



Cholesterol regulation of PIP₂: why cell type is so important

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A commentary on

How cholesterol regulates endothelial biomechanics

by Hong, Z., Staiculescu, M. C., Hampel, P., Levitan, I., and Forgacs, G. (2012). *Front. Physio.* 3:426. doi: 10.3389/fphys.2012.00426

Phosphatidylinositol 4,5-bisphosphate (PIP₂) is a phospholipid found in cell membranes, and has been indicated to play important roles in cytoskeletal organization, cell motility, transduction of extracellular signals, regulation of ion channels at the plasma membrane, endocytosis, phagocytosis, and endosome function. It has also been linked to cancer in humans (Di Paolo and De Camilli, 2006). PIP₂ can be hydrolyzed by membrane-bound phospholipase C beta into two second messengers, IP₃ and diacylglycerol (DAG). Plasmalemmal cholesterol has been demonstrated to regulate PIP₂ hydrolysis and thus its cellular function in skin fibroblasts and pancreatic β -cells (Kwik et al., 2003; Hao and Bogan, 2009).

In this original research article, Hong et al. (2012) address the role of plasmalemmal cholesterol in regulating the localization and metabolism of PIP₂ in endothelial cells and the result on cell stiffness. They suggest that a decrease in cholesterol leads to disruption of PIP₂ hydrolysis, which in turn results in increased cross-links between the membrane and cytoskeleton via PIP₂ and increased cell stiffness. These results are important for understanding certain diseases, such as atherosclerosis, in which cholesterol levels are central to the pathology.

The mechanism by which cholesterol regulates PIP₂ in the plasma membrane

may not be the same for different cell types. Cholesterol depletion in fibroblasts leads to decreased levels of PIP₂ in the plasma membrane, diminished membrane-cytoskeletal attachments, and decreased lateral motility (Kwik et al., 2003). Similarly, in cultured pancreatic β -cells, cholesterol depletion stimulates the hydrolysis of PIP₂, thus reducing the amount of PIP₂ at the plasma membrane (Hao and Bogan, 2009). These findings are in contrast to a study using HEK293 cells, in which membrane cholesterol enrichment promoted PIP₂ depletion (Chun et al., 2010). Cholesterol depletion in lymphoblasts results in decreased lateral mobility of membrane proteins (Kwik et al., 2003). PIP₂ lateral mobility has been described as low in atrial myocytes, and high in HEK293 cells and fibroblasts (Epand, 2008). Therefore, cholesterol may regulate PIP₂ differently in various cell types.

Compartmentalization and regulation of PIP₂ metabolism within the plasma membrane may contribute to differences observed between cell types (Epand, 2008; Kwiatkowska, 2010). Cholesterol-rich membrane microdomains (lipid rafts), which are known to be intimately involved in regulating a variety of G-protein coupled receptor-mediated functions, including those regulating PIP₂ metabolism (Allen et al., 2007), have bidirectional relationship with actin cytoskeleton. In response to external stimuli, G $\alpha_q/11$ subunits stimulate membrane-bound phospholipase C beta, which then cleaves PIP₂ into its two second messengers. Therefore, it is believed that the relationship among lipid raft-associated PIP₂, G-proteins, and actin has strong implications in regulating actin assembly to modify cell shape and

function. Conversely, actin associates with rafts and caveolae either as polymerized structures or as actin monomers, which might help to organize lipid raft domains and the molecules that are present in this structure to evoke a variety of cell signaling pathways in the cell interior (Caroni, 2001). Another exciting mechanism involves three proteins, namely GAP43, MARCKS, and CAP23, which accumulate at rafts, where they associate with PIP₂, and promote its retention and clustering. By modulating PIP₂ at plasmalemmal rafts, GAP43, MARCKS, and CAP23 regulate cell cortex actin dynamics through a common mechanism. It is believed that, in response to local signals, these proteins dissociate from PIP₂, creating local pools of free PIP₂, which result in diverse intracellular responses.

Nonetheless, the mechanisms through which PIP₂ effector molecules mediate the various cellular responses to localized liberation of PIP₂ are mostly unknown. Investigations in this direction will foster our understanding of cholesterol-mediated PIP₂ intracellular functions.

REFERENCES

- Allen, J. A., Halverson-Tamboli, R. A., and Rasenick, M. M. (2007). Lipid raft microdomains and neurotransmitter signalling. *Nat. Rev. Neurosci.* 8, 128–140.
- Caroni, P. (2001). New EMBO members' review: actin cytoskeleton regulation through modulation of PI(4, 5)P(2) rafts. *EMBO J.* 20, 4332–4336.
- Chun, Y. S., Shin, S., Kim, Y., Cho, H., Park, M. K., Kim, T. W., et al. (2010). Cholesterol modulates ion channels via down-regulation of phosphatidylinositol 4,5-bisphosphate. *J. Neurochem.* 112, 1286–1294.
- Di Paolo, G., and De Camilli, P. (2006). Phosphoinositides in cell regulation and membrane dynamics. *Nature* 443, 651–657.

- Epand, R. M. (2008). Proteins and cholesterol-rich domains. *Biochim. Biophys. Acta* 1778, 1576–1582.
- Hao, M., and Bogan, J. S. (2009). Cholesterol regulates glucose-stimulated insulin secretion through phosphatidylinositol 4,5-bisphosphate. *J. Biol. Chem.* 284, 29489–29498.
- Hong, Z., Staiculescu, M. C., Hampel, P., Levitan, I., and Forgacs, G. (2012). How cholesterol regulates endothelial biomechanics. *Front. Physio.* 3:426. doi: 10.3389/fphys.2012.00426
- Kwiatkowska, K. (2010). One lipid, multiple functions: how various pools of PI(4,5)P(2) are created in the plasma membrane. *Cell. Mol. Life Sci.* 67, 3927–3946.
- Kwik, J., Boyle, S., Fooksman, D., Margolis, L., Sheetz, M. P., and Edidin, M. (2003). Membrane cholesterol, lateral mobility, and the phosphatidylinositol 4,5-bisphosphate-dependent organization of cell actin. *Proc. Natl. Acad. Sci. U.S.A.* 100, 13964–13969.
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