Molecular Cell
Previews

Danger zone: The balance between fat-driven health and death

Jenny Jin,[1] Liam N. Stiles,[1] and Brent R. Stockwell[1,2,*]
[1]Department of Biological Sciences, Columbia University, New York, NY 10027, USA
[2]Department of Chemistry, Department of Pathology and Cell Biology, Irving Institute for Cancer Dynamics, Herbert Irving Comprehensive Cancer Center, Data Science Institute, Liver Disease Research Center, Columbia University, New York, NY 10027, USA
*Correspondence: bstockwell@columbia.edu
https://doi.org/10.1016/j.molcel.2025.08.027

Damage to polyunsaturated fats causes ferroptotic cell death. In this issue, Deng et al.[1] show that the incorporation of the fatty acid DHA into membranes is controlled by the protein UBXD8, as a natural mechanism to prevent overloading cells with dangerous fat, preventing ferroptosis.

Amid the popularity of fish oil supplements and health-promoting diets such as the Mediterranean diet, which leans into copious consumption of olive oil, it might be easy to forget that fat hasn't always been at the center of food and diet. Fat was once regarded as a simple source of energy, and its biological impact was mostly ignored for much of human history. Experiments in rodents with limited dietary fat suggested that fat molecules, known as lipids from the Greek λίπος (lipos) for fat, were not essential for animal development. However, that consensus shifted when researchers rigorously excluded fats from animal diets and rodents failed to develop normally.[2] The lipids known as linoleic acid and α-linolenic acid were discovered to be essential for mammals; thus, the term essential fatty acid was coined and came into common use. This discovery laid the foundation for the vast field of lipid biology and nutrition.[3]

These two essential fatty acids are converted biosynthetically into longer chain polyunsaturated fatty acids (PUFAs), including arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). While omega-6 PUFAs, such as AA, give rise to pro-inflammatory mediators, omega-3 PUFAs, such as DHA, are anti-inflammatory.[4]

While omega-6 and omega-3 fats have opposing roles on inflammation, they share a biological function as drivers of the cell death process known as ferroptosis.[5] Ferroptosis involves the iron-dependent oxidation of PUFA-containing lipids and has been implicated in a variety of diseases and normal biological processes.[6] PUFAs such as AA and DHA are susceptible to oxidation due to the positioning of the multiple carbon–carbon double bonds within these molecules.

PUFAs sensitize cells to ferroptosis and directly induce ferroptosis via increased production of PUFA-containing lipids[7]; their ferroptosis-promoting effects require that they become incorporated into larger membrane lipids. Lipids with either omega-6 or omega-3 PUFAs incorporated (or both) can be oxidized to drive ferroptosis.[8] It has not been clear whether cells control their propensity to undergo ferroptosis via limiting the extent of PUFA incorporation into membrane lipids; we now have the answer to this question from Deng et al.—yes, they do.

Deng et al. report the discovery of a fatty-acid-sensing mechanism that limits the accumulation of PUFAs into larger lipid structures within cell membranes (Figure 1). The authors found that the sensor protein UBXD8 activates the enzyme AGPAT3, which promotes incorporation of DHA into membrane lipids. In cultured cells, UBXD8 elimination reduced the abundance of DHA-containing lipids, thereby causing ferroptosis resistance. Likewise, AGPAT3 removal caused a similar effect. Increasing the amount of AGPAT3 in cells overcame the effect of eliminating UBXD8, confirming that these two proteins do indeed work together. Overloading cells with DHA disrupted the interaction between UBXD8 and AGPAT3, thus inhibiting DHA incorporation into membrane lipids. UBXD8 and AGPAT3 controlled DHA specifically, not the incorporation of other PUFAs such as AA.

Deng et al. further tested the role of this homeostatic mechanism in mice. They first found that knocking out the mouse gene *Ubxd8* was

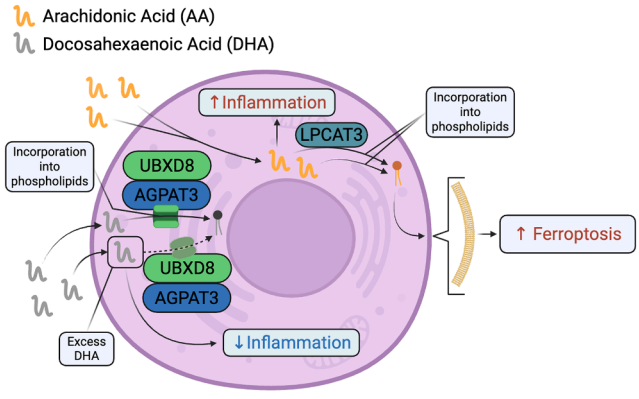

Figure 1. The UBXD8/AGPAT3 complex regulates DHA incorporation into lipids
While the polyunsaturated fatty acid (PUFA) arachidonic acid (AA) can be incorporated in excess amounts into membrane lipids via the action of LPCAT3, the incorporation of the PUFA docosahexaenoic acid (DHA) into membrane lipids is regulated by the UBXD8/AGPAT3 complex. When DHA is present in low amounts, it is incorporated into membrane lipids via this complex, but when present in excess, DHA inhibits the UBXD8/AGPAT3 complex, blocking further incorporation of DHA into membrane lipids and preventing ferroptosis. The total loss of UBXD8 also prevents DHA incorporation into membrane lipids, blocking ferroptosis.

lethal and prevented mouse embryos from surviving. However, when they knocked out *Ubxd8* specifically in mouse livers, they confirmed their results from cell culture studies—mouse livers without *Ubxd8* had fewer membrane lipids containing DHA. When they fed mice fish oil along with alcohol, which promotes liver ferroptosis, and deprived them of vitamin E, which protects against ferroptosis, the wild-type mice developed a marker of ferroptosis in their livers, whereas mice lacking *Ubxd8* were protected and showed no signs of ferroptosis. Thus, fish oil can indeed induce ferroptosis in mice under specific conditions—when co-administered with alcohol in animals that are deprived of vitamin E. However, *Ubxd8* loss protects against this damage, presumably due to its role in promoting DHA incorporation into membrane lipids.

Deng et al. demonstrated a key ferroptosis-control mechanism through which cells prevent accumulation of DHA-containing lipids. Their study has implications for the use of PUFAs in ferroptosis-sensitizing therapy, such as in cancer treatment. Specifically, AA may be more effective than DHA is in sensitizing cells to ferroptotic cell death; exogenous AA can overwhelm cells with oxidizable AA-containing lipids, whereas DHA incorporation is blocked by the UBXD8-AGPAT3 system. However, other regulators may exist for different PUFAs, and that may be a subject of future research. This study also provides implications for the effects of omega-3 PUFA supplementation using products such as fish oil; the DHA-specific sensing mechanism may prevent ferroptosis sensitization in the context of DHA supplementation, which may explain why this supplement is relatively safe, except for the unusual situation in which it is given in large amounts along with alcohol in animals deprived of vitamin E.[9]

Furthermore, this study provides one of the first ferroptosis-related distinctions between omega-3 and omega-6 fatty acids, leading to the question of why cells would evolve the capacity to limit DHA, but not AA, incorporation into membrane lipids. The authors posit that perhaps beyond ferroptosis protection, this mechanism may be required to shunt free DHA to drive the production of anti-inflammatory mediators. Indeed, this homeostatic sensor may have evolved as a ferroptosis-defense mechanism, since ferroptosis seems to be an ancient cell death process.[10]

DHA has a number of beneficial effects, including promoting visual acuity in infants, without promoting organ damage through ferroptosis; this study by Deng et al. provides a mechanism for this paradox, providing an explanation for how both babies and adults fed DHA supplements normally avoid the DHA danger zone of ferroptosis.

ACKNOWLEDGMENTS

The research of B.R.S. is supported by the National Cancer Institute (P01CA291697), Project ALS (PRALS CU23-1596), the American Lung Association (PG014050), and the DOD CDMRP (AL240118).

DECLARATION OF INTERESTS

B.R.S. is an inventor on patents and patent applications involving ferroptosis; co-founded and serves as a consultant to ProJenX, Inc; and serves as a consultant to General Proximity.

REFERENCES

1. Deng, Y., Vale, G., Liang, Y., Cui, S., Xu, S., McDonald, J., and Ye, J. (2025). Protection against Ferroptosis through Maintaining Homeostasis of Docosahexaenoate-Containing Phospholipids. Mol. Cell *85*, 3474–3485.e5.

2. Burr, G.O., and Burr, M.M. (1929). A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet. J. Biol. Chem. *82*, 345–367.

3. Spector, A.A., and Kim, H.Y. (2015). Discovery of essential fatty acids. J. Lipid Res. *56*, 11–21.

4. de, B.I., Witkamp, R., Zuilhof, H., Albada, B., and Balvers, M. (2019). The role of n-3 PUFA-derived fatty acid derivatives and their oxygenated metabolites in the modulation of inflammation. Prostaglandins Other Lipid. Mediat *144*, 1–12. 106351.

5. Dixon, S.J., Lemberg, K.M., Lamprecht, M.R., Skouta, R., Zaitsev, E.M., Gleason, C.E., Patel, D.N., Bauer, A.J., Cantley, A.M., Yang, W.S., et al. (2012). Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell *149*, 1060–1072.

6. Stockwell, B.R. (2022). Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell *185*, 2401–2421.

7. Yang, W.S., Kim, K.J., Gaschler, M.M., Patel, M., Shchepinov, M.S., and Stockwell, B.R. (2016). Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. Proc. Natl. Acad. Sci. USA *113*, E4966–E4975.

8. Shan, K., Feng, N., Zhu, D., Qu, H., Fu, G., Li, J., Cui, J., Chen, H., Wang, R., Qi, Y., and Chen, Y.Q. (2022). Free docosahexaenoic acid promotes ferroptotic cell death via lipoxygenase dependent and independent pathways in cancer cells. Eur. J. Nutr. *61*, 4059–4075.

9. Chang, J.P.C., Tseng, P.T., Zeng, B.S., Chang, C.H., Su, H., Chou, P.H., and Su, K.P. (2023). Safety of Supplementation of Omega-3 Polyunsaturated Fatty Acids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv. Nutr. *14*, 1326–1336.

10. Conrad, M., Kagan, V.E., Bayir, H., Pagnussat, G.C., Head, B., Traber, M.G., and Stockwell, B.R. (2018). Regulation of lipid peroxidation and ferroptosis in diverse species. Genes Dev. *32*, 602–619.