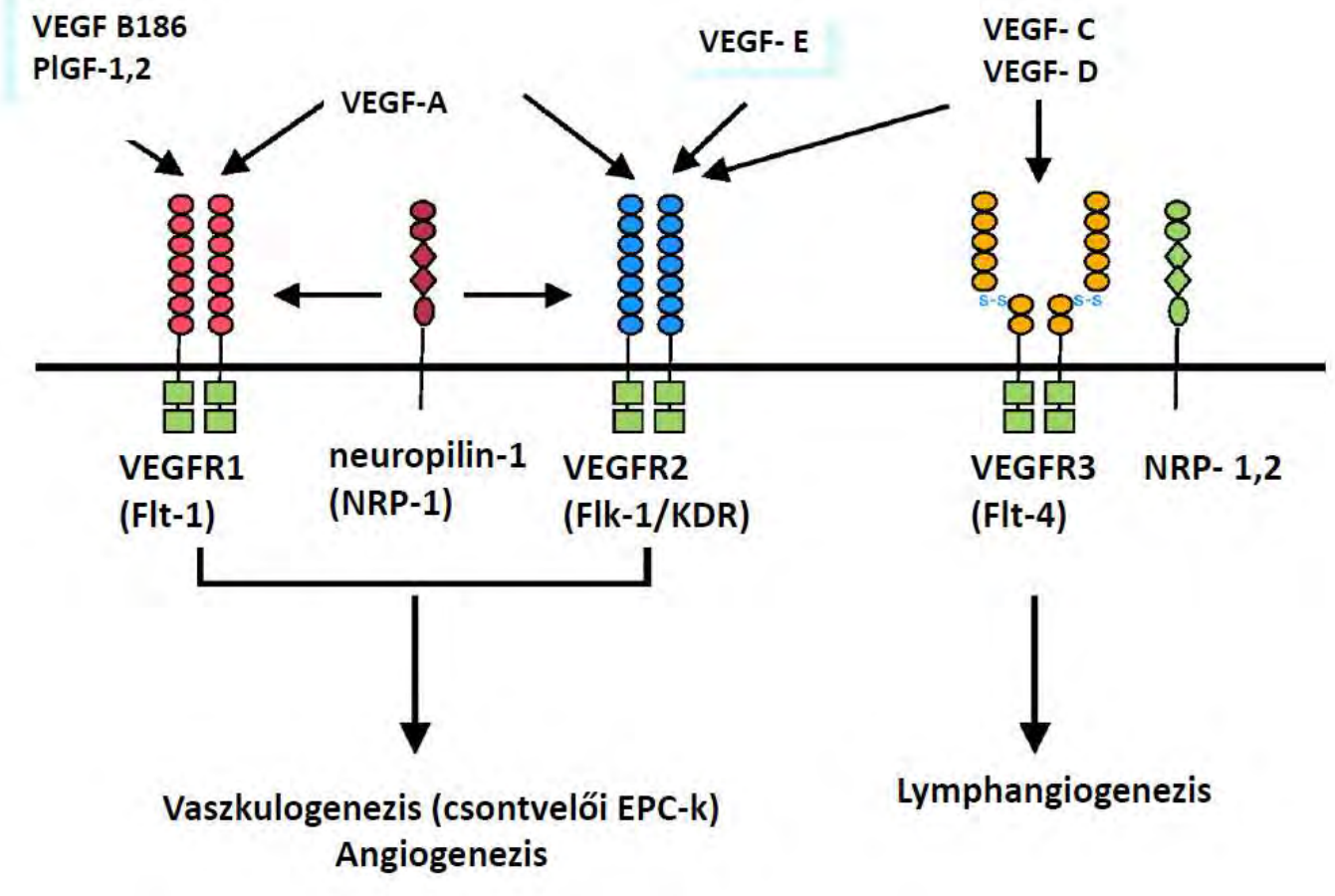
Szekanecz, In: Klinikai immunológia (szerkesztés alatt)

Angiogén mediátorok

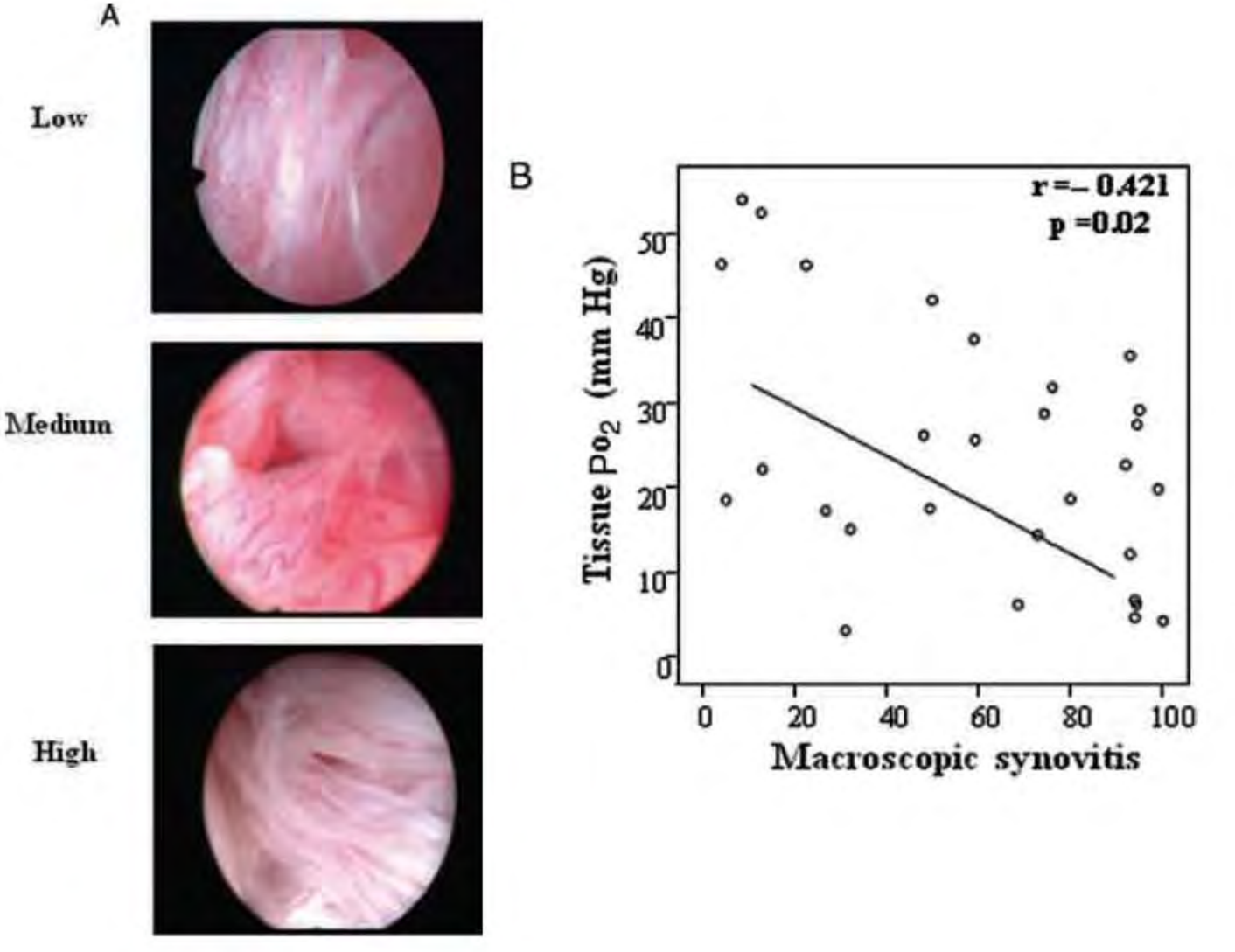


Szekanecz, Koch Nature Clin Pract Rheumatol 2007

A VEGF család és receptorai

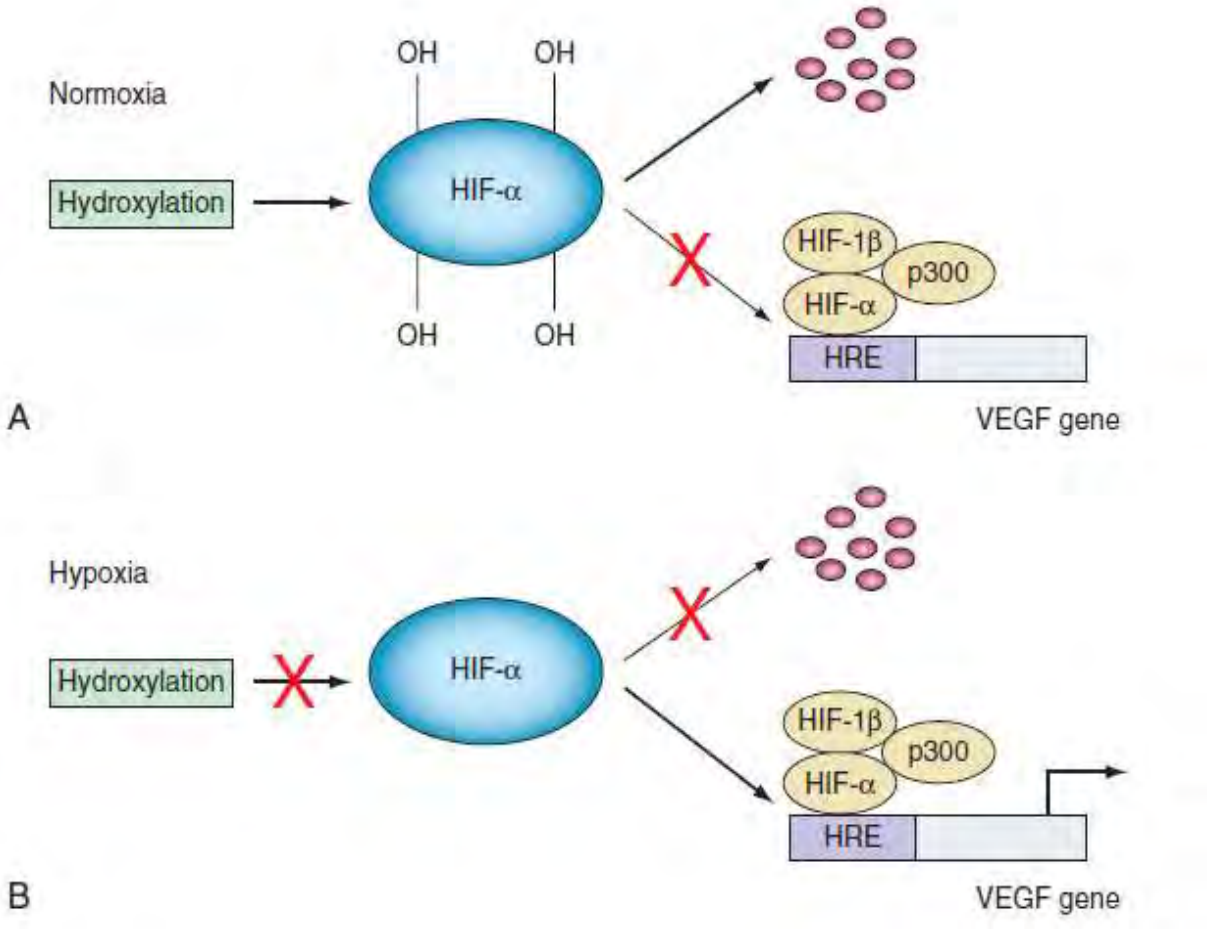


Gyulladások, tumorok: hypoxia



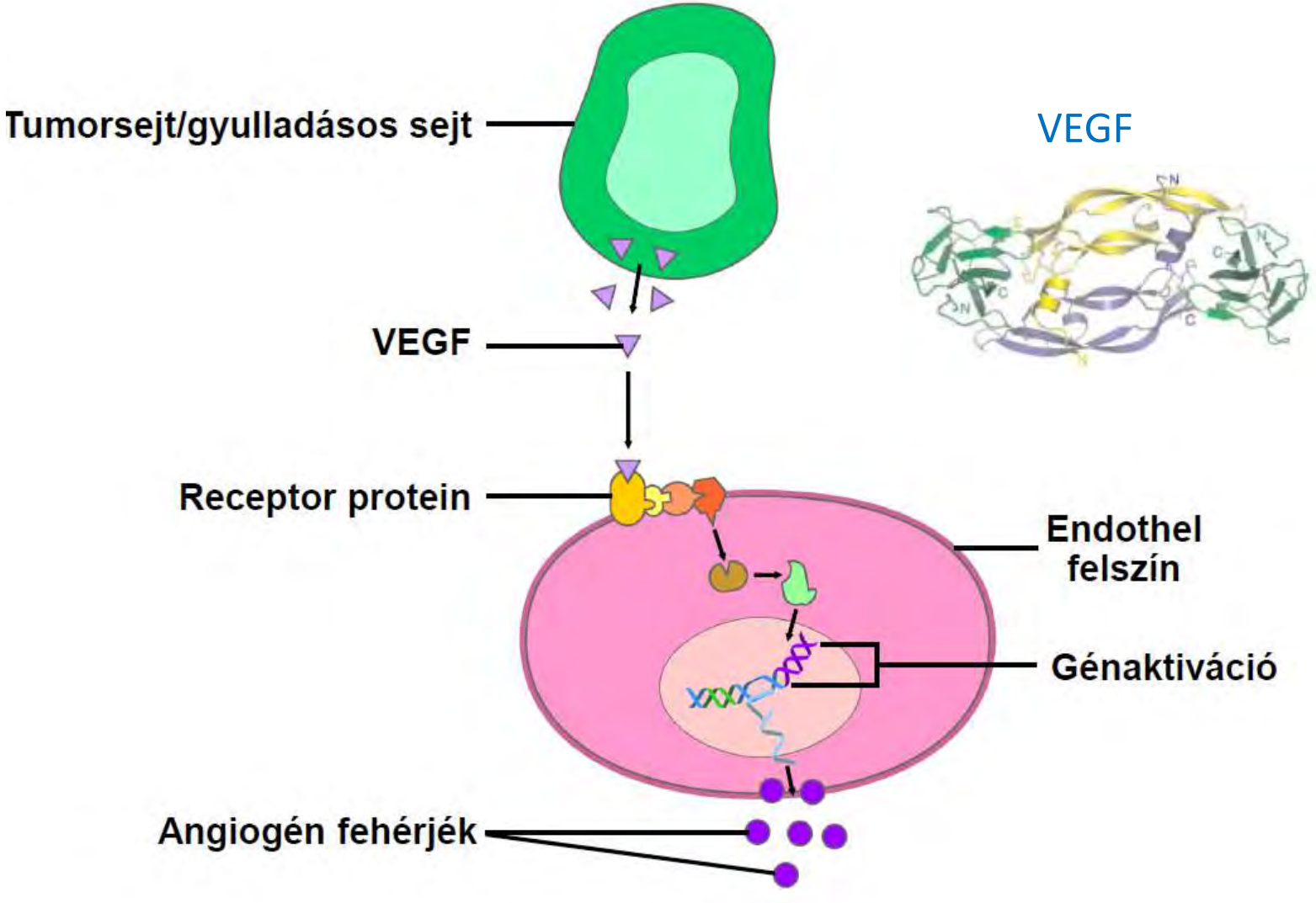
Ng et al, ARD 2012

Hypoxia – VEGF - HIF



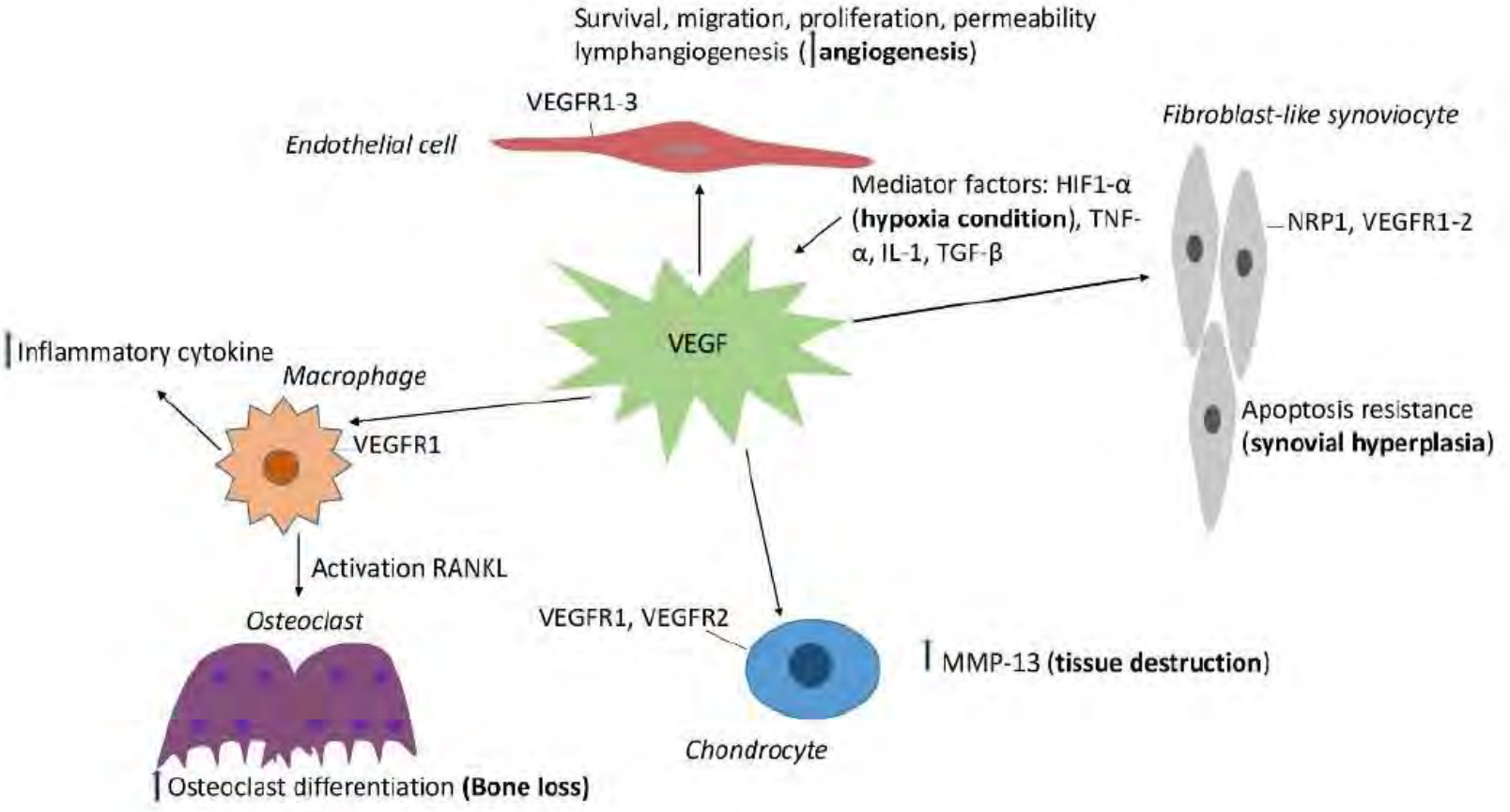
Szekanecz, Koch, Kelley's Textbook of Rheumatology, 2016

VEGF szignalizáció



VEGF

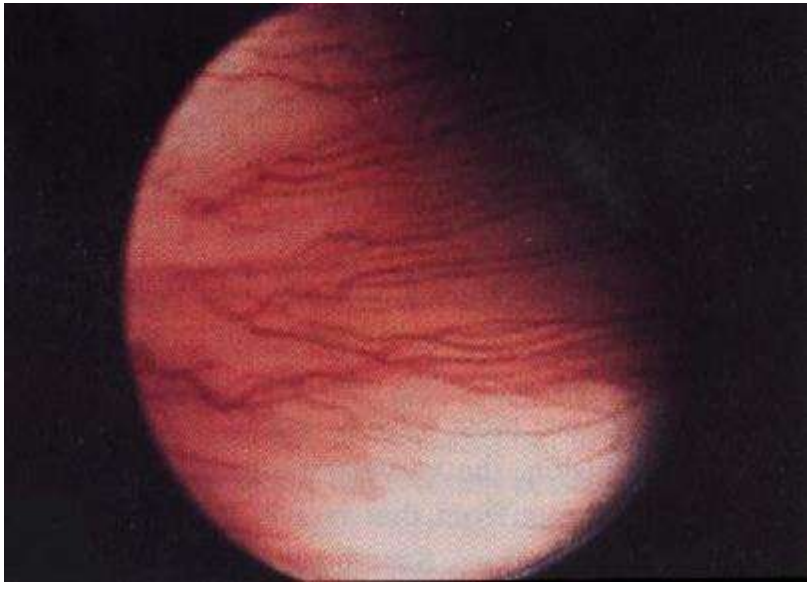
VEGF funkciók



Kwon et al, Int J Mol Sci 2021

Angiogenesis arthritisekben

PsA

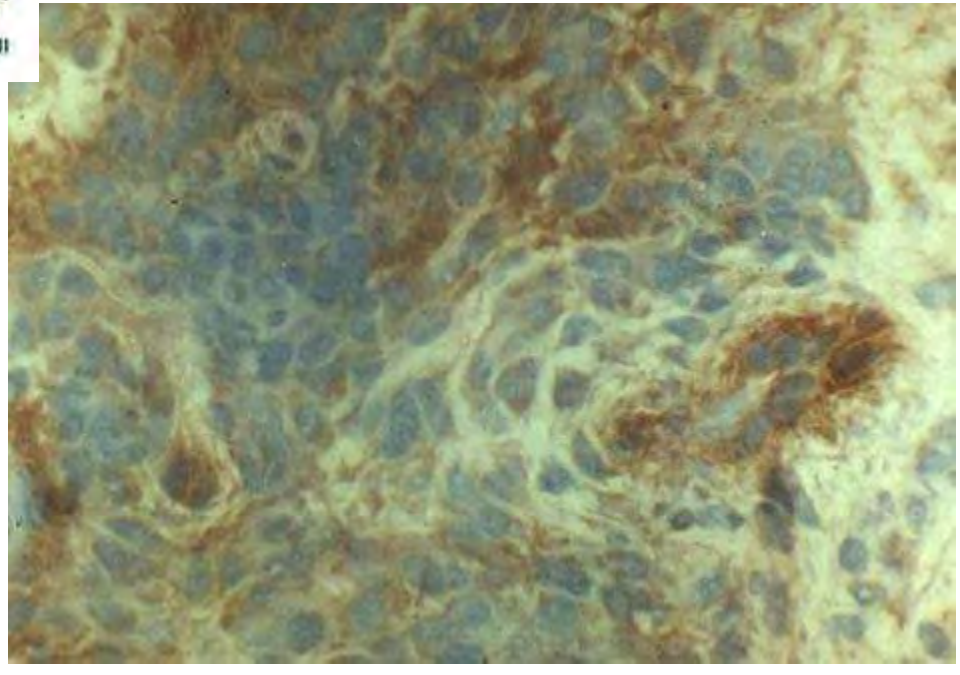


RA

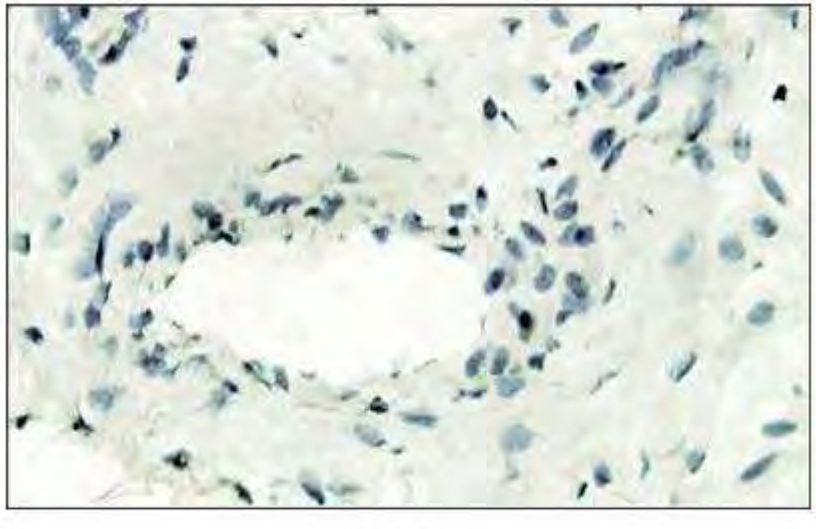
TABLE 1. Comparison of VEGF-1, IκBα, and NFκB expression in synovial tissue from patients with ERA and EPsA

	ERA ($n = 10$)	EPsA ($n = 10$)
VEGF-1	0.85 ± 0.34	2.4 ± 0.38

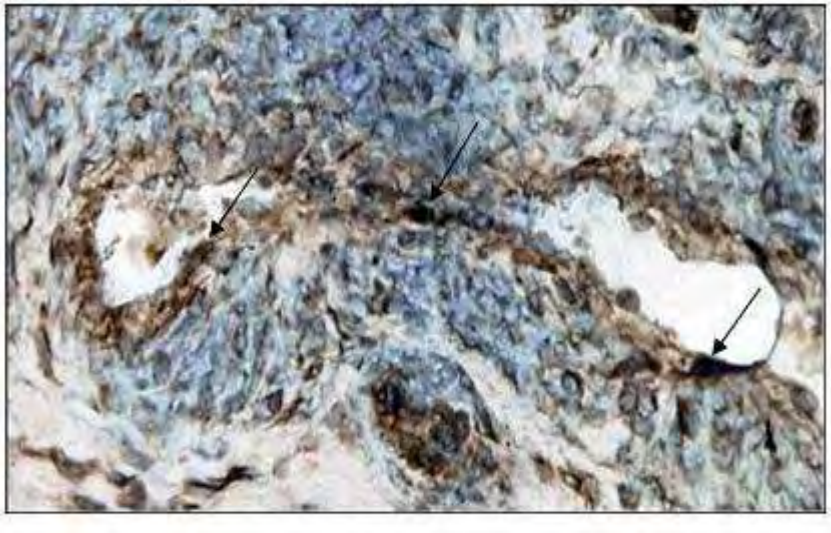
Reece et al, Arthritis Rheum 1999
Fearon et al, Ann NY Acad Sci 1999



RA synovium



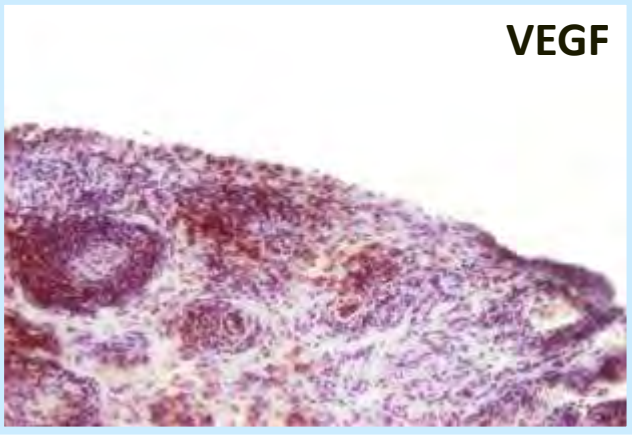
IgG



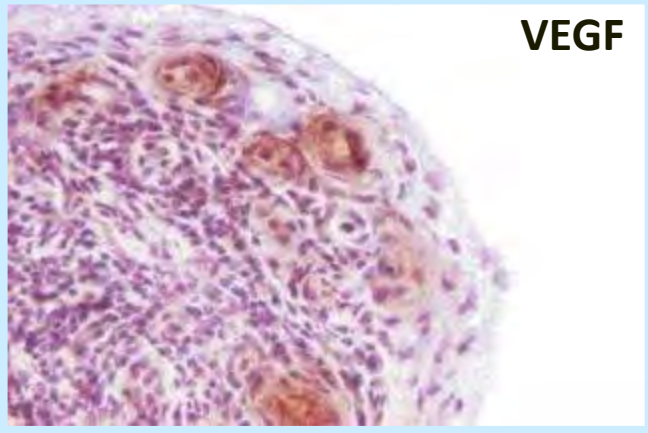
MIF

VEGF és Ang2 RA és PsA synoviumban

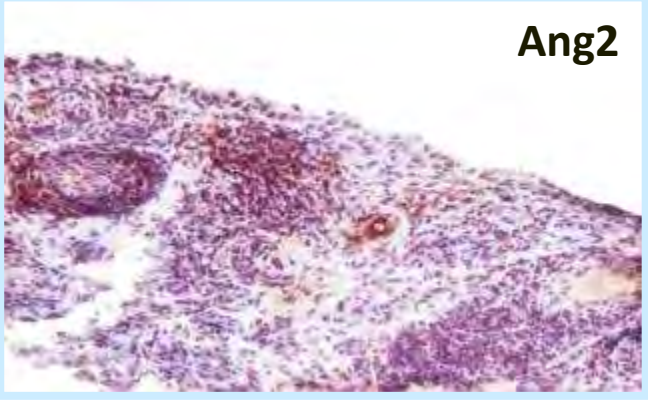
PsA



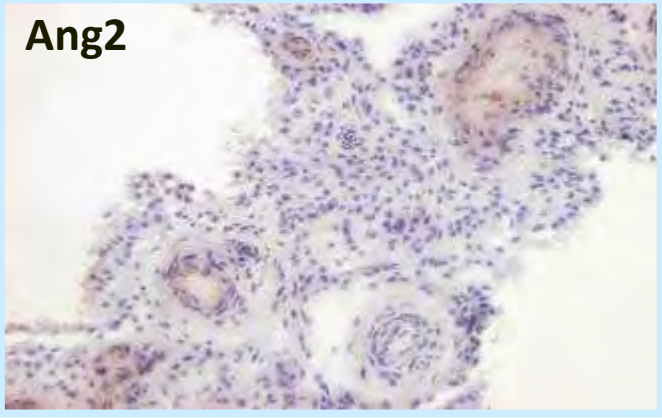
RA



PsA



OA



Fearon et al; 2003

RA: betegségtartam és aktivitás

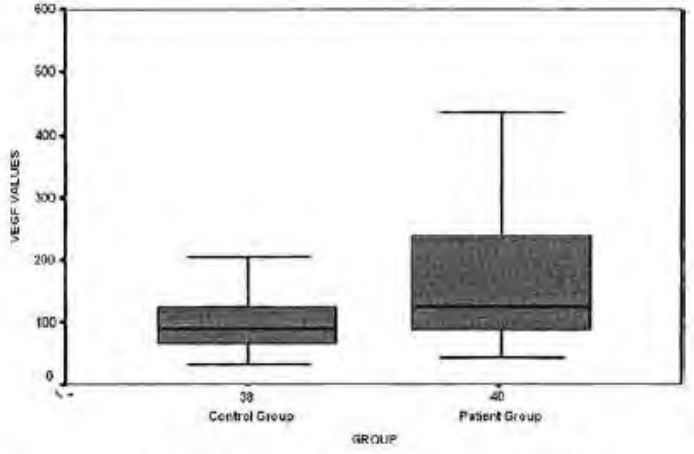
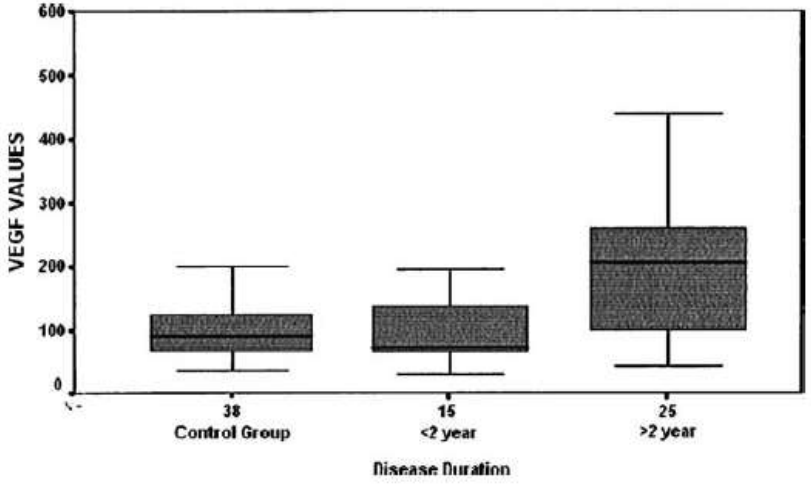


Fig. 1 Box plot graph of the distribution of VEGF values for control and RA patient groups



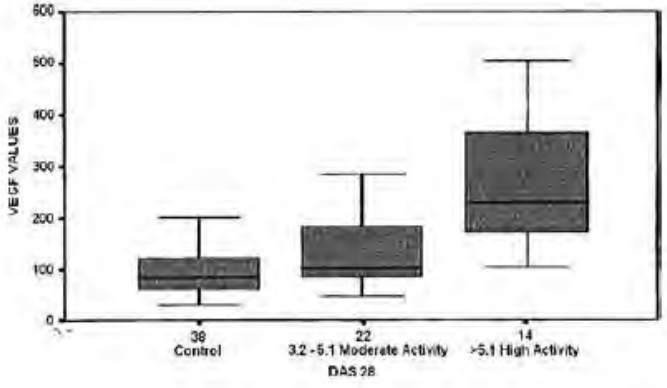
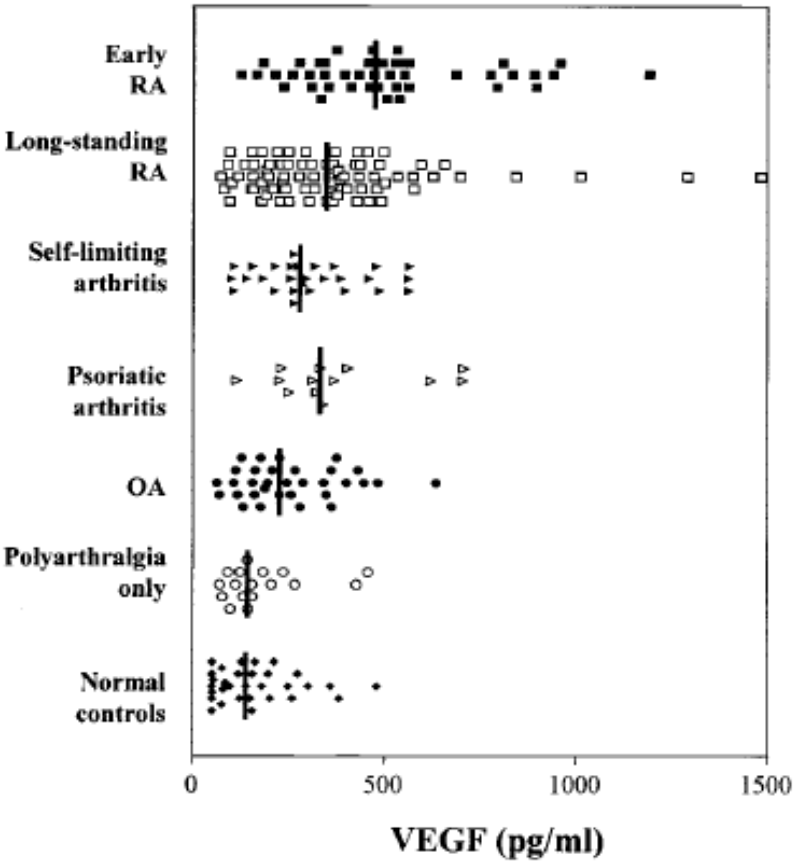
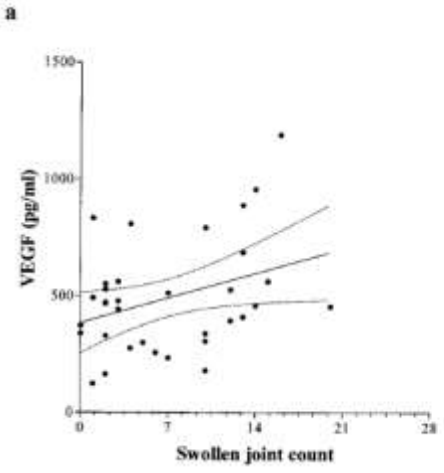


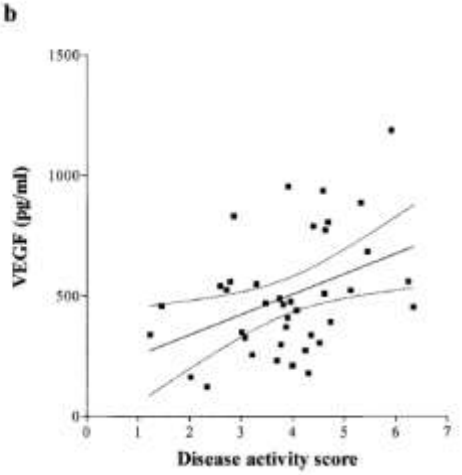
Fig. 3 Box plot graph of VEGF values for the control group and for moderate and high disease activity RA patient subgroups

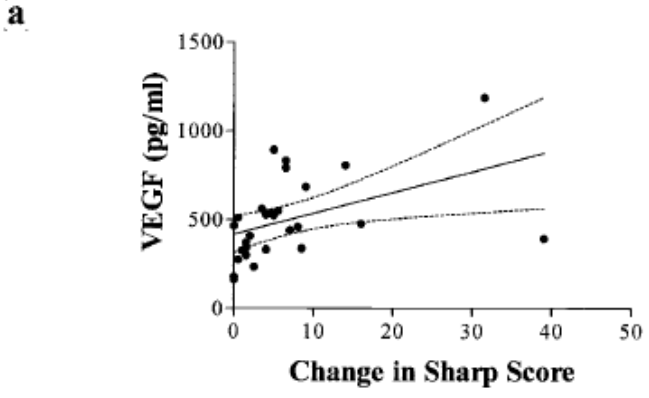
Ozgonenel et al, Clin Rheumatol 2010

VEGF: aktivitás és destrukció markere









Ballara et al, Arthritis Rheum 2001

SpA – VEGF aktivitási marker – anti-TNF

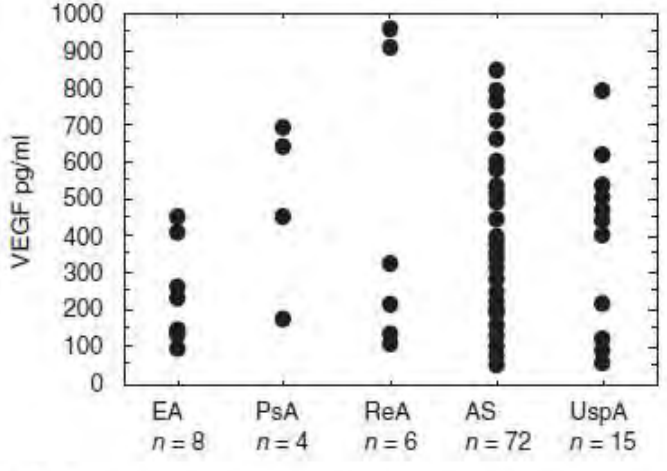
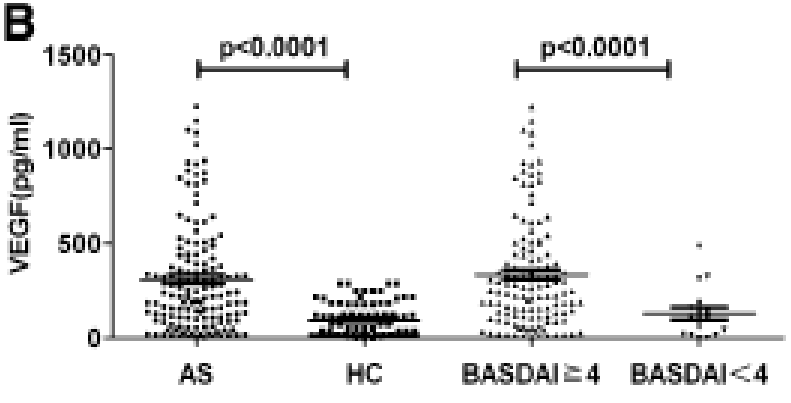
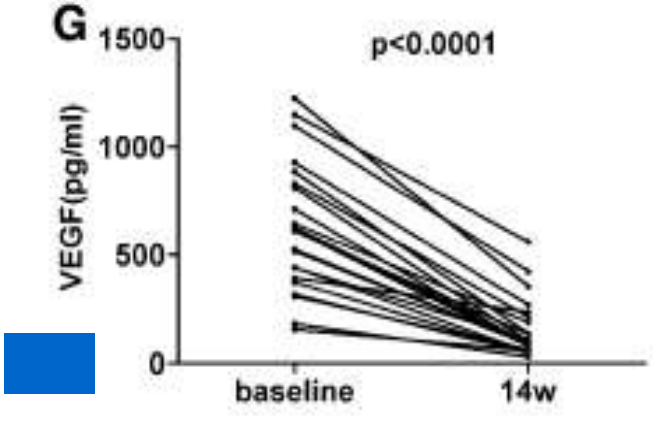


Fig. 2. Serum vascular endothelial growth factor concentration in the spondyloarthropathy subgroups. AS: ankylosing spondylitis; PsA: psoriatic arthritis; ReA: reactive arthritis; EA: enteropathic arthropathy; USpA: undifferentiated spondyloarthropathy.

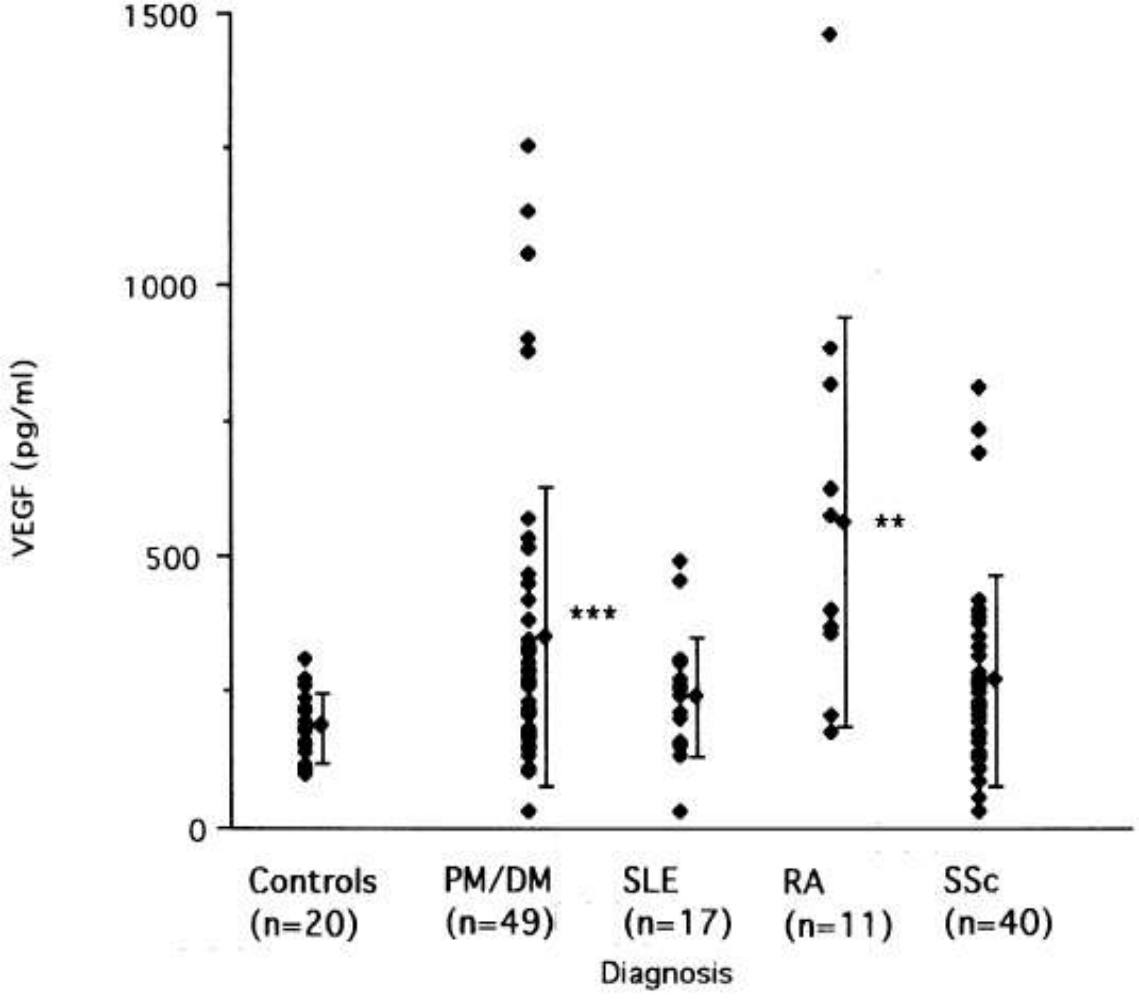
Drouart et al, Clin Exp Immunol 2013





Lin et al, Clin Exp Med 2015

VEGF autoimmun betegségekben



Kikuchi et al, Br J Dermatol 1998

Angiogenezis és VEGF a csontban

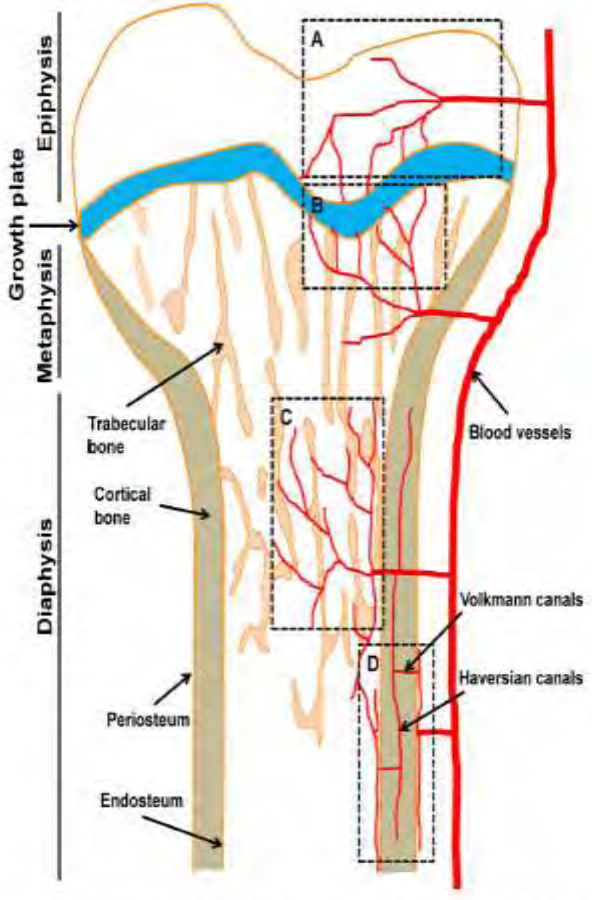


Fig. 1. Schematic diagram showing vascular supply in bone. Vascular supply is important for all regions of bone. Blood vessels invade into bone and provide nutrients and hormones required for development and remodeling at (A) trabecular bone within epiphysis, (B) cartilage-subchondral bone interface, (C) trabecular bone within diaphysis, and (D) cortical bone.

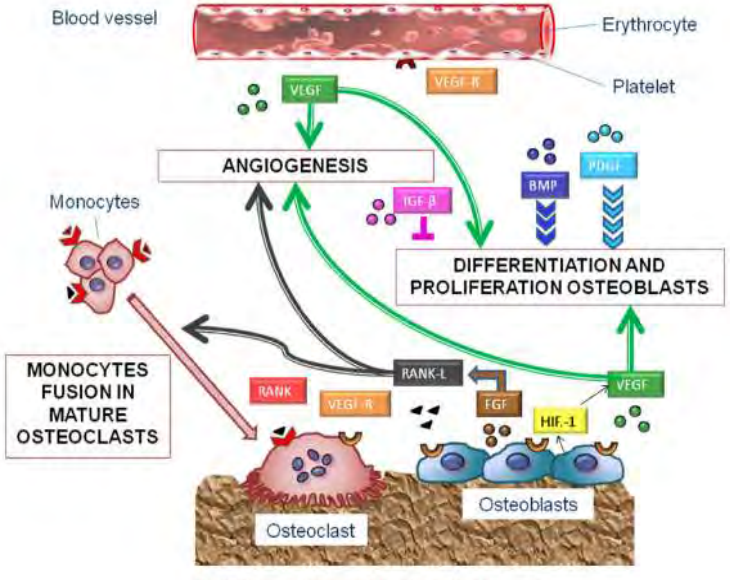
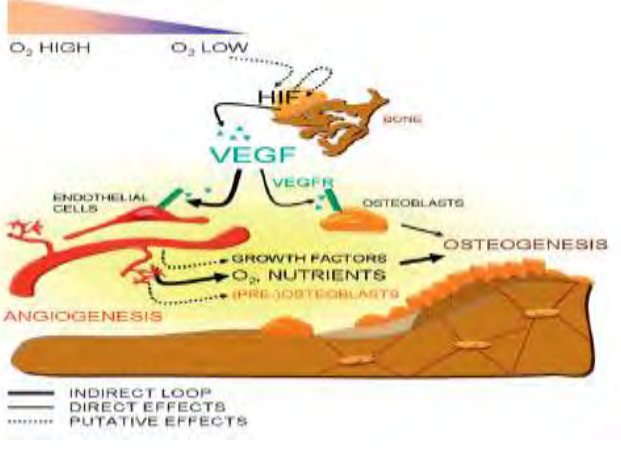
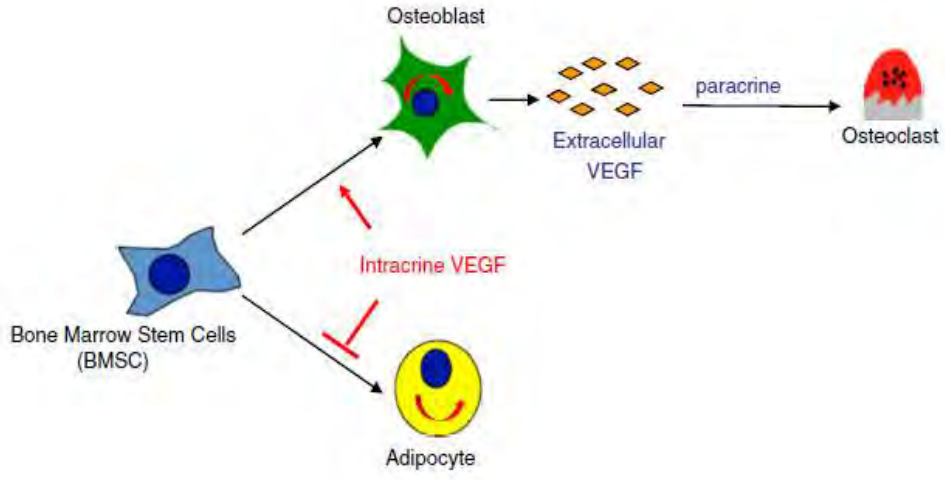


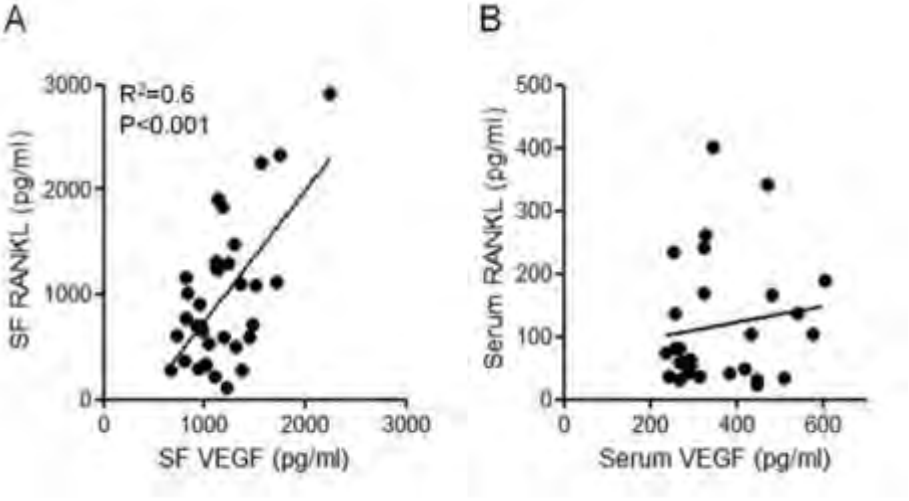
Fig. 2. Microenvironment during bone fracture repair.

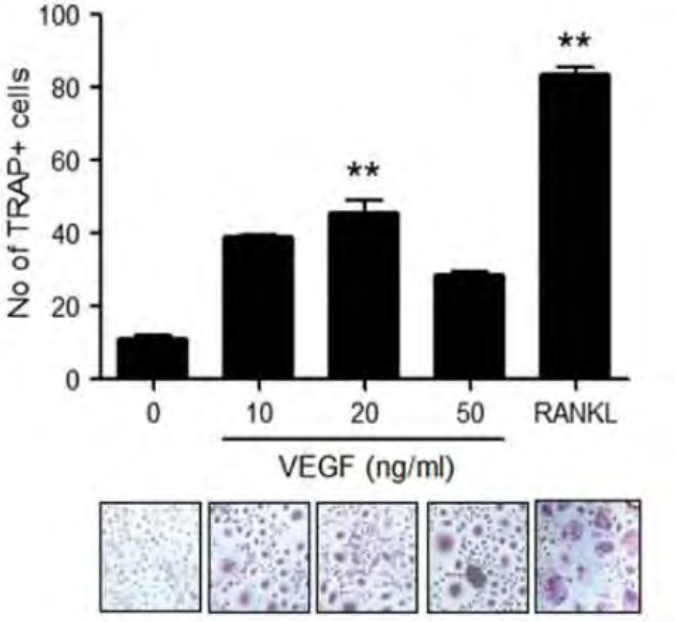


Chin et al, Cytokine Growth Fact Rev 2013
Schipani et al, JBMR 2009
Saran et al, Arch Biochem Biophys 2014

VEGF – osteoclastogenesis RA-ban



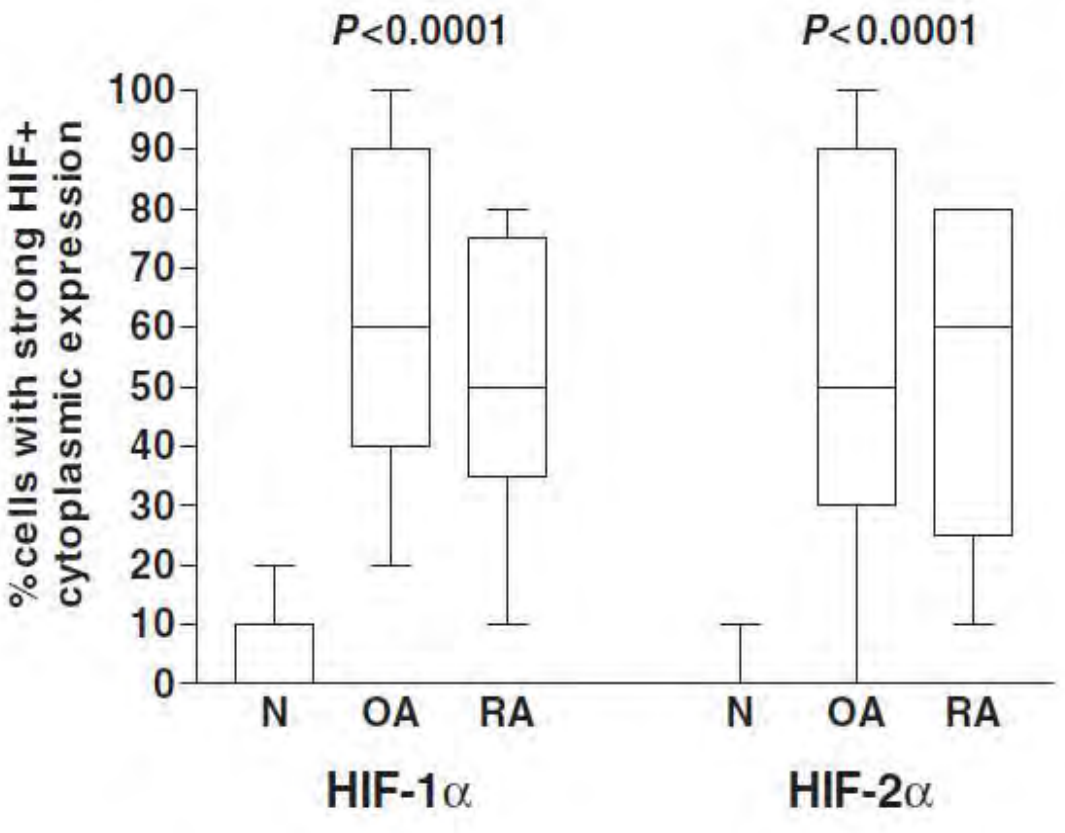




Monocyta osteoclastogenesis

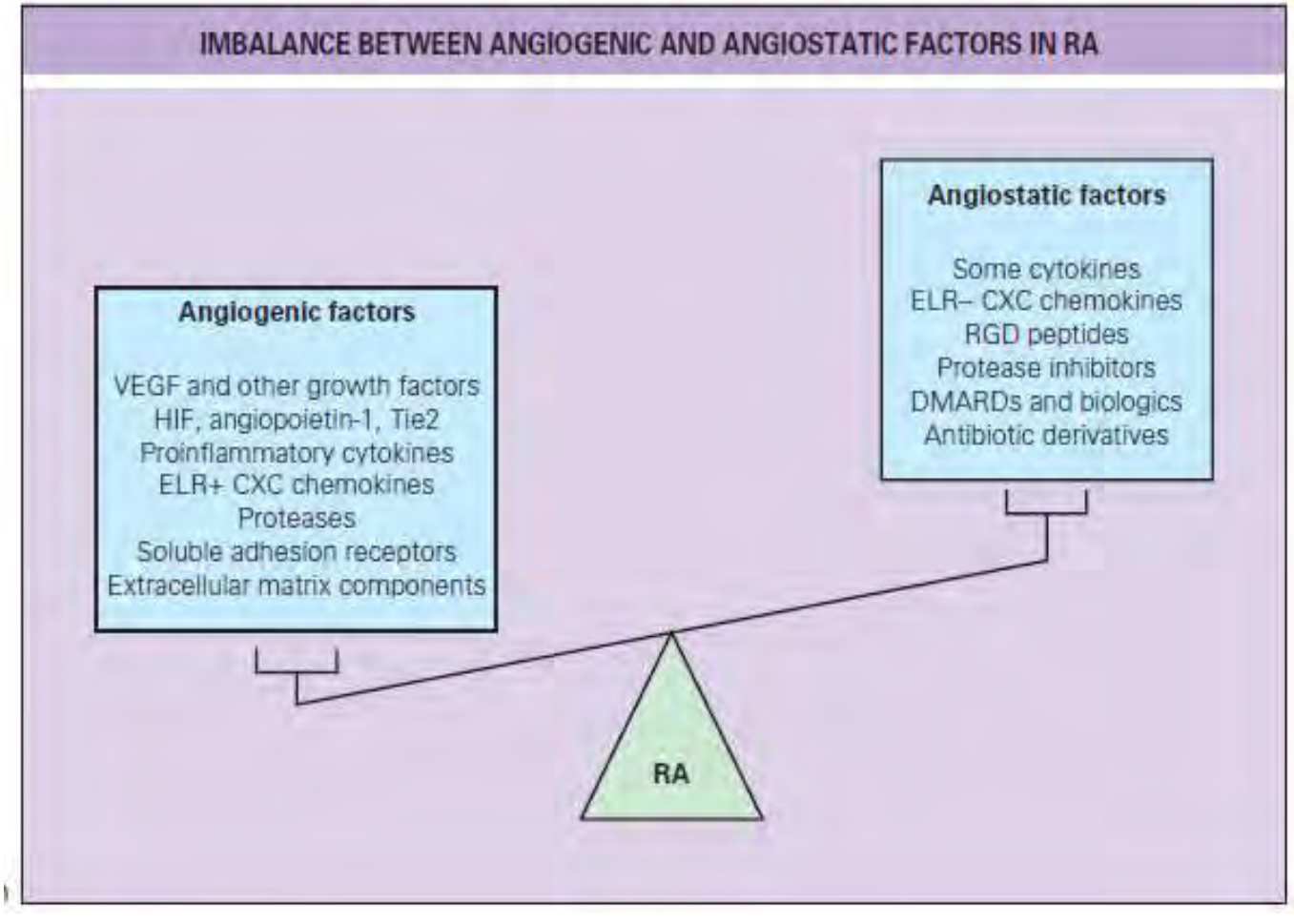
Liu et al, Arch Immunol Ther Exp 2014
Kim et al, PLOS One 2015

RA: HIF expresszió



Giatromanolaki et al, ART 2003

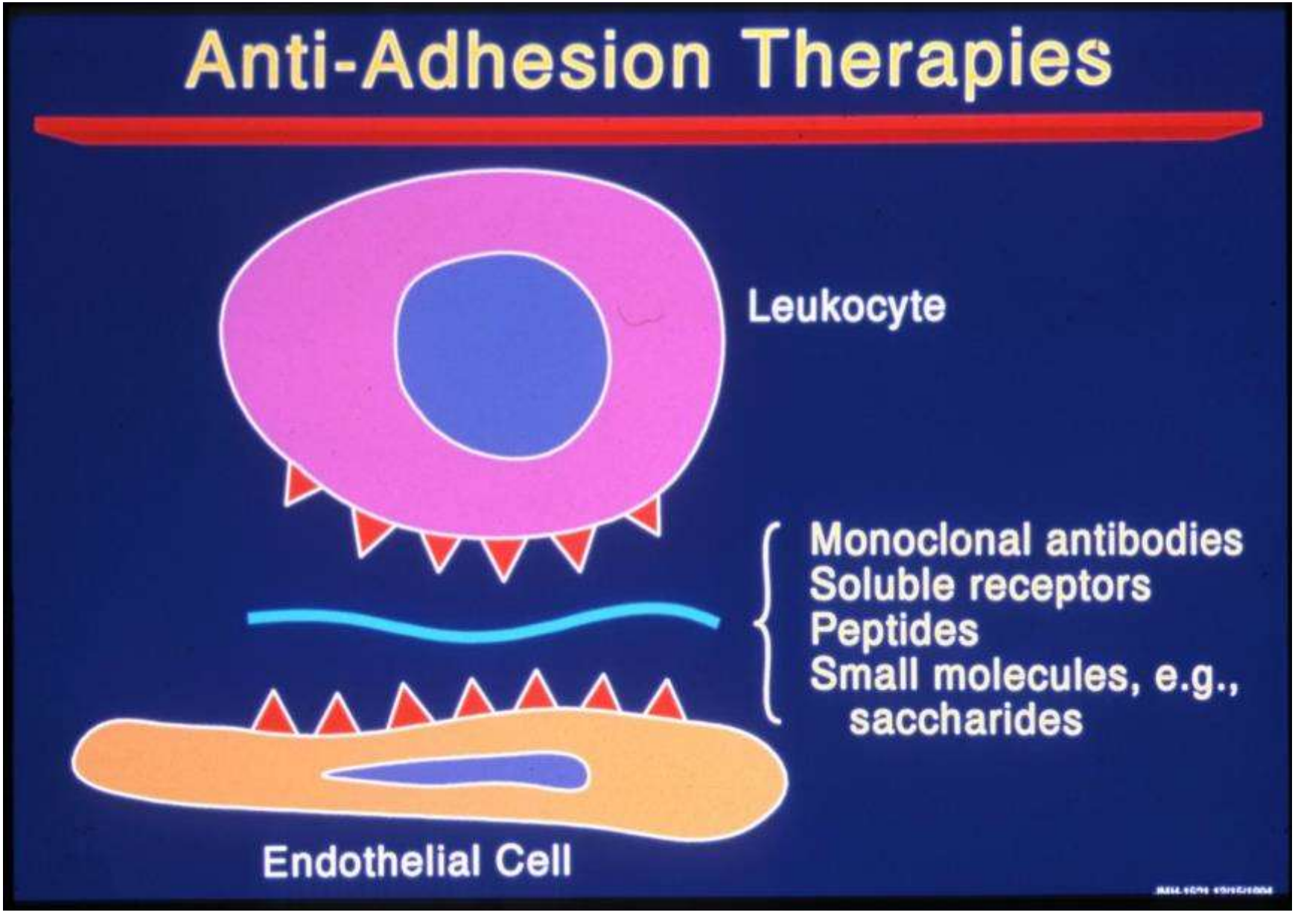
RA: angiogén és angiosztatikus mediátorok



Szekanecz, Koch, Hochberg's Rheumatology, 2014

Célzott terápiás lehetőségek (redundancia!)

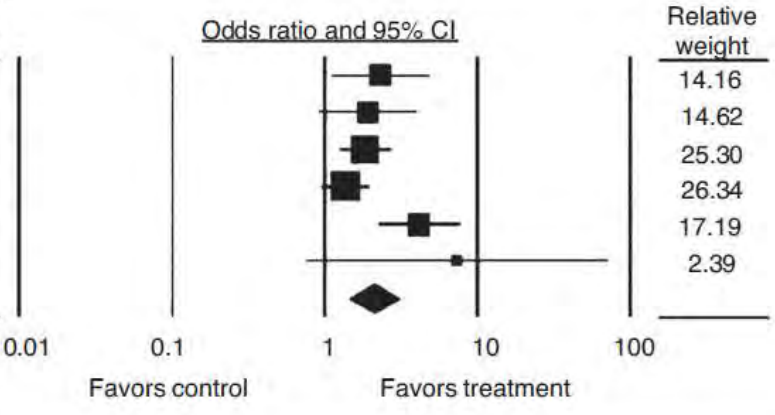
Terápia: adhézió gátlás



α4β7 integrin – vedolizumab (Crohn)

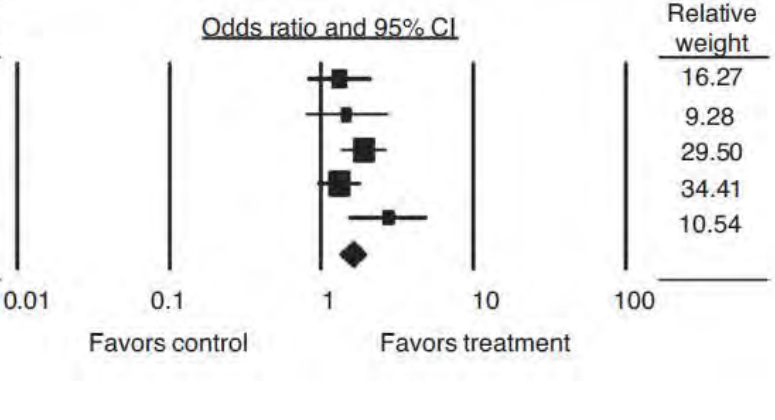
1st AU (year)	Clinical remission rate: Treatment	Clinical remission rate: Control	Statistics: Odds ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight
Sandborn (2013)	0.15	0.07	2.324	1.097	4.927	2.200	0.028	14.16
Feagan (2008)	0.34	0.21	1.921	0.925	3.990	1.750	0.080	14.62
Targan (2007)	0.38	0.25	1.839	1.257	2.691	3.136	0.002	25.30
Sandborn (2005)	0.37	0.30	1.370	0.964	1.948	1.755	0.079	26.34
Ghosh (2003)	0.61	0.27	4.184	2.229	7.854	4.456	0.000	17.19
Gordon (2001)	0.39	0.08	7.352	0.744	72.644	1.707	0.088	2.39
Total (Random)			2.108	1.460	3.043	3.980	0.000	

A Q statistic = 10.99, I^2 = 54.50%, P = 0.052



1st AU (year)	Clinical response rate: Treatment	Clinical response rate: Control	Statistics: Odds ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight
Sandborn (2013)	0.31	0.26	1.323	0.823	2.127	1.157	0.247	16.27
Feagan (2008)	0.50	0.41	1.462	0.780	2.741	1.185	0.236	9.28
Targan (2007)	0.60	0.44	1.909	1.342	2.716	3.597	0.000	29.50
Sandborn (2005)	0.56	0.49	1.325	0.956	1.836	1.689	0.091	34.41
Ghosh (2003)	0.63	0.38	2.743	1.521	4.946	3.354	0.001	10.54
Total (Fixed)			1.607	1.327	1.947	4.861	0.000	

B Q statistic = 6.15, I^2 = 34.99%, P = 0.188



+ α4β1 integrin – natalizumab (SM)

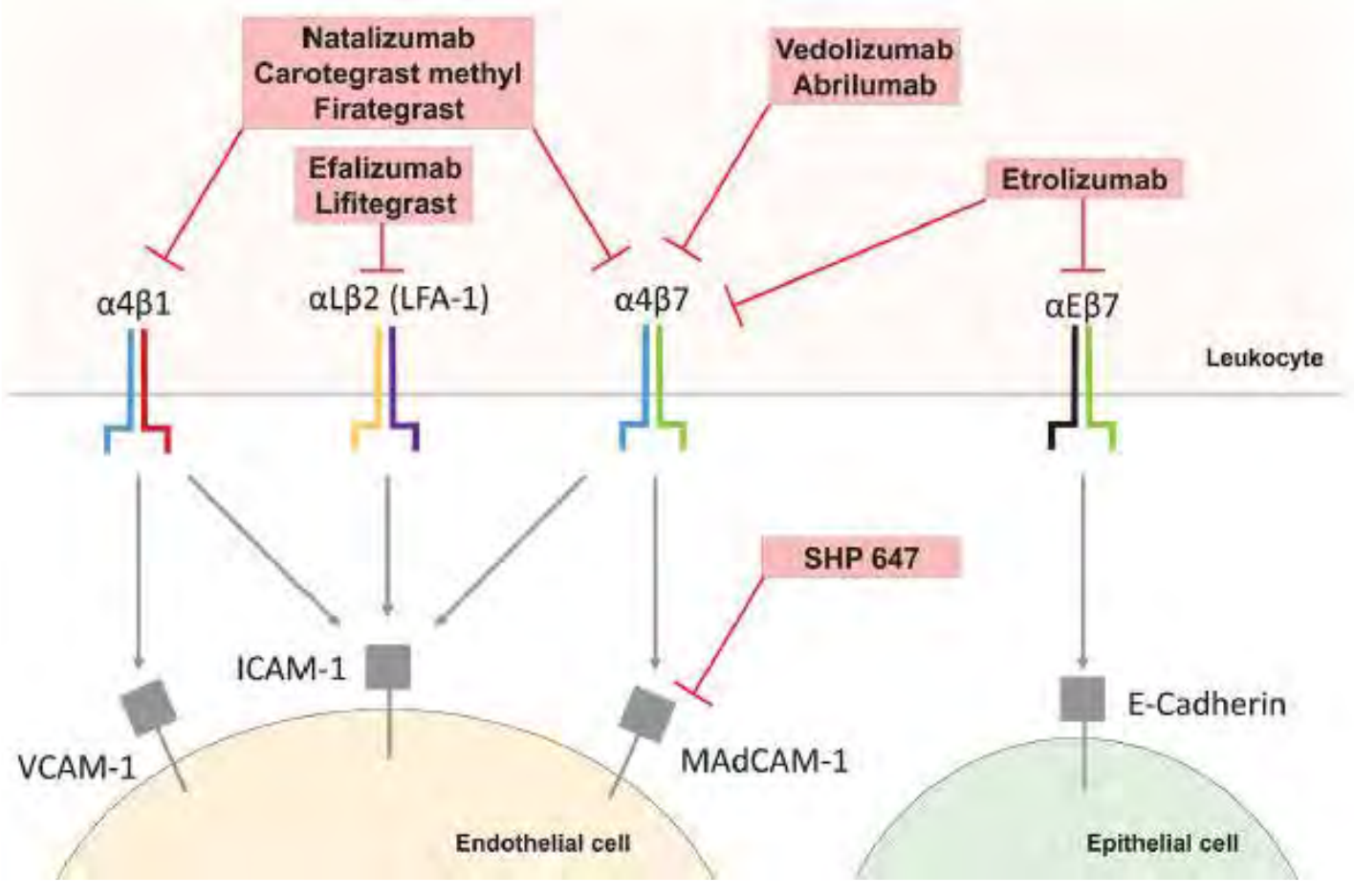
Lin et al, Medicine, 2015

α4β7 integrin – vedolizumab (IBD-extraintestinalis)

Study	Extraintestinal manifestation	Sample size	Study design	Main results
Feagan et al. [105]	Arthralgia/ arthritis	Total 1032 CD 759 UC 273	Post-hoc analysis of RCT	CD: VDZ less likely to be associated with new/worsening arthralgia/arthritis than PL; similar rates of sustained resolution with VDZ and PL; in patients achieving corticosteroid-free status, arthralgia/arthritis less likely with VDZ than PL UC: similar incidence of new/worsening arthralgia/arthritis with VDZ and with PL; in patients achieving corticosteroid-free status incidence of arthralgia/arthritis similar for VDZ and PL
Tadbiri et al. [110]		Total 294 CD 173 UC 121	Prospective multicenter cohort study	
	Arthralgia/ arthritis			16% (47/294) arthralgia arthritis at baseline; 35/47 peripheral, 6/47 axial, 6/47 both; remission in 44.7% (21/47) at 1 year; clinical remission and recent onset of articular symptoms were associated with EIM remission De novo arthralgia arthritis in 13.8% (34/247); 17/34 in clinical remission, 25/34 peripheral, 2/34 axial, 5/34 both; VDZ continued in 25/34 patients in combination with local therapy and analgesics
	Cutaneous			Erythema nodosum: remission in 2/2 cases Pyoderma gangrenosum: response in 0/1 case Leukocytoclastic vasculitis: response in 1/1 case Paradoxical manifestations in 4.8% (14/294) patients
Macaluso et al. [106]	Arthritis	Total 163 CD 84 UC 79	Prospective multicenter cohort study	Response in 39.5% (17/43) with active spondyloarthritis at baseline – 13/28 with peripheral involvement, 2/4 with axial involvement, 2/11 with combined involvement Three cases of de novo spondyloarthritis in patients with active luminal IBD
Dogné et al. [109]	Arthritis	Total 112 CD 59 UC 49 IC 4	Retrospective single-center cohort study	9.8% (11/112) developed axial or peripheral spondyloarthritis; 8/11 had active IBD; 7/8 changed treatment, the remaining patient improved with VDZ; in the 3/11 patients with inactive IBD, local corticosteroids, analgesics, and continuation of VDZ led to improvement
Phillips et al. [93]	Cutaneous	Total 11	Multicenter case series	Erythema nodosum: response in 2/4 cases Pyoderma gangrenosum: response in 0/1 cases Metastatic CD: remission in 1/3 cases Leukocytoclastic vasculitis: remission in 1/1 case
Caron et al. [116]	PSC	Total 75 CD 26 UC 49	Retrospective multi-center cohort study	No significant change in ALP
Christensen et al. [117]	PSC	Total 34 CD 16 UC 18	Retrospective multi-center cohort study	No significant change in ALP
Tse et al. [102]	PSC	Total 27 CD 10 UC 16 IC 1	Retrospective single-center cohort study	No significant change in ALP; radiologically stable disease at 12 months in 79% (19/24), consistent with natural history of PSC
Lynch et al. [118]	PSC	Total 102 CD 30 UC 66 IBD-U 6	Retrospective multi-center cohort study	Median ALP increased from 1.54 × ULN to 1.64 × ULN ($P = 0.018$); ≥ 20% decrease in ALP in 20.6% (21/102) of patients

Hanzel et bal, Drugs 2021

Anti-adhéziós terápiás lehetőségek



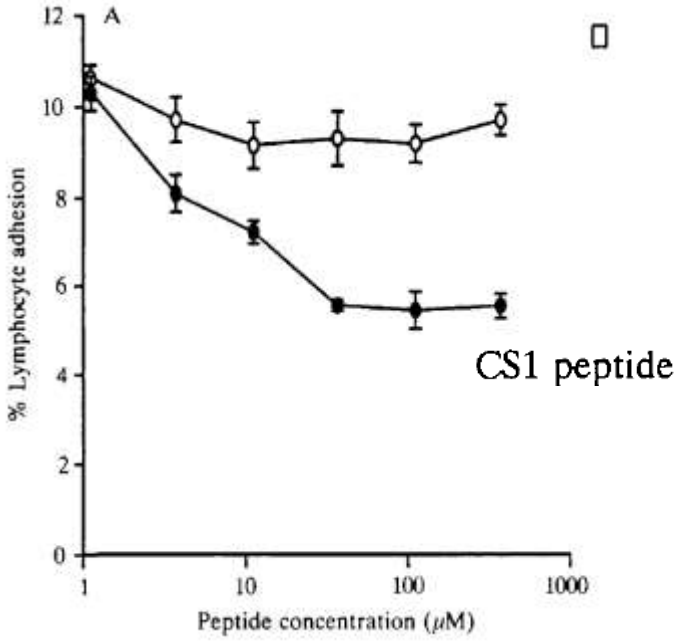
Baker & Isaacs, Ann Rheum Dis 2018

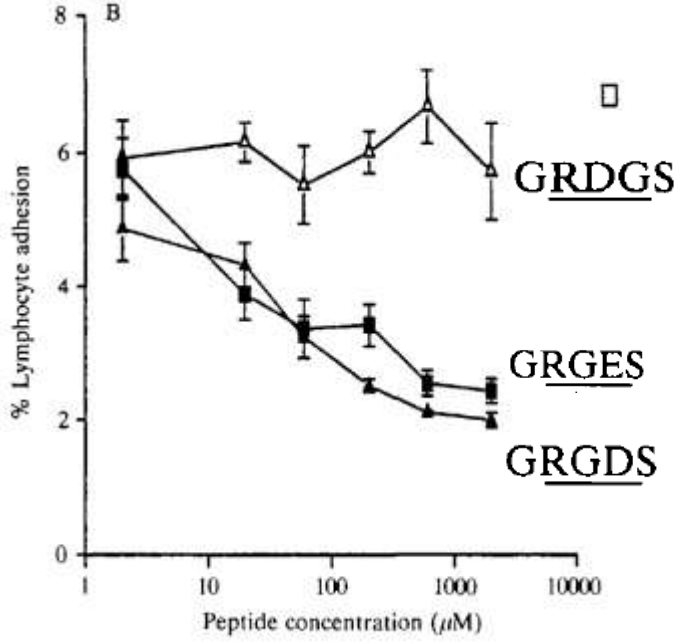
Anti-VCAM-1: transzplantáció, onkológia

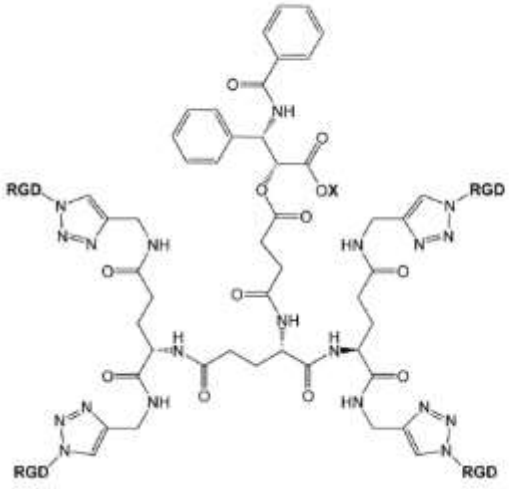
Disease	Animal Model	Applied Antibody	Effect	Reference
RA	DBA/1 mouse model of collagen-induced arthritis	Anti-VCAM-1 monoclonal antibody (M/K-2.7)	Reduction in overall clinical severity of disease	Carter et al., 2001 [55]
	Chimeric SCID mouse/human synovial tissue model	Anti-VCAM-1 polyclonal antibody	Inhibition of marrow-derived endothelial progenitor cell adhesion to RA synovial tissue	Silverman et al., 2007 [59]
Asthma	BALB/c mouse model of ovalbumin-induced asthma	Anti-VCAM-1 monoclonal antibody (M/K-1)	Prevention of eosinophil and lymphocyte infiltration into the trachea	Nakajima et al., 1994 [66]
	C57BL/6 mouse model of ovalbumin-induced asthma	Anti-VCAM-1 monoclonal antibody (M/K-2.7)	Inhibition of eosinophil and lymphocyte recruitment into the bronchoalveolar lavage fluid	Chin et al., 1997 [73]
	BALB/c mouse model of ovalbumin-induced asthma	Anti-VCAM-1 monoclonal antibody (HD101)	Attenuation of macrophage, neutrophil, and eosinophil recruitment into bronchoalveolar lavage fluid	Lee et al., 2013 [40]
Immune rejection	C3H/HEJ murine model of skin allograft	Anti-VCAM-1 monoclonal antibody (MK1.9)	Prolongation of skin allograft survival	Gorczynski et al., 1995 [85]
	CBA murine model of islet allograft	Anti-VCAM-1 monoclonal antibody (MK2.7)	Prolongation of islet allograft survival	Stegall et al., 2001 [86]
	C57BL/6 mouse model of cardiac allograft	Anti-VCAM-1 monoclonal antibody (M/K-2)	Prolongation of cardiac allograft survival	Pelletier et al., 1992 [83]
	C57BL/6 mouse model of islet allograft	Anti-VCAM-1 monoclonal antibody (MK2.7)	Prolongation of islet allograft survival	Lee et al., 2012 [43]
Cancer	Matrigel plug nude mouse model	Anti-VCAM-1 monoclonal antibody (M/K-2)	Inhibition of neovascularization	Garmy-Susini et al., 2005 [107]
	C57BL/6 mouse model of pulmonary metastasis	Anti-VCAM-1 monoclonal antibody (M/K-2)	Reduction of TNFα-enhanced pulmonary lung colonies	Okahara et al., 1994 [120]

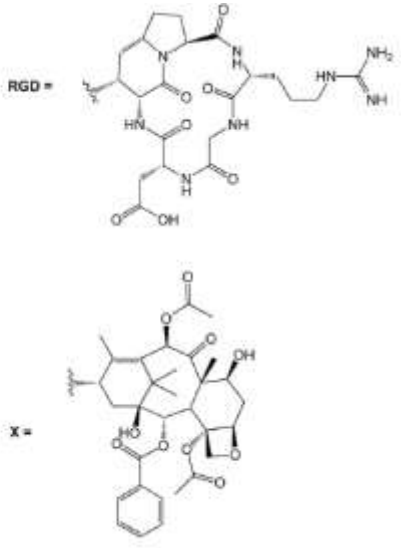
Kong et al, Int J Mol Sci 2018

Gyógyszer-peptid konjugátumok – fokozott hatás?



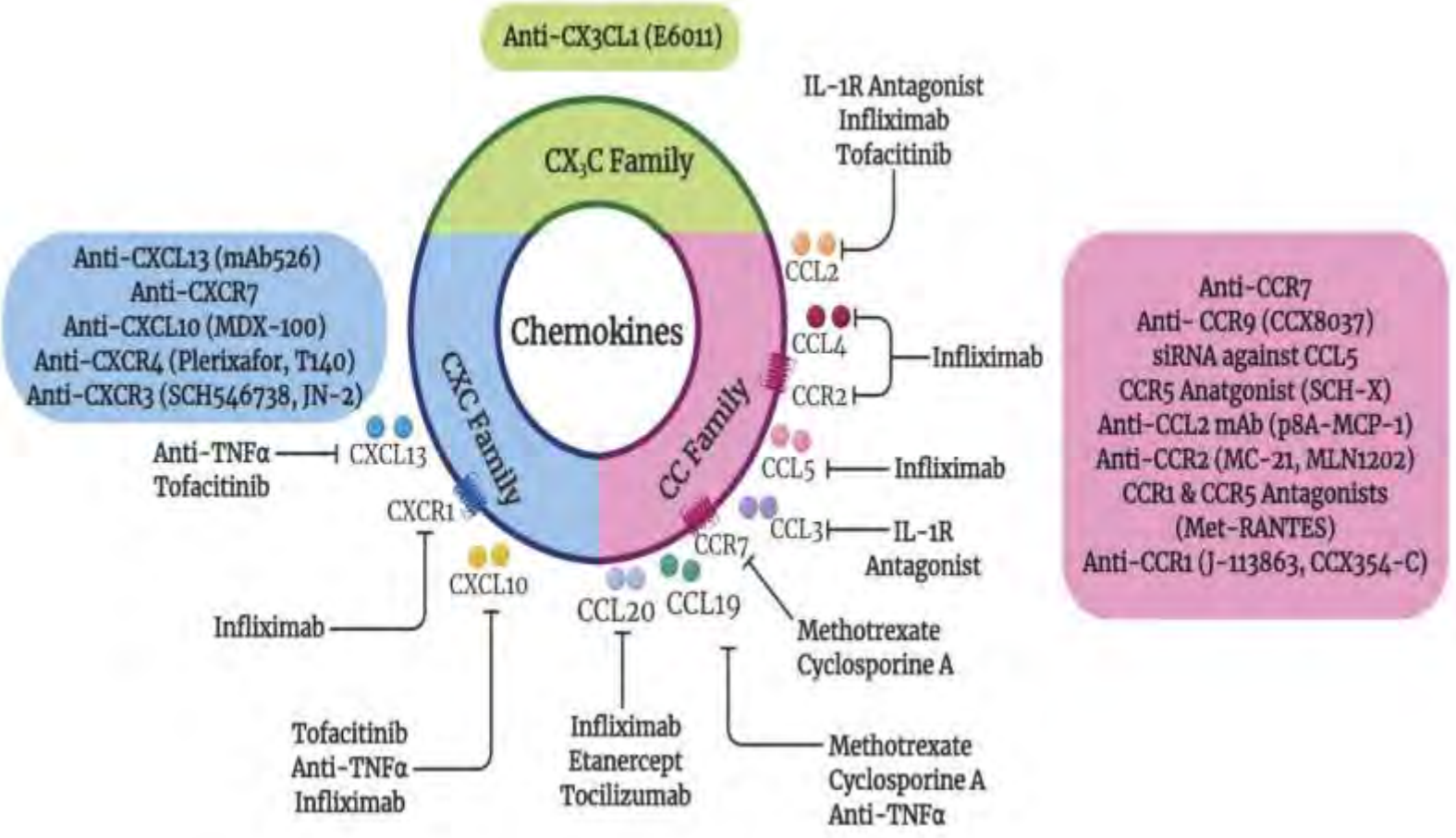






Seckanecz et al, J Cell Sci 1992
Moral et al, Curr Topics Med Chem 2017

Chemokin gátlás a reumatológiában: indirekt és direkt



Elemam et al, ImmunoTargets Ther 2020

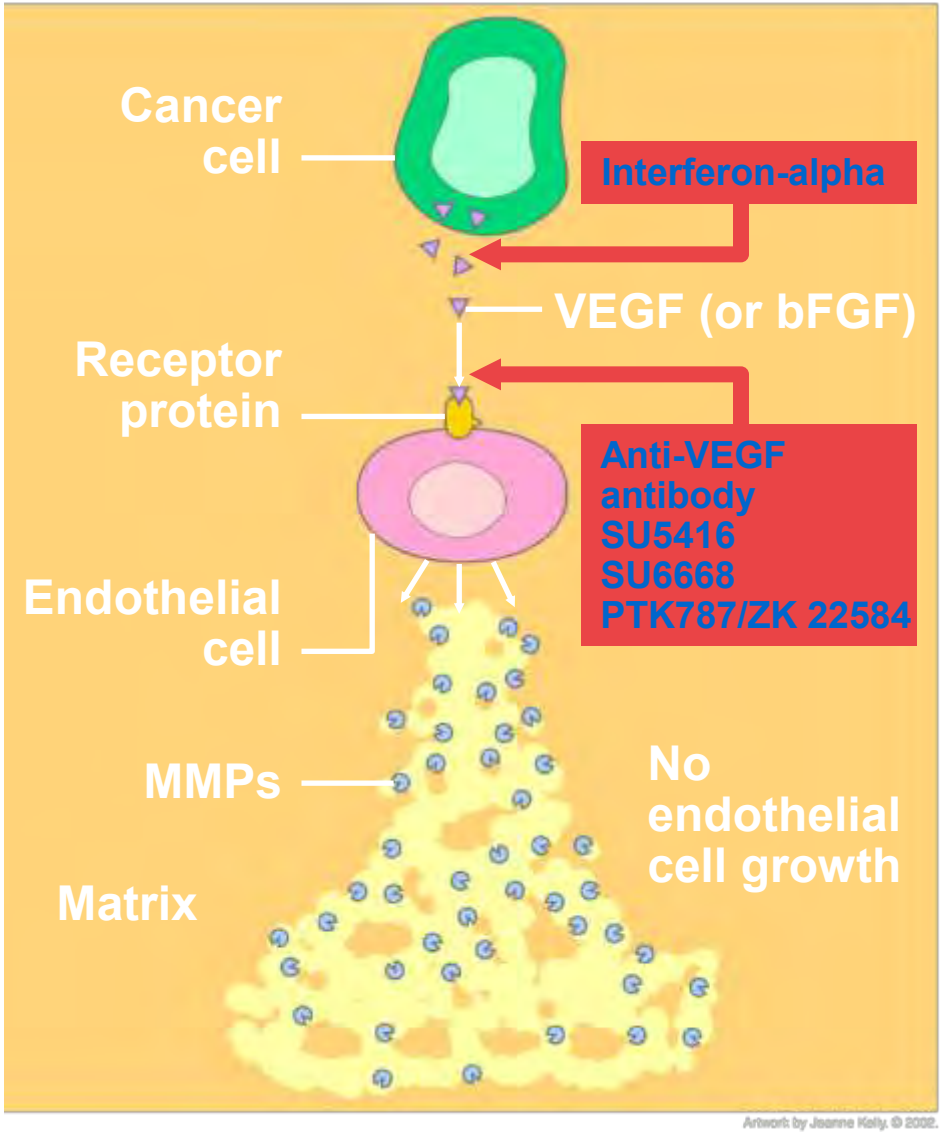
Chemokin gátlás a reumatológiában

Redundancia!

Target	Drug (Type of drug)	Type of study	Efficacy	Study outcome
CXCL10	MDX-1100 (antibody)	Phase II	Mildly effective	The ACR20 response at week 12 was 54% (MDX1100 and MTX) and 17% (placebo and MTX)
CCL2	ABN912 (antibody)	Phase Ib	Not effective	ABN912 did not result in any clinical improvement.
CCR1	CP-481,715 (small molecules)	Phase Ib	Mildly effective	CP-481,715 reduced tender and swollen joint count, and macrophages infiltration into the synovial tissue than those of placebo.
	CCX354-C (small molecules)	Phase II	Mildly effective	The ACR20 response at week 12 was 39% (placebo), 43% (CCX354-C; 100mg twice daily) and 52% (CCX354-C; 200 mg once daily)
	MLN3897 (small molecules)	Phase IIa	Not effective	The ACR20 response at week 12 was 35% (MLN3897) and 33% (placebo).
CCR2	MLN1202 (antibody)	Phase IIa	Not effective	Patients treated with CCR2 monoclonal antibody or placebo for 6 weeks. No clinical improvement
CCR5	SCH351125 (small molecules)	Phase Ib	Not effective	The ACR20 response at week 4 was 20% (SCH351125) and 33% (placebo).
	AZD5672 (small molecules)	Phase IIb	Not effective	The ACR20 response at week 12 was around 35% (AZD5672) and 38% (placebo).
	UK-427,857 (small molecules)	Phase IIa	Not effective	The ACR20 response at week 12 was 23.7% (UK-427,857) and 23.8% (placebo).
CX,CL1	E6011 (antibody)	Phase I/II	Effective? (no placebo)	~60% treated patients had at ACR20 response at week 12.

Miyabe et al, JMA Journal 2020

Angiogenezis gátlás



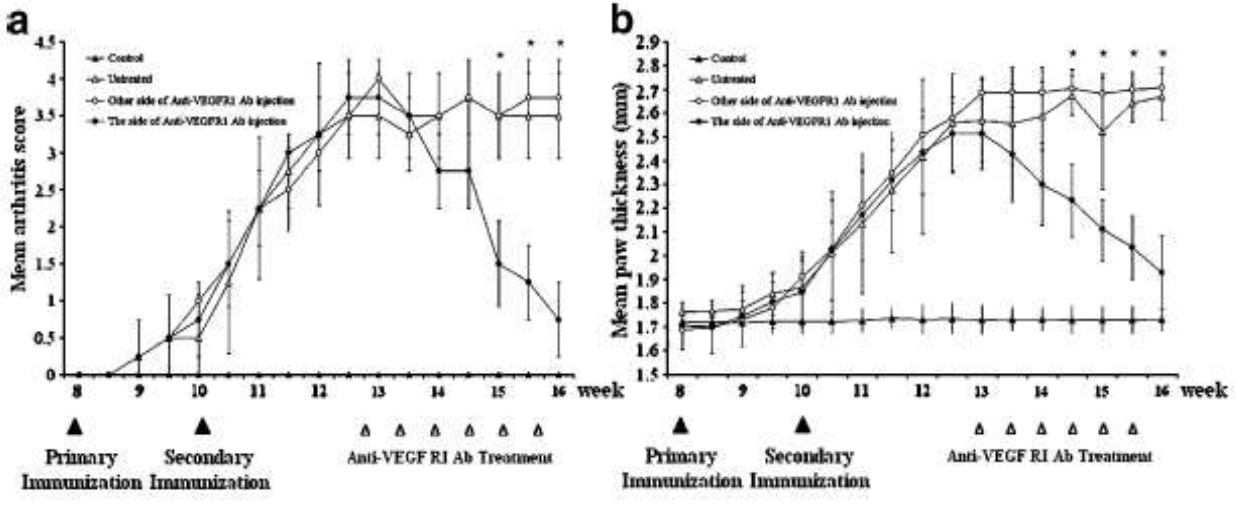
VEGF targeting – RA/OA

Table 3. Anti-VEGF and Antiangiogenic Treatments in Chondral Defect, Osteochondral Defect, Osteoarthritis, and Rheumatoid Arthritis Animal Models

Treatment	Model	Results	Ref.
VEGF inhibitor	OCD/CD	↑ Cartilage repair	(133)
	OA	↓ OA progression and pain	(52)
	RA	↓ Disease severity	(89,137–139,141–143)
VEGFR inhibitor	RA	↓ Disease severity	(90,138,144,145)
PPI-2458	OA	↓ OA progression and pain	(149)
	RA	↓ Disease severity	(150,151)
TNP-470	RA	↓ Disease severity	(152)
TSP-1	OCD/CD	↑ Cartilage repair	(157)
	OA	↓ OA progression	(158)
	RA	↓ Disease severity	(159,160)
Chm-1	OCD/CD	↑ Cartilage repair	(129)
Endostatin	RA	↓ Disease severity	(168–173,188)
Angiostatin	RA	↓ Disease severity	(178)
K1-5	RA	↓ Disease severity	(179)
ExTek	RA	↓ Disease severity	(180)
Suramin	OCD/CD	↑ Cartilage repair	(186)

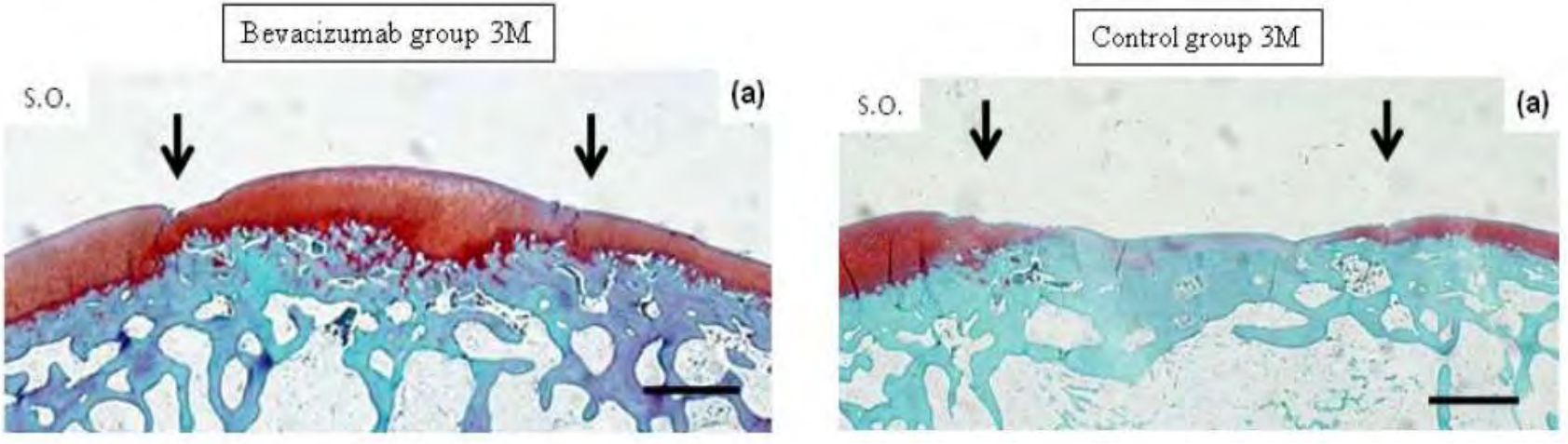
Hamilton et al, JBMR 2016

VEGF targeting – anti-VEGF-RI ab (CIA)

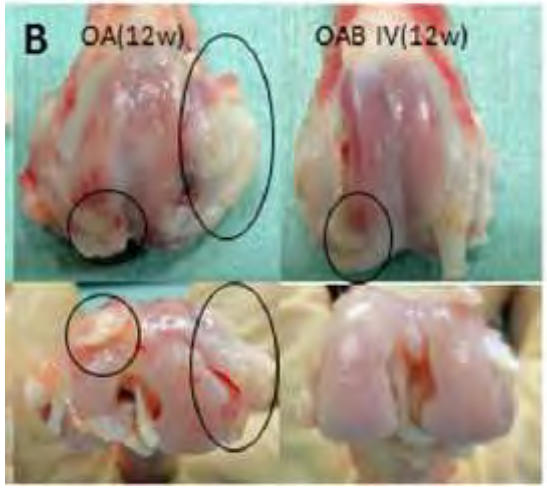


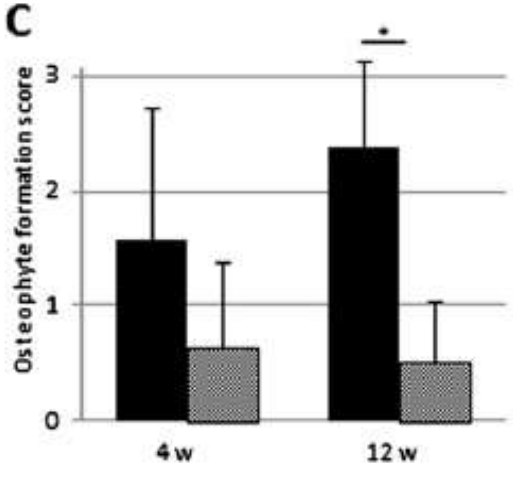
Choi et al, Clin Rheumatol 2009

VEGF targeting – iv bevacizumab – porcdefektusok/OA



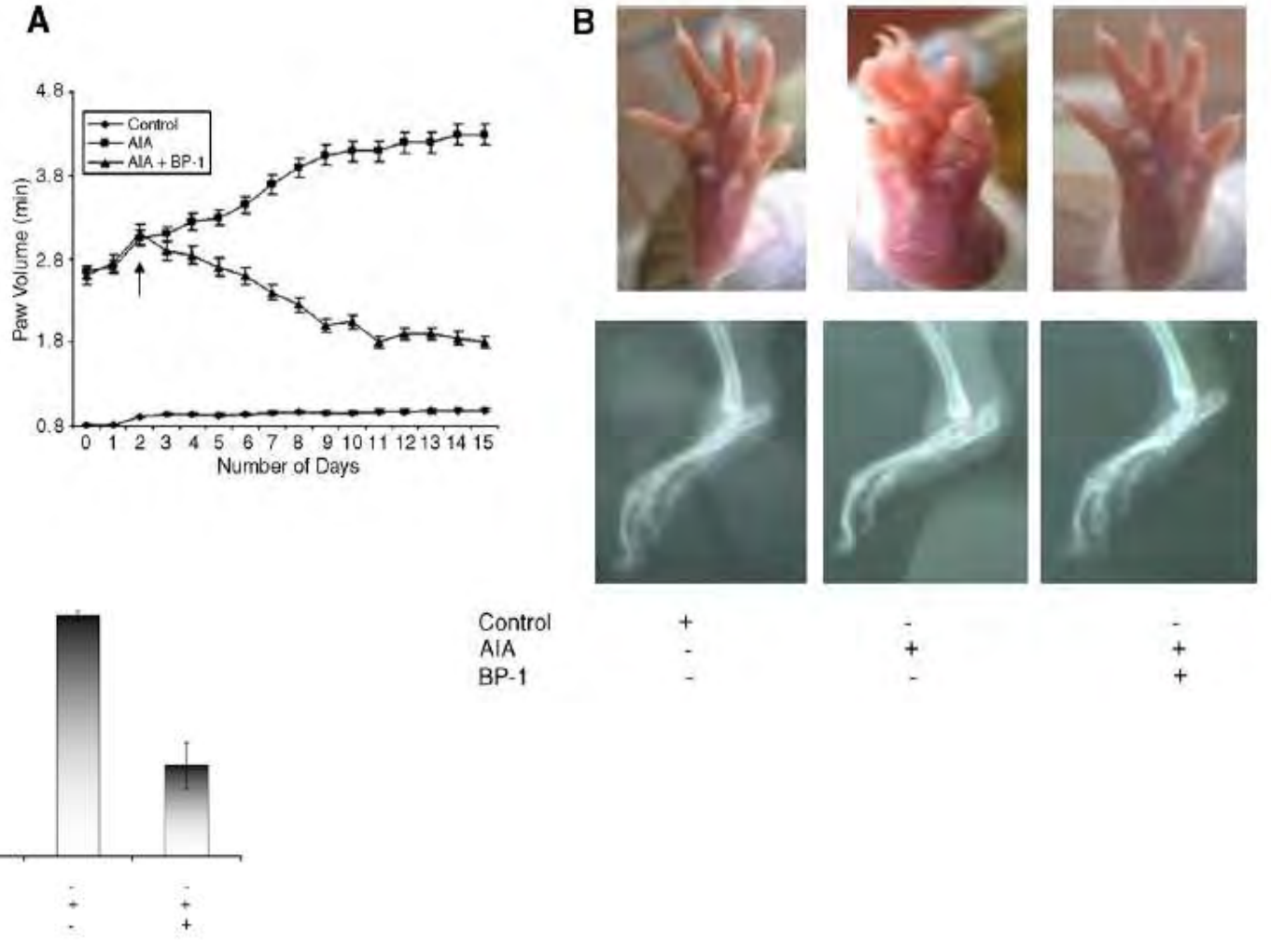
Safranin O festés





Nagai et al, ART 2010; 2014

HIF targeting (BP1) – arthritis modell



Shankar et al, Biophys Biochem Res Commun 2009

Angiogenesis gátlás

Table 1 | **FDA-approved compounds that target angiogenesis pathways**

Compound	Pathway	Indication	Reference
Sunitinib	Tyrosine kinase	Renal cell carcinoma, gastrointestinal stromal tumour	Furuya *et al.* (2014)[86]
Pazopanib	Tyrosine kinase	Renal cell carcinoma, soft tissue carcinoma	Bukowski *et al.* (2010)[66]
Bortezomib	NFκB	Multiple myeloma	Kwak *et al.* (2011)[68]
Tacrolimus	JNK, p38	Organ transplantation, eczema	Choe *et al.* (2011)[72]
Tofacitinib	JAK3	Rheumatoid arthritis	van Vollenhoven (2013)[113]
Dasatinib	Src kinase	Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Ozanne *et al.* (2014)[123]

Még 22 molekula klinikai és 7 preklinikai vizsgálatban

Tas et al. Nat Rev Rheumatol. 2016;12:111–22.

A terápiás kudarc magyarázatai

Redundancy of chemokines and chemokine receptors

- Multiple ligands can exist for one receptor, as well as multiple receptors for one chemokine, so blocking a specific chemokine or receptor might not be effective; however, the importance of redundancy has been challenged[71,86,108,109]

Cross-species target prediction

- A chemokine-receptor inhibitor can have different affinity for the rodent and human forms of the targeted receptor. For example, both CCR2 and CCR5 show considerable species-specific variation[98,102,104,105,108,110]

Structure modification

- Citrullination of chemokines can alter their receptor-binding characteristics, rendering blocking agents ineffective[33]

Cleavage of chemokines by proteases

- Enzymes such as matrix metalloproteinases can cleave chemokines, potentially altering receptor targeting[111,112]

Choice of dosage and timing

- Doses of agents and timing of delivery chosen for studies might not result in therapeutically optimal levels *in vivo*[81,108]

Undesired inhibition of anti-inflammatory cells

- In addition to the blockade of inflammatory cells, chemokine-pathway targeting can simultaneously affect anti-inflammatory cells, such as regulatory T cells[113,114]

Interference with homeostatic function

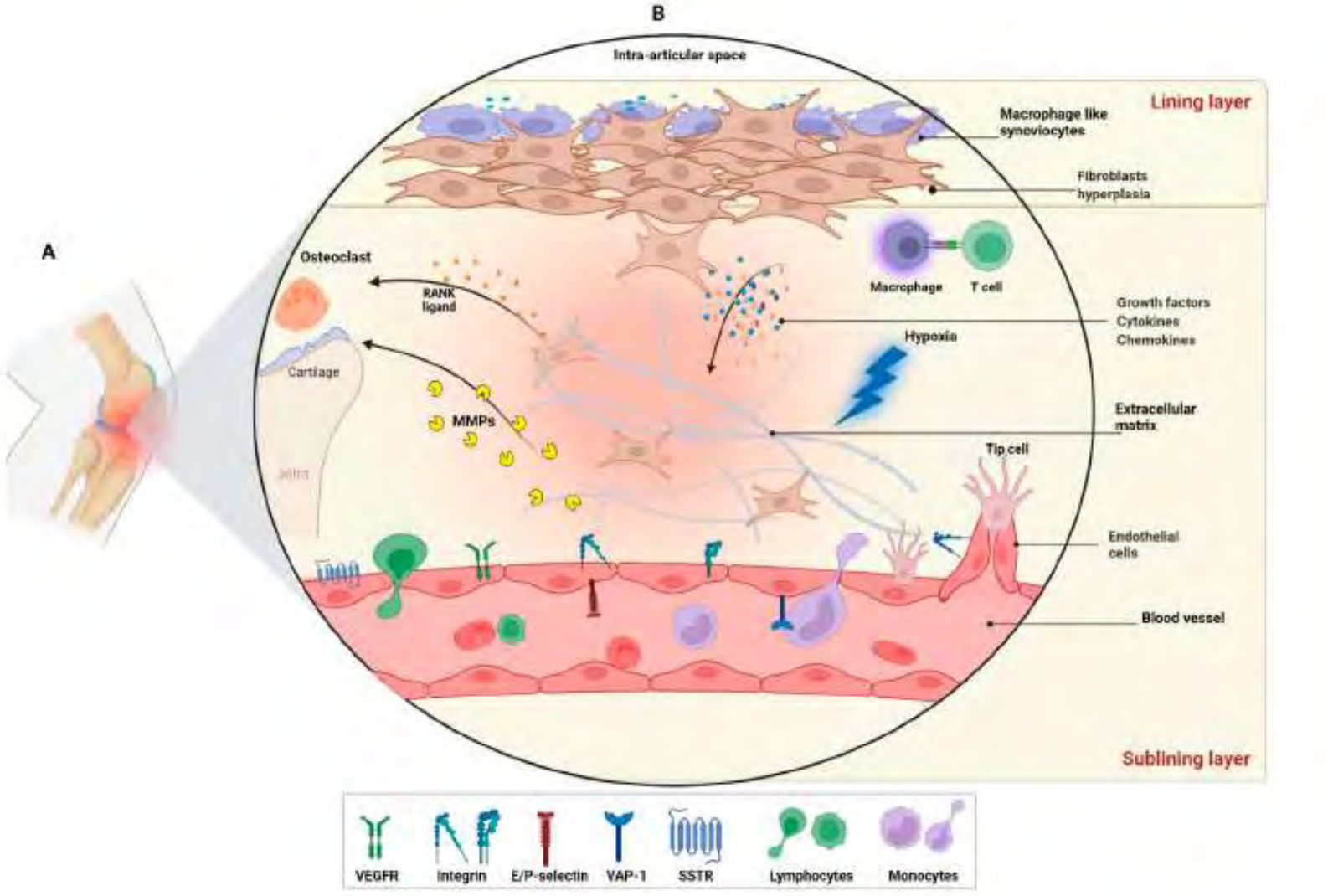
- In addition to inflammation, several chemokines (including CXCL12, CXCL13, CXCL16, CCL19 and CCL21) affect homeostatic functions, such as lymphoid development and physiological homing. Chemokine blockade might interfere with these physiological processes[1,2,15,115,116]

Insufficiency of receptor occupancy

- Continuous, high levels of receptor occupancy might be required throughout the period of treatment, to prevent chemokine signalling[96–98]

Szekanecz & Koch. Nat Rev Rheumatol. 2016;12:5–13.

Összefoglalás



Khodadust et al, Int J Mol Sci 2022