Cell biology research: The mystery of cholesterol homeostasis

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Kazumitsu Ueda, PhD from Kyoto University, WPI-iCeMS, unveils the mystery of cholesterol homeostasis in this cell biology research focus

Cholesterol is a crucial component of the plasma membrane (PM) that surrounds every human cell, helping to maintain a distinct intracellular environment from the external one. While some cholesterol in the body is obtained from daily food, it is synthesised in all body cells, and cellular cholesterol concentration is highly regulated. However, cholesterol has gained a bad reputation for harming health. In this article, the physiological role of cholesterol will be reconsidered.

Mystery of cellular cholesterol homeostasis

Cholesterol is synthesised in the endoplasmic reticulum (ER) and is also taken up from the blood as low-density lipoprotein (LDL) in body cells. Cholesterol synthesis and uptake are both regulated by the complex of sterol regulatory element–binding protein (SREBP) and SREBP cleavage–activating protein (SCAP), which reside in the ER membrane.

While the SCAP–SREBP system controls PM cholesterol levels, which hold 60-90 % of a cell's total cholesterol, it is regulated by ER cholesterol levels with approximately 5 mol%, serving as the threshold. This represents the sharpest regulation among biological reactions in the human body, even sharper than the hemoglobin-oxygen interaction, an important reaction for life.

The mechanism of this precise regulation has been intensively studied and revealed [(1)]. However, it remains a mystery how the SCAP–SREBP system in the ER can monitor PM cholesterol levels, why it is regulated at 5 mol%, and why the regulation needs to be so precise.

Aster-A/GramD1a bridges a gap between PM and ER when needed

The key to solving these mysteries lies in Aster-A/GramD1a and ABCA1. Aster-A/GramD1a is an integral ER membrane protein that bridges the gap between PM and ER at the PM-ER contact sites when needed. Under normal conditions, Aster-A/GramD1a diffuses throughout the ER network. However, when PM inner leaflet cholesterol increases, it remains at the PM-ER contact sites and transports cholesterol down the concentration gradient.

Considering that ER cholesterol content is maintained at 5 mol% by the SCAP-SREBP complex, PM inner leaflet cholesterol, which is accessible to Aster-A/GramD1a, should be kept at a maximum of this concentration. Aster-A/GramD1a is constantly and ubiquitously expressed in the human body, making it possible to respond to the local and temporal increases in PM cholesterol at the thousands of PM-ER contact sites for cholesterol internalisation [(2)]. This enables the SCAP-SREBP system to continuously sense PM cholesterol levels.

Trans-bilayer lipid asymmetry is functionally important for cells

The lipid compositions of the two leaflets of the PM are strikingly different. Glycolipids, phosphatidylcholine, and sphingomyelin are predominantly located in the outer leaflet, whereas phosphatidylserine (PS) is found in the inner leaflet. PS is continuously moved from the outer leaflet to the inner leaflet by phospholipid flippases, creating a negatively charged environment where important intracellular proteins, such as protein kinase C, are activated. PS is also exposed to the cell surface by phospholipid scramblaces, serving as an “eat-me” signal when cells undergo apoptosis. Thus, trans-bilayer lipid asymmetry is functionally important for cells.

Cholesterol is also asymmetrically distributed

In 2017, Liu et al. [(3)] reported that the cholesterol level in the inner leaflet is 10-fold lower than that in the outer leaflet: approximately 3 mol% in the inner leaflet, while 40-50 mol% in the outer leaflet. This sparked a heated debate. However, as described above, PM inner leaflet cholesterol is likely maintained at less than 5 mol%, while some inner leaflet cholesterol molecules could be sequestered by membrane proteins such as caveolin-1 [(4)]. Given that the PM cholesterol content is calculated 30-40 mol%, it is also likely that the cholesterol content in the outer leaflet exceeds 40 mol%.

ABCA1 moves cholesterol from the inner leaflet to the outer leaflet

ABCA1, a member of the ATP binding cassette (ABC) transporters, moves cholesterol from the inner leaflet to the outer leaflet of the PM. Because ABCA1, Aster-A and SCAP–SREBP are ubiquitously expressed throughout the human body, the cholesterol gradient is created in all body cells.

ABCA1 was initially identified as essential for high-density lipoprotein (HDL) formation through genetic analysis of Tangier disease. ABCA1 loads cholesterol and phosphatidylcholine onto apolipoprotein A-I, a lipid acceptor in the blood, to generate nascent HDL. The two activities of ABCA1, nascent HDL generation and cholesterol transfer to the outer leaflet, are regulated separately [(5)]. Therefore, ABCA1 moves cholesterol to the outer leaflet and helps eliminate excess cholesterol to maintain an appropriate concentration gradient.

The ABCA1–cholesterol signaling axis and evolution

To maintain cholesterol levels in the inner leaflet below that of ER (5 mol%), ABCA1, Aster-A, and SCAP/SREBP work cooperatively, consuming a significant amount of energy. Is this effort solely for maintaining cellular cholesterol homeostasis?

Liu et al. [3] proposed that the cholesterol concentration gradient between two leaflets allows cholesterol to function as an intramembrane signaling molecule. When cells are stimulated with the growth factor Wnt3, ABCA1 activity is temporarily suppressed, leading to a localised increase in cholesterol within PM inner leaflet. As a result, a cytosolic signaling molecule, which has a cholesterol-binding domain, is recruited to the PM to stimulate the Wnt3 signaling. This signal transduction plays a crucial role in regulating cell division and differentiation.

Given that the amino acid sequences of ABCA1, Aster-A, and SCAP are highly conserved among mammals, birds, and fish, the role of cholesterol as an intramembrane signaling molecule due to ABCA1-mediated asymmetric cholesterol distribution could be common among these animals. The evolution of the ABCA1–cholesterol signaling axis might have enabled vertebrates to develop complex developmental processes and sophisticated body plans.

“Good cholesterol” and “bad cholesterol” hypotheses need to be reconsidered

To maintain an appropriate cholesterol level in the PM, HDL formation by ABCA1 is tightly controlled through various processes. Therefore, an appropriate level of HDL cholesterol is an indicator of normal expression and function of ABCA1. Extremely low or high HDL levels in the blood could indicate defects in the regulation of ABCA1 expression and function. The generally accepted “good cholesterol” hypothesis needs to be reconsidered. Similarly, reconsideration of the “bad cholesterol” hypothesis may also be needed.

References

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