COMManDing lymphocyte migration

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Summary of research

Lymphocyte migration is mediated by G protein-coupled receptors (GPCRs) that respond to chemoattractive molecules, represented by chemokines. Agonist binding to GPCRs activates heteromeric G proteins to regulate the generation of second messengers that modulate downstream signaling. Agonist-occupied GPCRs are phosphorylated by GPCR kinases (GRKs) and subsequently recruit β-arrestins that serve as scaffolds to activate signaling molecules, including mitogen-activated protein kinases (MAPKs). The GRK family consists of seven mammalian members, among which GRK2, GRK3, GRK5, and GRK6 are expressed ubiquitously. Different GRKs phosphorylate distinct sites on the C-terminal tail of the receptor, establishing a barcode that dictates the functional consequences of β-arrestin engagement. Thus, specific targeting of GRKs to activated GPCRs is crucial for signal transduction. However, the molecular mechanism that determines the specificity of GRK targeting is poorly understood. In a new study published in *The Journal of Experimental Medicine*, a research team led by Kazuhiro Suzuki (Professor, Immunology Frontier Research Center, Osaka University) identified a protein complex consisting of copper metabolism MURR1 domain-containing (COMMD) 3 and COMMD8 (COMMD3/8 complex) as an adaptor that selectively recruits a specific GRK to chemoattractant receptors and promotes lymphocyte migration.

In search of factors involved in GRK recruitment to chemoattractant receptors, the researchers identified COMMD8 as a protein that binds to the C-terminal tail of a chemokine receptor CXCR4. Additional screening revealed the interaction of COMMD8 with COMMD3. These proteins constitutively formed a complex in the cytosol, but were translocated to the plasma membrane after stimulation of CXCR4. The COMMD3/8 complex also interacted with other G protein-coupled chemoattractant receptors, including CXCR5, CCR7, and the oxysterol receptor EBI2, after activation of the receptors. Interestingly, COMMD3 and COMMD8 were degraded by the proteasome in the absence of the other, and deficiency of either protein produced the same phenotypes, indicating that both COMMD3 and COMMD8 are required for the stability and function of their complex. Deficiency

of COMMD3 or COMMD8 in B cells reduced their chemotactic responses through the receptors to which the COMMD3/8 complex was recruited. Thus, the COMMD3/8 complex is a positive regulator of chemoattractant receptor signaling.

Mechanistic analysis for the action of the COMMD3/8 complex demonstrated that this protein complex functions as an adaptor that selectively recruits GRK6 to chemoattractant receptors in a GRK2/3-dependent manner, which promotes MAPK activation and consequently lymphocyte migration (Fig. 1). It has been suggested that the specificity of GRK recruitment to GPCRs is determined by the relative expression levels of individual GRKs, which vary among cell type, and distinct receptor conformations induced by ligand binding. This new study has identified a GRK-recruiting adaptor, the COMMD3/8 complex, as an additional determinant of GRK specificity for GPCRs.

Consistent with the reduced chemotactic responses of COMMD3- and COMMD8-deficient B cells, the mutant B cells showed multiple defects in their migration in vivo (Fig. 2A). Additionally, deficiency of COMMD3 or COMMD8 in B cells severely impaired humoral immune responses (Fig. 2, B and C). Therefore, the COMMD3/8 complex is essential for proper functioning of the immune system. By exploiting the unique property of the COMMD3/8 complex, it would be possible to degrade and disable the protein complex by pharmacological disruption of the interaction between COMMD3 and COMMD8. Development of such drugs would provide a novel approach for immune regulation, which may be applicable to the treatment of immune disorders.

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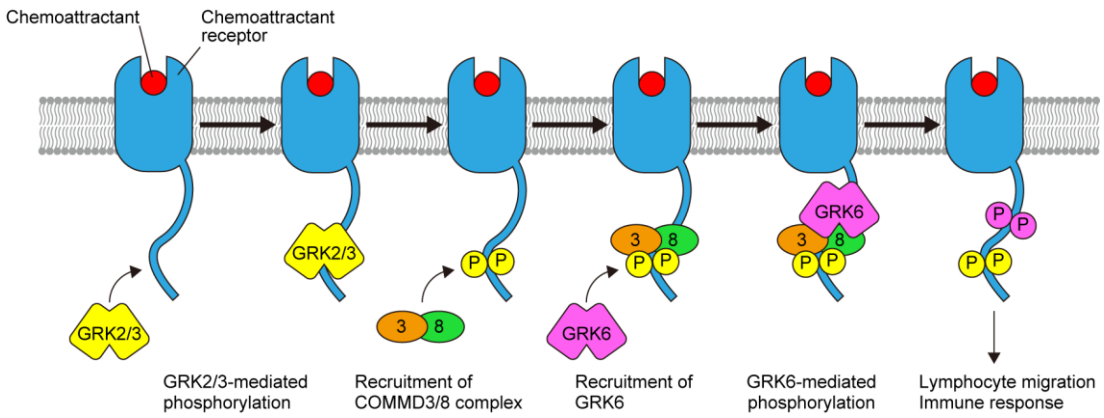

Figure 1. Proposed role of the COMMD3/8 complex in chemoattractant receptor signaling.

The COMMD3/8 complex recruits GRK6 to chemoattractant receptors through a stepwise mechanism: (i) the C-terminal tail of the activated receptor is phosphorylated by GRK2 and GRK3. (ii) the COMMD3/8 complex is associated with the receptor tail through electrostatic interactions with the phosphorylated residues. (iii) GRK6 is recruited to the receptor through the interaction with the COMMD3/8 complex and phosphorylates the C-terminal tail.

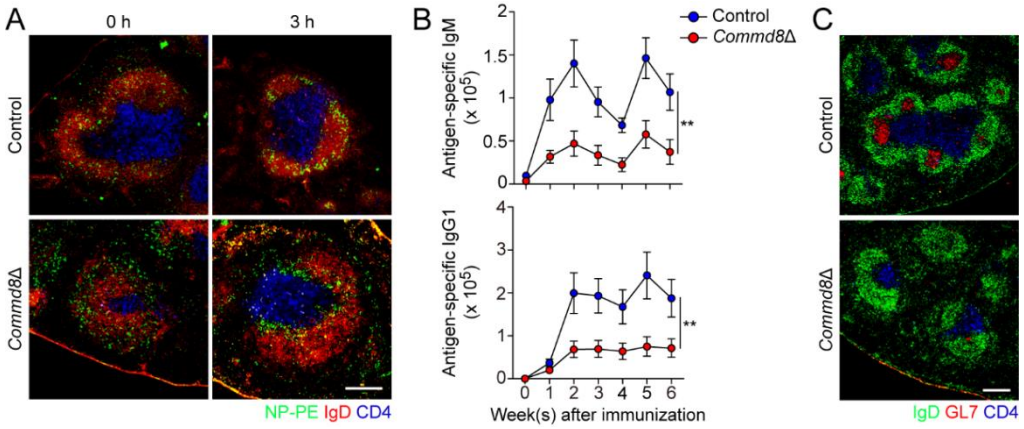

Figure 2. Deficiency of the COMMD3/8 complex impairs B cell migration and humoral immune responses.

(A) COMMD8-deficient (*Commd8*Δ) activated B cells (NP-PE$^+$, green) show impaired migration toward the outer region of B cell follicles (IgD$^+$ areas, red) at 3 h after immunization. (B and C) B cell-specific COMMD8-deficient mice show severe defects in the antibody response (B) and generation of germinal center B cells (GL7$^+$, red) (C). CD4 (blue) was labeled to define T cell areas in the spleen. $^{**}P < 0.01$, paired *t*-test. Scale bars, 200 μm.