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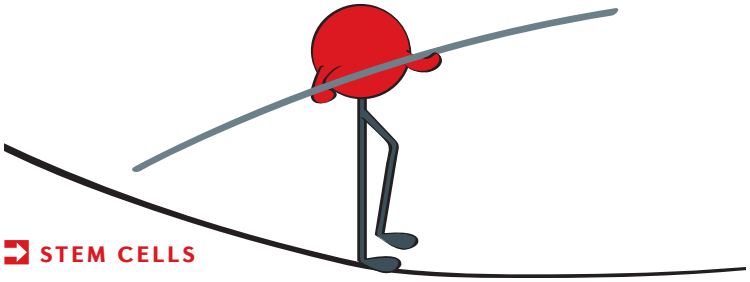

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STEM CELLS

A balancing act of lipids

Cell membranes are mainly composed of lipids. In addition to serving as structural elements, membrane lipids contribute to the regulation of various cellular processes, such as cell signalling, membrane dynamics and metabolism. Alterations in membrane lipid composition have been correlated with human pathologies, including cancer, neurodegeneration and diabetes. However, how specific changes in membrane lipid composition link to disease is largely unknown. Tontonoz and colleagues now show that lack of phospholipid remodelling enzyme lysophosphatidylcholine acetyltransferase 3 (LPCAT3) in intestinal stem cells (ISCs) results in intestinal hyperproliferation and that this overgrowth is driven by an excess of cholesterol produced in response to changes in phospholipid composition.

LPCAT3 is a crucial determinant of membrane lipid composition that incorporates polyunsaturated fatty acids into phospholipids. When investigating the effects of LPCAT3 deficiency *in vivo*, the authors observed intestinal hypertrophy in intestine-specific *Lpcat3*-knockout mice. Moreover, this hypertrophy was accompanied by increased proliferation of ISCs and consequent expansion of stem and progenitor cell populations. Deletion of *Lpcat3* also increased the size, number and complexity of organoids generated from intestinal crypts (in which ISCs reside), which was counteracted by supplying liposomes containing polyunsaturated phosphatidylcholine. This suggested that depriving membranes of polyunsaturated phospholipids increases proliferation and self-renewal of ISCs.

Gene expression analyses revealed strong activation of genes involved in sterol biosynthesis upon *Lpcat3* deletion in intestinal crypts. This increase in gene expression was accompanied by increased nuclear levels of sterol regulatory element-binding protein 2 (SREBF2) — the key activator of sterol biosynthetic genes. In agreement with these observations, the levels of free cholesterol were higher in cultured, LPCAT3-deficient intestinal crypts. Thus, LPCAT3 deficiency increases cholesterol biosynthesis and total cholesterol levels in intestinal crypts.

Inhibition of cholesterol biosynthesis suppressed the overgrowth and hyperproliferation phenotype driven by *Lpcat3* knockout both in mice and in intestinal organoids. Conversely, supplementation with cholesterol increased the growth of wild-type intestinal organoids and proliferation of ISCs in mice. Similarly, intestinal-specific *Srebf2*-transgenic mice, which are characterized by increased cholesterol biosynthesis in the intestinal epithelium, exhibited intestinal hypertrophy and expansion of the proliferating cell population. These observations indicate that cholesterol is a mitogen for ISCs that can drive intestinal hypertrophy when supplied in excess.

Deletion of *Lpcat3* or introducing the *Srebf2* transgene into adenomatous polyposis coli mutant mice, which are predisposed to intestinal tumorigenesis, further exacerbated cancer burden by increasing intestinal tumour incidence and decreasing animal survival. Concomitant inhibition of cholesterol biosynthesis alleviated this tumour-promoting effect, suggesting that excess cholesterol contributes to intestinal tumorigenesis.

In summary, this study revealed a link between phospholipid remodelling and cholesterol biosynthesis and the contribution of this axis to pathological intestinal hypertrophy. Alterations of membrane lipid metabolism and supply can have a considerable impact on tissue homeostasis, and further studies are needed to better understand the complex roles of membrane lipids in cell biology.

Paulina Strzyz

> “excess cholesterol contributes to intestinal tumorigenesis”

ORIGINAL ARTICLE Wang, B. *et al.* Phospholipid remodeling and cholesterol availability regulate intestinal stemness and tumorigenesis. *Cell Stem Cell* http://doi.org/10.1016/j.stem.2017.12.017 (2017)

FURTHER READING Harayama, T. & Reizman, H. Understanding the diversity of membrane lipid composition. *Nat. Rev. Mol. Cell Biol.* http://doi.org/10.1038/nrm.2017.138 (2017)

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