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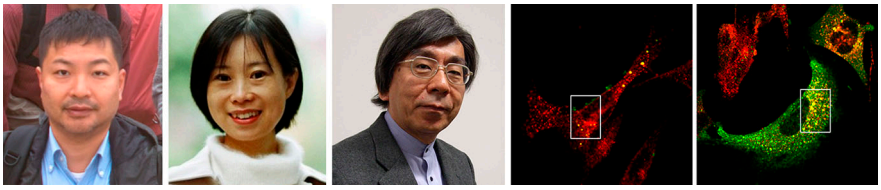
KIF13B erects an endocytic scaffold

A kinesin motor promotes the endocytosis of the membrane receptor LRP1 by recruiting it to caveolae.

Focal Point



PHOTOS COURTESY OF THE AUTHORS

(Left to right) Yoshimitsu Kanai, Daliang Wang, and Nobutaka Hirokawa investigate the function of the kinesin motor KIF13B and reveal an unexpected, motor-independent role for the protein in promoting the caveolin-mediated endocytosis of the membrane receptor LRP1. KIF13B (green) forms part of a scaffolding complex that links LRP1 (red) to the caveolar coat protein caveolin-1 at the plasma membrane (second from right), stimulating the receptor's internalization into endosomes (far right). LRP1 and KIF13B are enriched at the sinusoidal plasma membrane of hepatocytes, where LRP1 is responsible for the uptake of low-density lipoprotein and other proteins from the bloodstream. Blood cholesterol levels are accordingly elevated in mice lacking KIF13B.

Microtubule-based kinesin motor proteins have many cellular functions, including the transport of various cargoes to different parts of the cell (1). Kanai et al. uncover an unexpected, motor-independent function for one kinesin, KIF13B, in promoting the endocytosis of a membrane receptor that regulates cholesterol levels in the blood (2).

There are 45 kinesins in the human genome, and the functions of many of them remain unknown. Nobutaka Hirokawa and colleagues at The University of Tokyo study many members of this family, including a ubiquitously expressed kinesin called KIF13B. "We knocked out the KIF13B gene in mice to investigate the kinesin's in vivo function," says Hirokawa. "But the phenotype of these mutant mice was very subtle. They had no major histological or behavioral differences."

But Hirokawa and his colleagues Yoshimitsu Kanai and Daliang Wang persevered and eventually found that mice lacking KIF13B had elevated levels of cholesterol in their blood, as well as increased amounts of the blood-clotting protein factor VIII (2). KIF13B is particularly abundant in the liver, and the researchers discovered that the kinesin concentrates at the sinusoidal plasma membrane of hepatocytes, where material such as the cholesterol-carrying low-density lipoprotein (LDL) is taken up from neighboring blood vessels. In cultured cells, LDL was internalized into KIF13B-positive endosomes, but LDL uptake was reduced in the absence of the kinesin.

> "KIF13B works as a scaffold... to internalize LRP1 and its ligands via caveolin-dependent endocytosis."

The membrane receptor LRP1 binds and internalizes numerous ligands, including LDL and factor VIII, via clathrin- and caveolin-dependent pathways (3, 4). Kanai et al. found that LRP1 colocalized with KIF13B at the plasma membrane and in endosomes. Re-expressing KIF13B in knockout cells increased the number and size of LRP1-containing endosomes, indicating that the kinesin promotes LRP1's endocytosis. Similarly, KIF13B colocalized with the caveolar coat protein caveolin-1 and spurred the protein's translocation from the plasma membrane into early endosomes. In the absence of KIF13B, LRP1 failed to colocalize with caveolin-1, suggesting that the kinesin enhances LRP1 endocytosis by recruiting it into caveolae.

Surprisingly, KIF13B's motor and microtubule-binding domains weren't required to promote LRP1 internalization. Rather, the kinesin stimulated LRP1 endocytosis through its central region, which consists of three distinct domains: an FHA domain that binds to the GTPase-activating protein centaurin-α1, an MBS domain that interacts with the scaffold protein hDLG1, and a coiled-coil domain that, Kanai et al. showed, binds to a protein called utrophin. "We found that KIF13B binds to LRP1 via hDLG1 and to caveolin-1 via utrophin," Hirokawa explains. "So KIF13B works as a scaffold at the plasma membrane to internalize LRP1 and its ligands via caveolin-dependent endocytosis. This scaffolding function is very unexpected for a motor protein, but, after LRP1 is internalized, KIF13B could work as a motor to transport the endosomes through the cytoplasm."

"Clathrin-mediated endocytosis has been studied intensively," Hirokawa continues. "But this is the first study to identify a mechanism for caveolin-mediated internalization." The process may be regulated by KIF13B's FHA domain, which, by binding to centaurin-α1, switches on the endocytosis-promoting GTPase Arf6 (5). Hirokawa wants to investigate this possibility and to determine whether KIF13B also controls LRP1 endocytosis and blood cholesterol levels in humans. In addition, Hirokawa suspects that KIF13B could control the endocytosis of other cell surface proteins. "KIF13B is ubiquitously expressed, and there are several hDLG family members," he explains. "Together, they could work to regulate the caveolin-mediated endocytosis of different ligands in different tissues."

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4. Zhang, H., et al. 2004. *J. Biol. Chem.* 279:2221–2230.
5. Venkateswarlu, K., et al. 2005. *J. Cell Sci.* 118:2471–2484.