Hücresel ve antikor aracılı immün effektör yanıt

Family	Ligands	Examples
Antigen receptors found on T cells and B cells (T-cell receptor and B-cell receptor)	MHC class I or II loaded with peptide for T-cell receptors, soluble or surface antigens for B-cell receptor	TCR BCR
C-type lectin domain family	Glycans, Actin, MHC class I	Dectin-1, NKG2, BDCA2
CD300 family	Unknown	CD300A
Classical Fc receptor family	Fc region of antibody	FcγRI, FcγRII
Fc receptor-like family	Unknown	FCRL1
KIR family	MHC class 1	KIR2DL1, KIR3DL2, KIR2DS1
LILR family	MHC class 1	LILRB4
Natural cytotoxicity triggering receptor (NCR) family	Viral hemagglutinins, heparan sulfate proteoglycans, activation-induced C-type lectin	NKp44, NKp46, NKp30
Paired immunoglobulin-like receptor (PILR) family	PILR-associating neural protein (PANP), HSV-1 glycoprotein B	PILRA, PILRB
SIGLEC family	Endogenous and pathogen-derived sialylated glycans	SIGLEC1, SIGLEC8, SIGLEC7, SIGLEC2
CD28 family	B7 family of membrane proteins	CD28, CTLA-4, ICOS, BTLA
CD200R family	CD200	CD200R1, CD5, CD6
Signal-regulatory protein (SIRP) family	CD47, surfactant proteins e.g. SPA1	SIRPα
Signaling lymphocytic activation molecule (SLAM) family	Homophilic (bind SLAM family members), CD48	SLAMF1, SLAMF3
Collagen receptors	Collagen	LAIR1 OSCAR GPVI

Non-catalytic tyrosine-phosphorylated receptors (NTRs)
https://en.wikipedia.org/wiki/Non-catalytic_tyrosine-phosphorylated_receptor
immunoreceptors or Src-family kinase-dependent receptors
https://en.wikipedia.org/wiki/Immunoreceptor_tyrosine-based_activation_motif

Immunoreceptor tyrosine-based activation motifs (ITAMs)
Yxx(L/I)x6-8Yxx(L/I) ITAMs recruits activating kinases to the NTR

Immunoreceptor tyrosine-based inhibitory motifs (ITIMs)
(S/I/V/L)xYxx(I/V/L) bind to cytoplasmic tyrosine phosphatases

Immunoreceptor Tyrosine-based Switch Motifs (ITSMs)
TxYxx(I/V) may induce both activator and inhibitory signals
SLAM family receptors

Immunoglobulin Tail Tyrosine Motifs (ITTMs)
YxNM signature - costimulatory effect

(1) kinetic segregation,
(2) kinetic proofreading
(3) receptor scanning
(4) serial triggering

van der Merwe PA, Dushek O. Mechanisms for T cell receptor triggering. Nat Rev Immunol. 2011 Jan;11(1):47-55. doi: 10.1038/nri2887. Epub 2010 Dec 3. PMID: 21127503.

sensitivity

TCRs are 'restricted' to
a subset of MHC molecules
on an APC
--> only a single
peptide-MHC ligand
trigger...

discrimination

noise signal

self peptide-MHC >>> foreign agonist peptide-MHC

10

number of occupied TCRs

$$C = \frac{A}{2}\left[P_T + T_T + K_d - \sqrt{(P_T + T_T + K_d)^2 - 4P_T T_T}\right]$$

C: # engaged TCR complexes
A: contact interface area
P_T: peptide complex concentration
T_T: TCR complex concentration

noise signal

half-life of 1second (k_{off}=0.69s^{-1}) — half-life of 5seconds (k_{off}=0.14s^{-1})

k_{on}= 0.001$\mu m^2/s$

C = 1.2 μm^{-2} — C = 0.42 μm^{-2}

S/N = 0.33

serial-triggering model

$$Rate_{bindingEvents} = k_{off}\, C$$

noise signal

R_{be} = 68 s^{-1} — R_{be} = 4.2 s-1

S/N = 0.07

kinetic proof-reading model

$$Rate_{productiveBindingEvents} = k_{off}\, C \exp(-k_{off}\, \tau).$$

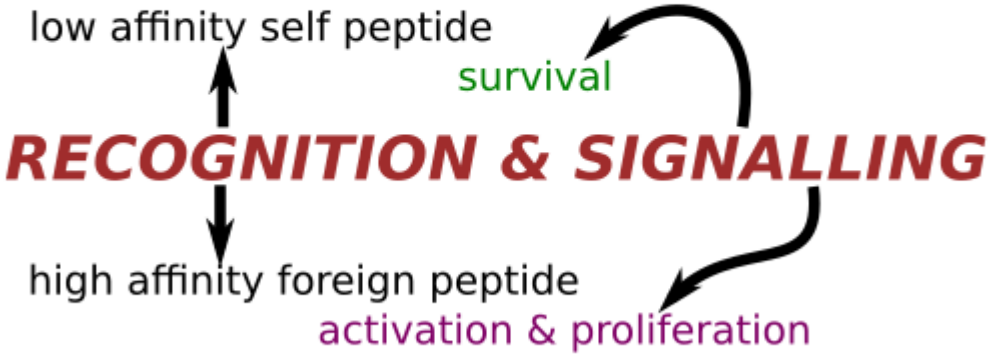
noise τ = 5s **signal**

R_{pbe} = 2.1 s^{-1} — R_{pbe} = 2.2 s^{-1}

S/N = 1.1

antigen must remain bound long enough to allow sufficient CD3 phosphorylation

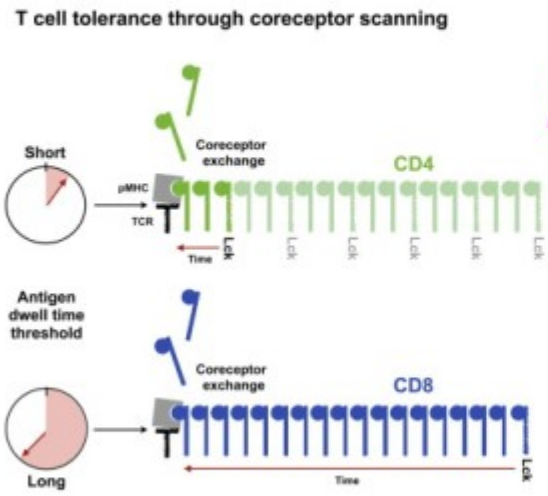
versatility



structural diversity

TCRs trained with self ligands...

...need to recognize foreign peptide

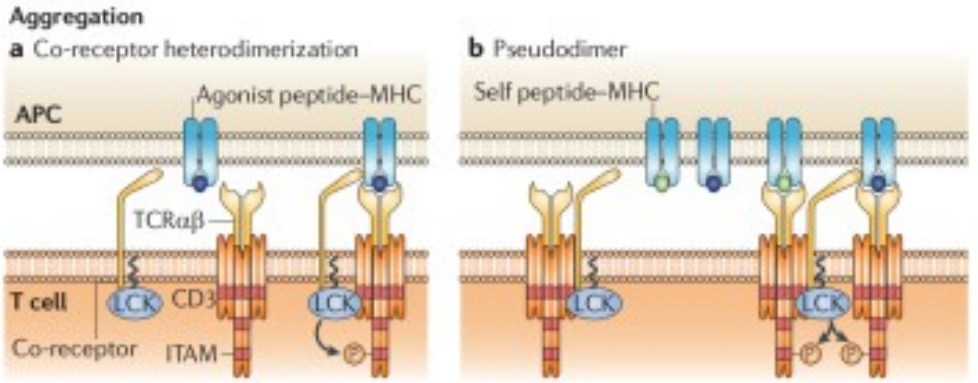


receptor scanning

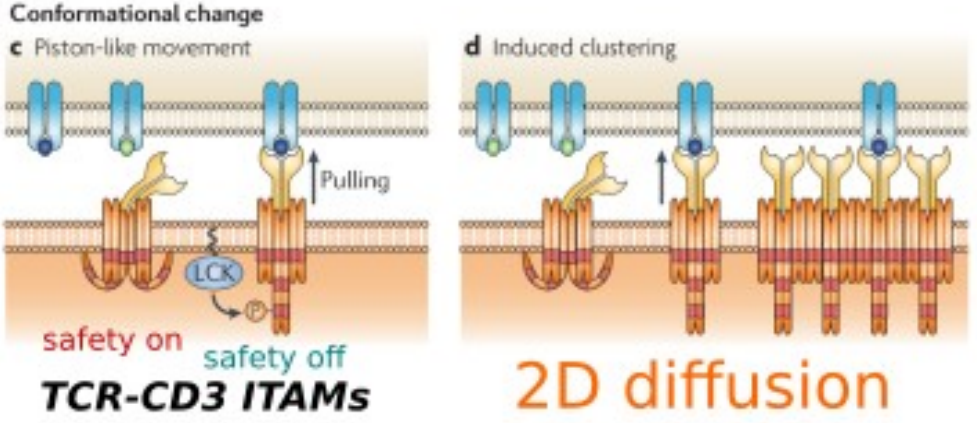
pMHC - TCR scans coreceptor molecules (CD4 or CD8) until it finds one coupled to LCK

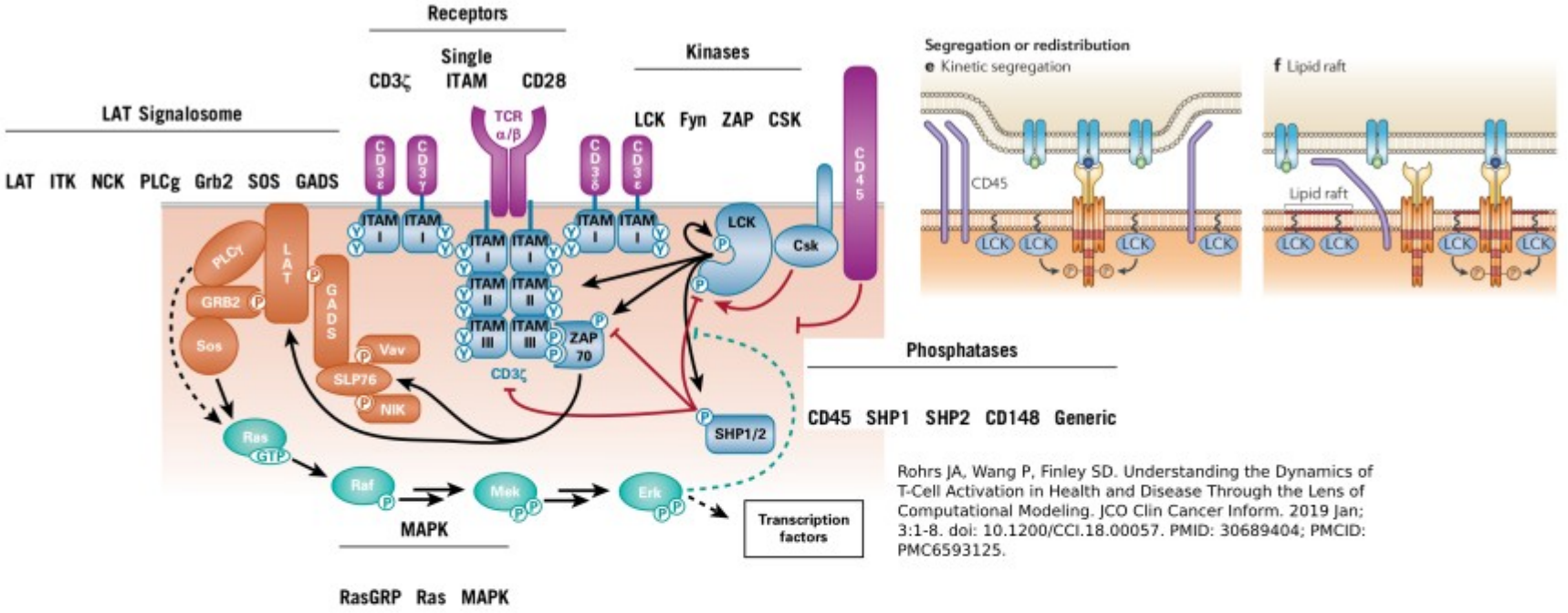
Stepanek O, Prabhakar AS, Osswald C, King CG, Bulek A, Naeher D, Beaufils-Hugot M, Abanto ML, Galati V, Hausmann B, Lang R, Cole DK, Huseby ES, Sewell AK, Chakraborty AK, Palmer E. Coreceptor scanning by the T cell receptor provides a mechanism for T cell tolerance. Cell. 2014 Oct 9;159(2):333-45. doi: 10.1016/j.cell.2014.08.042. Epub 2014 Oct 2. PMID: 25284152; PMCID: PMC4304671.

van der Merwe PA, Dushek O. Mechanisms for T cell receptor triggering. Nat Rev Immunol. 2011 Jan;11(1):47-55. doi: 10.1038/nri2887. Epub 2010 Dec 3. PMID: 21127503.

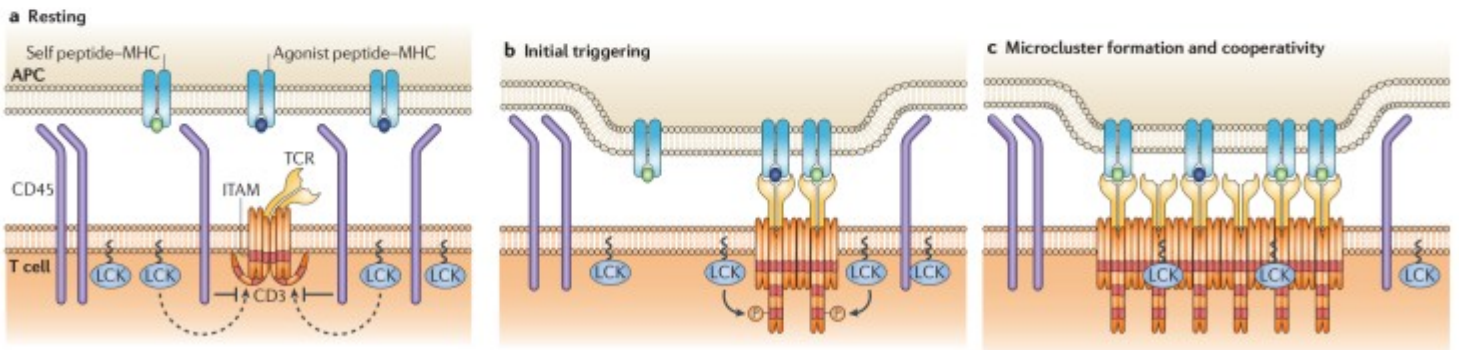


engagement --> 10-100 TCR microclusters form
MHC-self-peptide + MHC-agonist-peptide --> ?enhance clustering already agregated islands of TCRs?

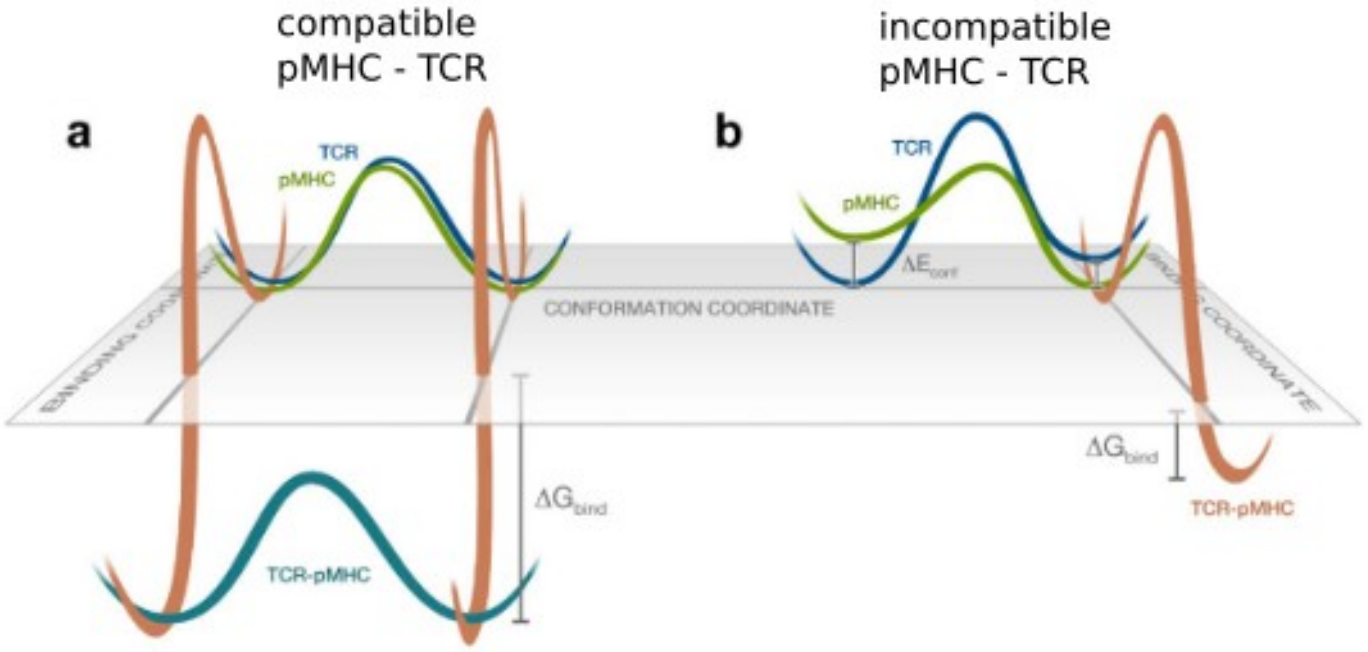




Rohrs JA, Wang P, Finley SD. Understanding the Dynamics of T-Cell Activation in Health and Disease Through the Lens of Computational Modeling. JCO Clin Cancer Inform. 2019 Jan; 3:1-8. doi: 10.1200/CCI.18.00057. PMID: 30689404; PMCID: PMC6593125.

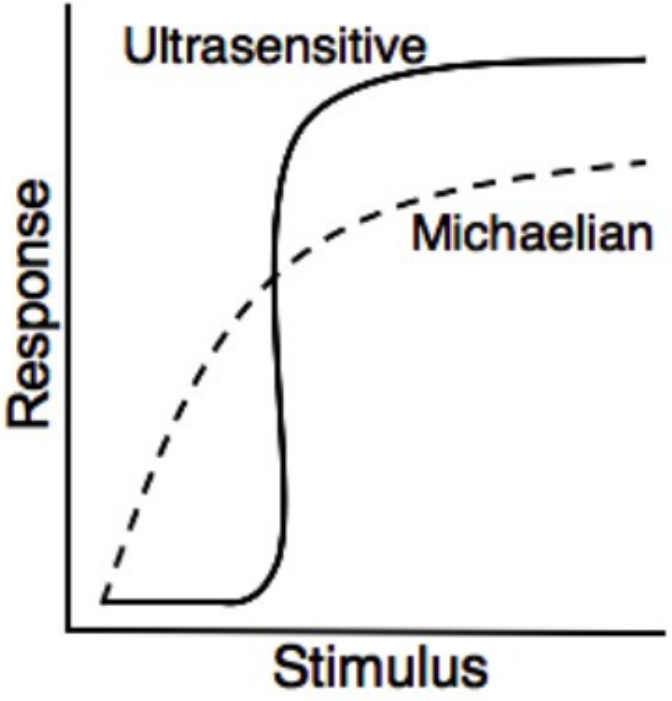


van der Merwe PA, Dushek O. Mechanisms for T cell receptor triggering. Nat Rev Immunol. 2011 Jan;11(1):47-55. doi: 10.1038/nri2887. Epub 2010 Dec 3. PMID: 21127503.



Hawse WF, De S, Greenwood AI, Nicholson LK, Zajicek J, Kovrigin EL, Kranz DM, Garcia KC, Baker BM. TCR scanning of peptide/MHC through complementary matching of receptor and ligand molecular flexibility. J Immunol. 2014 Mar 15; 192(6):2885-91. doi: 10.4049/jimmunol.1302953. Epub 2014 Feb 12. PMID: 24523505; PMCID: PMC3992338.

ultrasensitivity



https://en.wikipedia.org/wiki/Ultrasensitivity

Multistep mechanisms (examples: cooperativity)[12] and multisite phosphorylation[13]

Buffering mechanisms (examples: decoy phosphorylation sites)[14] or stoichiometric inhibitors[15]

Changes in localisation (such as translocation across the nuclear envelope)

Saturation mechanisms (also known as zero-order ultrasensitivity)[16]
Positive feedback[17]

Allovalency

Non-Zero-Order Ultrasensitivity in Membrane Proteins

Dissipative Allostery

serial triggering

Corzo J. Time, the forgotten dimension of ligand binding teaching. Biochem Mol Biol Educ. 2006 Nov;34(6):413-6. doi: 10.1002/bmb.2006.494034062678. PMID: 21638733.

$$P + L \underset{K_{off}}{\overset{K_{on}}{\rightleftharpoons}} P{\cdot}L$$

K_{on}: the second-order rate constant of the binding reaction ($M^{-1}s^{-1}$)

K_{off}: the first-order rate constant for the dissociation of the protein-ligand complex (s^{-1})

$K_d = K_{off} / K_{on}$

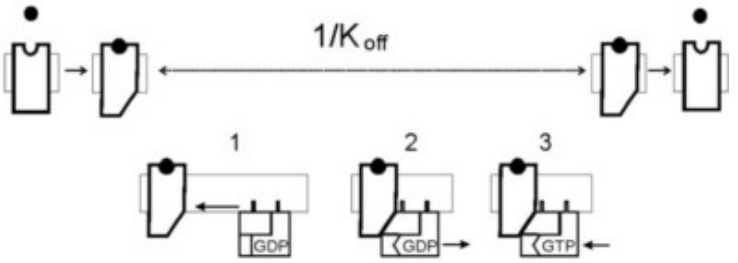
K_d: the equilibrium constant for the dissociation equilibrium (M)

$MeanLife_{complex} = 1 / K_{off}$

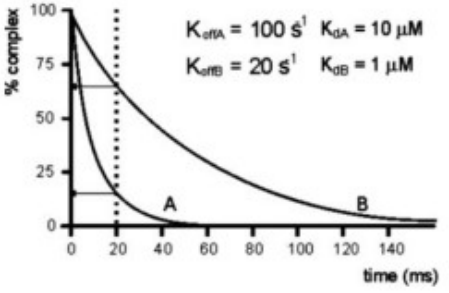
$HalfLife_{complex} = 2 / K_{off}$

Calculated mean lifetimes (in seconds otherwise indicated) of protein ligand complexes for different K_d and K_{on} values

K_d M	K_{on}		
	1.10^4	1.10^6	1.10^8
		$M^{-1}s^{-1}$	
1.10^{-3}	0.1	0.001	1.10^{-5}
1.10^{-4}	1.0	0.01	1.10^{-4}
1.10^{-5}	100	0.1	0.001
1.10^{-6}	1000	1.0	0.01
1.10^{-7}	16.7 min	10	0.1
1.10^{-8}	166.7 min	100	1.0
1.10^{-9}	1.2 days	16.7 min	10
1.10^{-10}	11.6 days	166.7 min	100



P + L ⇄ PL → effect



T hücresinin aktive olması için '*eşik sayıda*' TCR'ın aktive olması gerek...