Systematic lipidomics to uncover new membrane lipid functions

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The control of membrane lipid homeostasis is an essential process that allows cells to maintain both their energetic balance and the structural integrity of their different membrane systems. However, despite the importance of this process, and although most of the enzymes involved in lipid metabolism have been already identified, little is known about the regulatory mechanisms.
In order to have a broader overview about how membrane lipid metabolism is orchestrated in cells, we present in this work a strategy that allows the monitoring of lipid changes in cells using a large-scale RNAi screening of human kinases combined with targeted lipidomic analysis by mass spectrometry. Statistical analysis of the screening highlights some genes whose knockdown induces changes in sphingolipid levels. Among them, cells lacking bromodomain-containing protein 3 (BDR3) have been found to have an increase in ceramide levels in different human cell lines, together with a decrease in glucosylceramide. Also, other changes in glycerophospholipids (i.e. ether-lipids, saturated lipids) can be detected, which shows that a membrane lipid remodelling takes place upon BRD3 knockdown by siRNA or by CRISPRi technology. These changes are accompanied by an increase in oxidative stress levels and affect plasma membrane properties, as detected *in vivo* using mechanosensitive membrane probes. We propose a metabolic and/or functional crosstalk between ether-lipids and sphingolipids that may be important for the adaptation of cells against oxidative stress, showing the importance of maintaining membrane lipid homeostasis to preserve cell viability under stress conditions.