How two key proteins orchestrate flip-flopping cholesterol in the cell membrane

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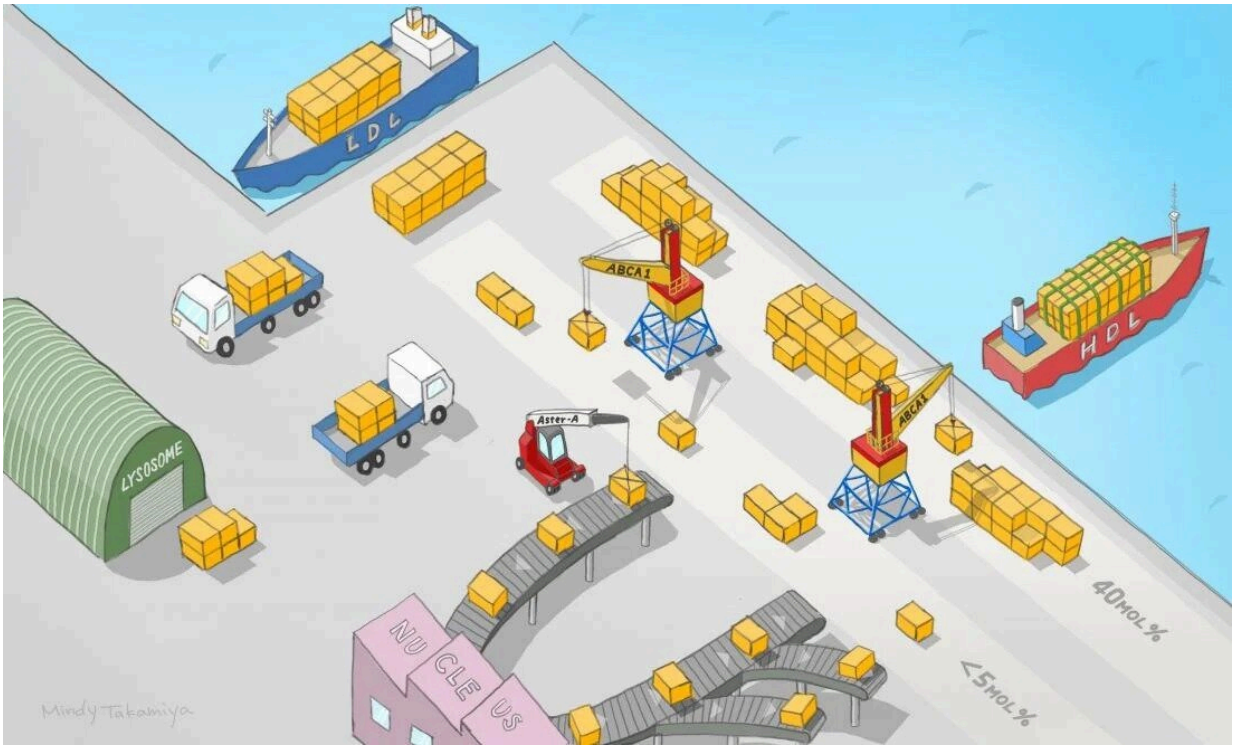

Cholesterol transporter protein ABCA1 at the plasma membrane, and cholesterol transfer protein Aster-A at the endoplasmic reticulum membrane, function cooperatively to keep the amount of cholesterol (cargo) in the inner plasma membrane low. Credit: Mindy Takamiya/Kyoto University iCeMS

Cholesterol is an essential component of the membrane surrounding every human cell, despite its poor reputation as a health concern when its

blood levels are too high. The key to health is having the right amount of cholesterol in the right places. Maintaining appropriate levels is known as cholesterol homeostasis.

Researchers at the Institute for Integrated Cell-Material Science (iCeMS) at Kyoto University in Japan have gained new insights into how cells achieve cholesterol homeostasis within the cell membrane. The findings are published in the *Journal of Biological Chemistry*.

Cholesterol molecules are packed inside the cell membrane at levels that control membrane fluidity, thickness and flexibility. These characteristics are vital for making the membrane a selective semi-permeable barrier, with crucial control over what substances can travel into and out of cells.

"Disturbances in cholesterol homeostasis can lead to some serious diseases, but it has been unclear how cells detect and respond to changes in cholesterol levels in the cell membrane," says iCeMS cellular biochemist Kazumitsu Ueda.

Ueda and his colleague Fumihiko Ogasawara have now revealed a vital role of two proteins in maintaining an appropriate distribution of cholesterol inside cells and their membranes.

The first protein, called ATP-binding cassette A1 (ABCA1) translocates cholesterol within the membrane. The cell membrane is composed of a lipid bilayer, with inner and outer layers of fatty molecules (phospholipids, cholesterol, and glycolipids) oriented in opposite directions.

A key new insight reported in this current study is that the ABCA1 protein controls the transfer of cholesterol molecules from the inner layer to the outer layer. The researchers call this process "cholesterol

flopping." Their previous work explored this protein's role in facilitating cholesterol transfer through the bloodstream in the form of high-density lipoprotein (HDL), sometimes called good cholesterol.

Ueda and Ogasawara also uncovered details of how a second protein—cholesterol transfer protein Aster-A—acts cooperatively with ABCA1 to maintain the crucial asymmetric distribution of cholesterol, with more cholesterol in the outer layer of the cell membrane than the inner. Aster-A is located inside the cell embedded in the endoplasmic reticulum. When there is an increase in the cholesterol level in the inner layer of the cell membrane, Aster-A forms a bridge transferring cholesterol from the cell membrane to the endoplasmic reticulum.

The researchers describe how the asymmetric distribution of cholesterol in the membrane allows it to serve a signaling function, influencing other cellular processes in ways that depend on the degree of asymmetry. They suggest that this explains why defects in the normal functioning of ABCA1 can cause faulty molecular signaling that may lead to cancer and autoimmune diseases.

"The progress we have made needs to be built on to better understand all the implications of these cholesterol homeostasis processes in both health and disease," Ueda concludes. He hopes this may eventually open new avenues to treating diseases linked to cholesterol imbalance.

More information: Fumihiko Ogasawara et al, ABCA1 and cholesterol transfer protein Aster-A promote an asymmetric cholesterol distribution in the plasma membrane, *Journal of Biological Chemistry* (2022). DOI: 10.1016/j.jbc.2022.102702

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