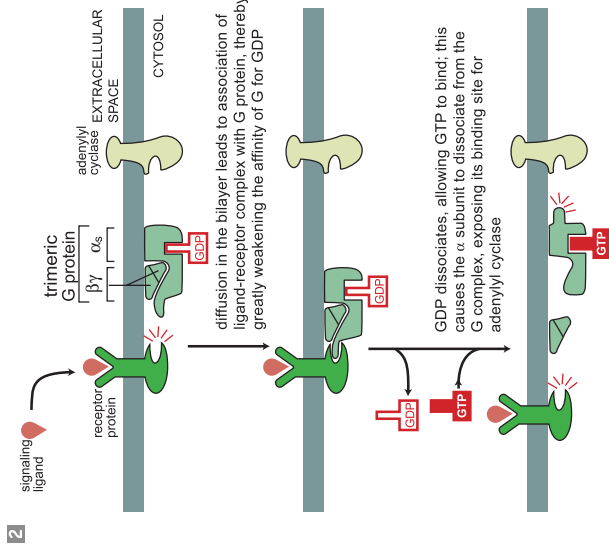
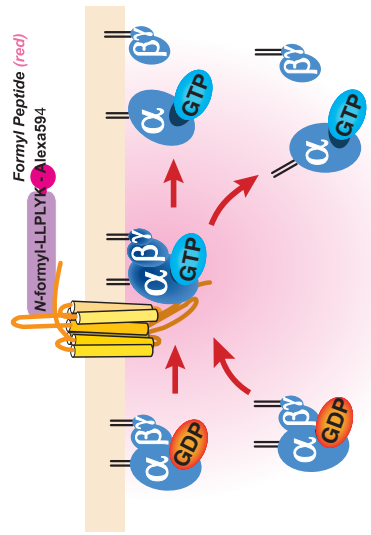


Lueke, H. et al., Structural changes in bacteriorhodopsin during ion transport at 2 Å resolution. *Science* 286:255 (1999)

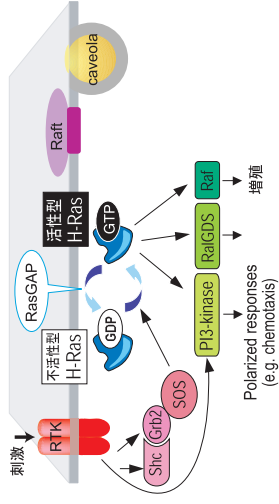


Modified from *Molecular Biology of the Cell* (3rd ed.), p. 739

3 Binding of Gα_{i2} to Liganded Receptor

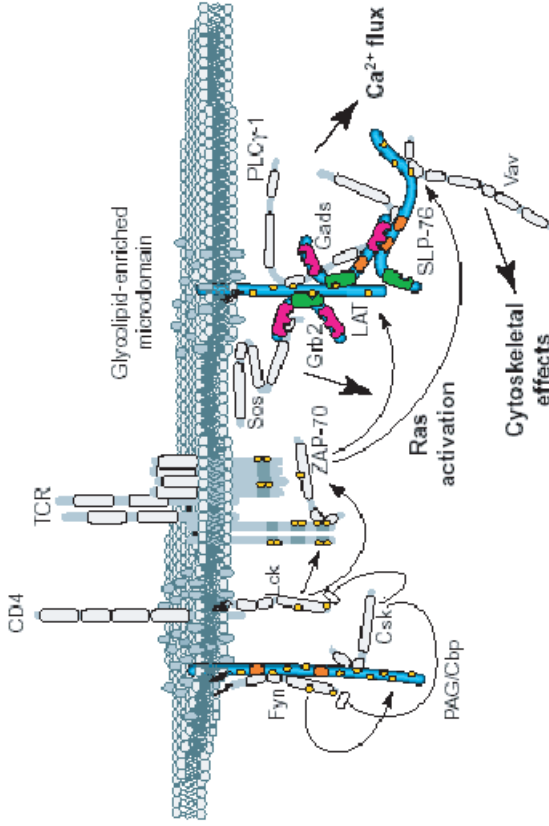


4 Rasの活性化/RTK下流のアダプターラフト/カベオラ



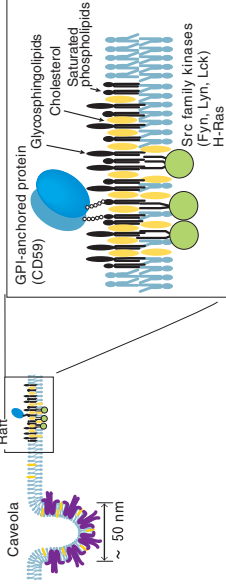
生化学アッセイで2倍の活性があったとして、すべての分子の活性が2倍になったのか、1%の分子の活性が100倍になったのか、しかも、例えば細胞の先端だけにその1%の分子が集まっているかもしれない

5 *1

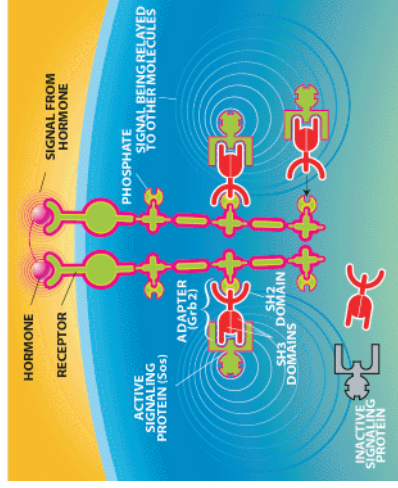


Immunology Today

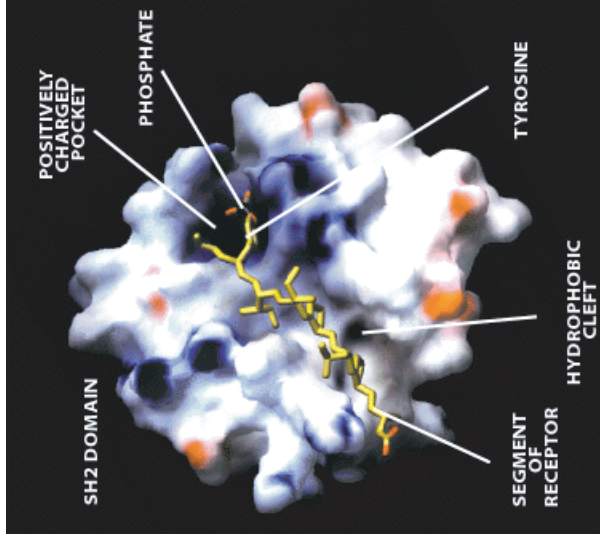
Fig. 3. A model for the role of adapters in T-cell receptor signaling. Recognition of MHC/peptide complexes by the TCR is thought to induce receptor clustering (not shown) and activation of the PTKs Lck, Fyn and ZAP-70. Their substrates include the adapters (shown in an identical color scheme to Figs 1 and 2) LAT, SLP-76 and PAG/Cbp, which upon phosphorylation can recruit other SH2 domain-containing proteins into signaling complexes. LAT and SLP-76 are thought to play a central role in coupling PTK activation to downstream responses. Phosphorylated LAT recruits PLC- γ 1 and Grb2/Sos complexes to the plasma membrane, which results in calcium mobilization and Ras/MAPK activation. SLP-76 is indirectly linked to LAT via the adapter protein Gads. Phosphorylated SLP-76 can bind Vav, a GEF for Rac GTPases, which may effect cytoskeletal reorganization. The recently identified adapter PAG/Cbp may downregulate TCR signaling by recruiting the PTK Csk, a negative regulator of Lck and Fyn. Since Lck, Fyn, LAT and PAG/Cbp are palmitoylated, many of the above described signaling complexes may form in the GEMs.



7 *2



Adapter molecules, which consist entirely of linker modules such as SH2 and SH3, turn out to be important players in many signaling pathways. They enable cells to make use of proteins that would otherwise be unable to hook into a given communication circuit. Here, for instance, the adapter protein Grb2 (red) draws an enzymatic protein—Sos—into a pathway headed by a receptor that itself has no means of interlocking with Sos.



SH2 DOMAIN (globular structure) in a signaling molecule is bound to a segment of a receptor (stick model). The two fit together in part because a positively charged pocket in SH2 is attracted to a negatively charged phosphate that has been added to the amino acid tyrosine in the receptor. Also, the nearby amino acids in the receptor fit snugly into a hydrophobic (water-hating) groove on SH2. All SH2 domains can bind to phosphate-bearing tyrosines, but they differ in their binding partners because they vary in their ability to lock onto the amino acids that lie next to tyrosine in a protein.

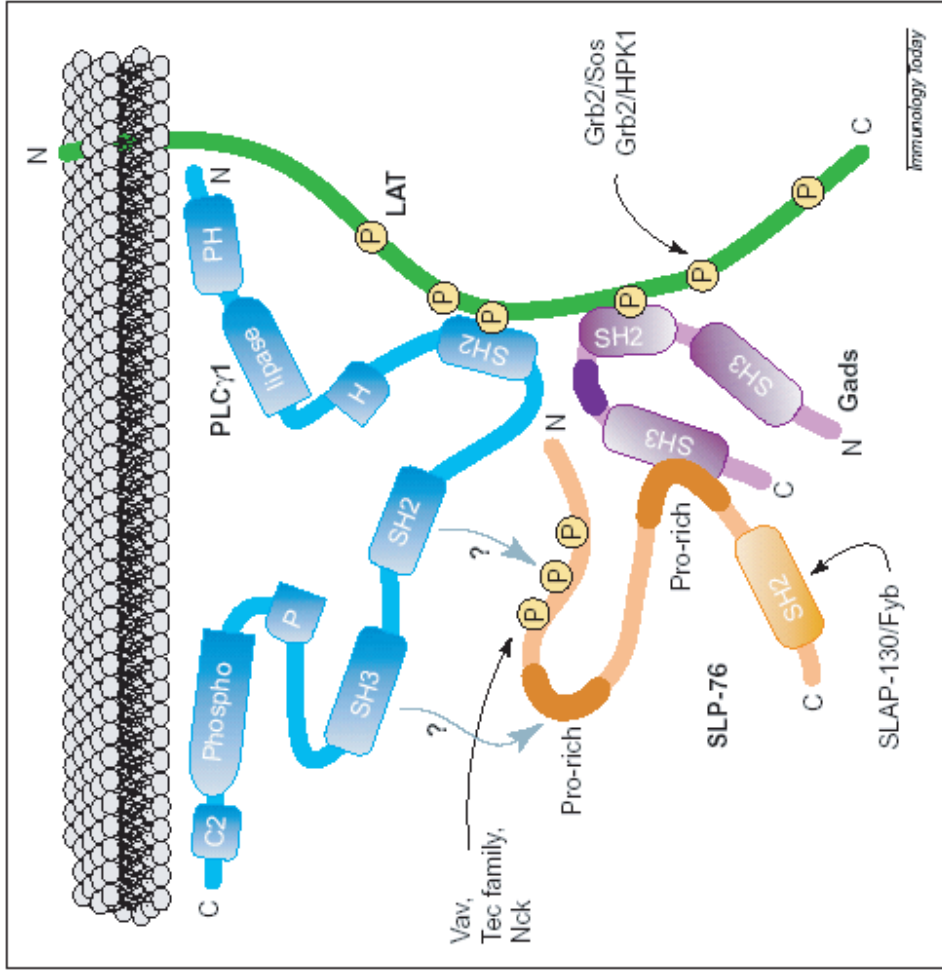


Fig. 4. A model of the LAT/SLP-76 signalingosome. The LAT/SLP-76 complex may be an example of a quantal unit of signal transduction, or a signalingosome. We propose that LAT, Gads, SLP-76 and PLC-gamma1 achieve a relatively stable and specific complex through the avidity effects and spatial constraints imposed by multi-domain interactions. Each domain/motif interaction has been demonstrated biochemically with the exception of the SLP-76/PLC-gamma1 interaction, which is hypothetical. The LAT/SLP-76 signalingosome has the potential to recruit Grb2/Sos and Grb2/HPK1 complexes, Itk, Vav, Nck and SLAP-130/Fyb, thus effecting calcium mobilization, Ras activation and cytoskeletal changes.

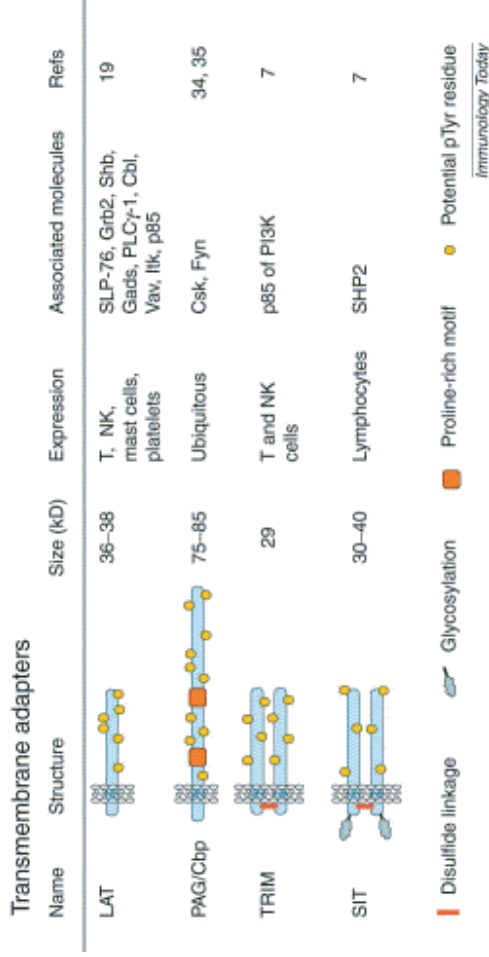


Fig. 2. Transmembrane adapter proteins with a potential role in antigen receptor signaling. The domain structure of each adapter is shown in diagrammatic form, followed by size (kD) on SDS PAGE under reducing conditions, expression pattern, associated molecules and key references. Abbreviations: Cbl, Casitas B lineage lymphoma protein; Csk, c-src tyrosine kinase; Fyn, proto-oncogene tyrosine-protein kinase Fyn; Gads, Grb2-related adapter downstream of Shc; Grb2, growth factor receptor-bound protein 2; Itk, interleukin-2-inducible T-cell kinase; LAT, linker for activated T cells; PAG/Cbp, phosphoprotein associated with GEMs/Csk-binding protein; PLC, phospholipase C; p85, regulatory subunit of phosphatidylinositol 3-kinase; Shb, Src homology 2 domain-containing transforming protein B; SHP2, SH2 domain-containing tyrosine phosphatase 2; SIT, SHP2-interacting transmembrane adapter protein; SLP-76, SH2 domain-containing leukocyte protein of 76 kD; TRIM, TCR-interacting molecule; Vav, Vav oncogene.

Cytoplasmic adapters

Name	Structure	Size (kD)	Expression	Associated molecules	Refs
Bam32		32	B cells	PLCγ-2	53
BLNK		65	B cells and macrophages	PLCγ-2, Btk, Nck, Vav, Grb2	5, 27
BRDG1		37	B cells and myeloid cells	Tec	54
Cbl family		120	Ubiquitous	Grb2, p85, Crk, SLAP, Syk, ZAP-70, BLNK	42
CLNK		54	T, NK, and mast cells	p92	5
Crk family		28, 40, 42	Ubiquitous	Cbl, C3G, Paxillin, Cas	55
Dok family		56, 62	Leukocytes	SHIP, RasGAP, LAT, SLP-76, Sap	36, 39
GAB family		97, 115	Ubiquitous	SHP2, Grb2, CrkL, p85	56
Gads		40	T, NK, macrophages, mast cells, platelets	LAT, SLP-76, Shc, HPK1	6
Grap		28	Lymphocytes	LAT, Shc, Sos, Sam68	6
Grb2		28	Ubiquitous	Cbl, LAT, Sos, HPK1, SLP-76, Shc, SHP2	6
Lnk		75	Lymphocytes	Lck, CD3ζ	57
Nck		47	Ubiquitous	PAK, SLP-76, Sos, Cbl, WASP, IRS-1, NIK	58
RIBP		45	T and NK cells	Txk, Itk, Lck	59
Sap		15	T and NK cells	2B4, SLAM, Dok	5
Shb		55, 66	Ubiquitous	LAT, p85, Src, Eps8, Grb2, CD3ζ, PLCγ-1	5
Shc		46, 52, 66	Ubiquitous	SHIP, Grb2, RasGAP, ZAP-70, CD3ζ, Igα/β	60
SKAP55		55	T cells	SLAP-130, Fyn	6
SLAP		34	Lymphocytes	ZAP-70, SLP-76, Cbl, Vav, CD3ζ	49
SLAP-130/ Fyb		130	T and myeloid cells	Fyn, SKAP55, SLP-76	6
SLP-76		76	T, NK, macrophages, mast cells, platelets	Gads, Vav, Itk, LAT, SLAP-130, Nck, Grb2	5, 27
SOCS family		N-terminus has variable length	Leukocytes	Tec, JAKs, STATs, Elongins B and C	61
3BP2		80	Lymphocytes	LAT, Cbl, ZAP-70, Grb2, PLCγ-1, Syk	62



12 *3

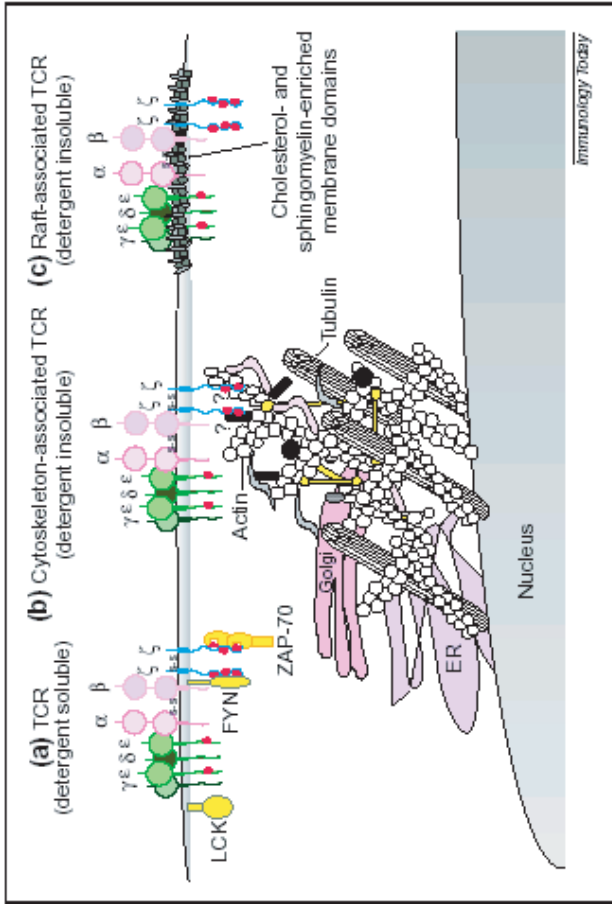
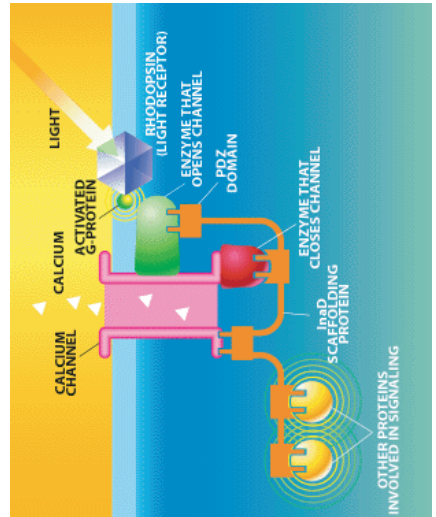
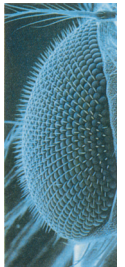


Fig. 1. Schematic representation (not to scale) illustrating the putative TCR populations expressed on the T-cell surface. Red circles indicate the TCR α and β chain immunoreceptor tyrosine-based activation motifs (ITAMs) that are known to undergo phosphorylation in vivo upon TCR stimulation. (a) The detergent-soluble TCR, which is neither associated with the cytoskeleton, nor localized to Raft membrane microdomains. The key protein tyrosine kinases (PTKs) involved in early TCR activation (of which FYN and ZAP-70 bind to the detergent-soluble zchain) are shown in yellow. (b) The cytoskeleton-associated TCR, which is linked either directly or indirectly to actin microfilaments via cytoskeleton-associated z(CSKA-z). Question marks denote putative linker proteins that might serve to bridge z to the cytoskeleton. (c) The recently described raft-associated TCR localizes to membrane microdomains that are enriched in cholesterol and sphingomyelin. Throughout the figure, s-s indicates disulfide bonding. Abbreviations: ER, endoplasmic reticulum; TCR, T-cell receptor.

13 *2



Scaffolding proteins, which hold onto several other proteins, can ensure that multiple signaling molecules act almost simultaneously. One, InaD (diagram), operates in cells of the fruit-fly eye—a compound structure containing many smaller eyes (photograph)—and participates in sending visual messages to the brain. Three of the scaffold's five "PDZ" linker domains separately grasp an ion channel, an enzyme that opens the channel when light hits a nearby light receptor (rhodopsin) and an enzyme that closes the channel promptly thereafter. Two more PDZ domains help to relay information by holding other signaling molecules in place.



14

Bacteria, Plants
Seven activities in seven separate polypeptides



Vertebrates
Seven activities in one large polypeptide

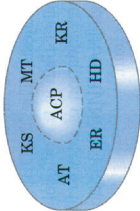
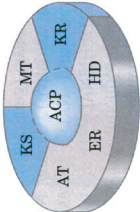


figure 21-7

Structure of fatty acid synthase. The fatty acid synthase from bacteria and plants is a complex of at least seven different polypeptides. In yeast, all seven activities reside in only two polypeptides, and in vertebrates, in a single large polypeptide.

Yeast

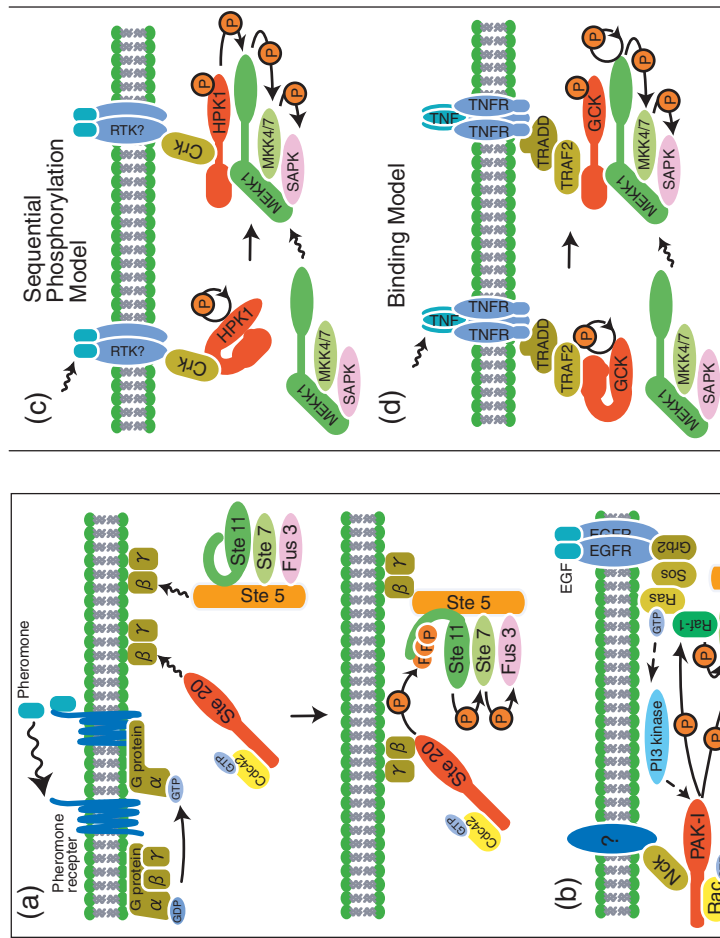
Seven activities in two separate polypeptides



Lehninger

Principles of Biochemistry 3rd. edition, p.777

15



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*2 J. D. Scott and T. Pawson (2000)

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Scientific American, June, p.72-79

*3 S. Caplan and M. Baniyash (2001)

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