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Preview

Metabolite buffering of labile iron governs ferroptosis

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Iron abundance alone does not determine ferroptosis sensitivity. In this issue of *Cell*, Sharma and colleagues identify polyamines as endogenous metabolic buffers that reduce the chemical accessibility of labile iron, revealing an unexpected function for one of the cell's most abundant metabolite classes while raising new questions about the organization of intracellular iron metabolism.

Iron presents cells with a fundamental challenge. As an essential cofactor, iron supports diverse biological processes, ranging from cellular respiration to DNA synthesis and oxygen transport.[1] Yet the same redox chemistry that enables these functions also underlies the generation of reactive oxygen species (ROS).[1,2] Cells therefore devote sophisticated machinery to regulate iron uptake, storage, and utilization.[1] Within cells, iron exists primarily in oxidized (Fe^{3+}) and reduced (Fe^{2+}) states, with the latter participating in Fenton chemistry to generate damaging ROS, inducing lipid peroxidation and ferroptosis.[1–4] Despite extensive knowledge of iron metabolism, how cells regulate the chemical accessibility and reactivity of iron within the cytosolic labile iron pool remains incompletely understood.

In this issue of *Cell*, Sharma and colleagues identify polyamines as endogenous buffers of redox-active Fe^{2+},[5] revealing an unexpected mechanism by which cells regulate sensitivity to ferroptosis. Cellular iron exists in multiple coordination environments including ferritin, heme, Fe–S clusters, and metalloproteins, whereas it is generally thought that only a relatively small fraction remains capable of driving oxidative chemistry.[1] Rather than altering total cellular iron, polyamines bind and reduce the fraction of labile Fe^{2+} that promotes lipid peroxidation and ferroptosis[5] (Figure 1). Together with a recent complementary study,[6] these findings indicate that polyamines function as endogenous metabolites that actively shape the chemical behavior of intracellular iron and govern cellular sensitivity to ferroptosis. This work suggests that the chemical accessibility of the labile iron pool, rather than its abundance alone, is a critical determinant of ferroptosis, thereby shifting attention upstream of lipid peroxide detoxification and toward the catalytic iron that initiates oxidative membrane damage.

The connection between polyamine metabolism and ferroptosis emerged from an unbiased genome-wide CRISPR screen that identified a synthetic lethal interaction between polyamine depletion and loss of GPX4.[5] Indeed, polyamine depletion increased lipid peroxidation and ferroptosis sensitivity.[5] These effects were independent of canonical regulators of ferroptosis, such as GPX4, FSP1, and membrane lipid composition. Sharma and colleagues propose that polyamines function as low-affinity, high-abundance buffers of the labile iron pool (Figure 1). Consistent with this model, polyamine depletion resulted in an increase in redox-active iron in cells and the polyamine spermine directly chelated Fe^{2+} *in vitro*.[5] Although individual polyamine-iron interactions are relatively weak, millimolar intracellular concentrations collectively reduce the availability of Fe^{2+} for Fenton chemistry while avoiding the complete sequestration expected from high-affinity iron chelators. This mechanism provides a compelling explanation for why cells maintain such high concentrations of polyamines despite the substantial energetic cost of their synthesis and homeostatic regulation. Future studies exploring how cells regulate polyamine abundance and composition will be important for determining how the labile iron pool is buffered to suppress ferroptosis while still preserving iron availability for essential metabolic functions.

The physiological relevance of polyamine-based iron buffering is strengthened by a recent study demonstrating that spermine directly buffers Fe^{2+} *in vivo*, influencing hepatocellular carcinoma progression and ischemia-reperfusion injury.[6] This function of spermine is particularly relevant in the liver, the major iron-storage organ, where the authors found that an ALDH18A1-polyamine biosynthesis pathway enables tumor cells to buffer iron, evade ferroptosis, and survive under iron-rich oxidative stress conditions.[6] Whether similar mechanisms determine ferroptosis susceptibility across other tissues and disease contexts remains an important question. Differences between the studies regarding the relative contributions of individual polyamines,[5,6] particularly spermine and spermidine, for Fe^{2+} buffering highlight unresolved questions and warrant further investigation into how polyamine composition and cellular context shape ferroptosis sensitivity.

A significant technical advance accompanying this study is the development of a genetically encoded fluorescent reporter for redox-active Fe^{2+}.[5] Compared to chemical probes, genetically encoded reporters offer advantages such as stable expression, quantitative robustness, improved subcellular targeting, live-cell imaging, and compatibility with genetic perturbations. By

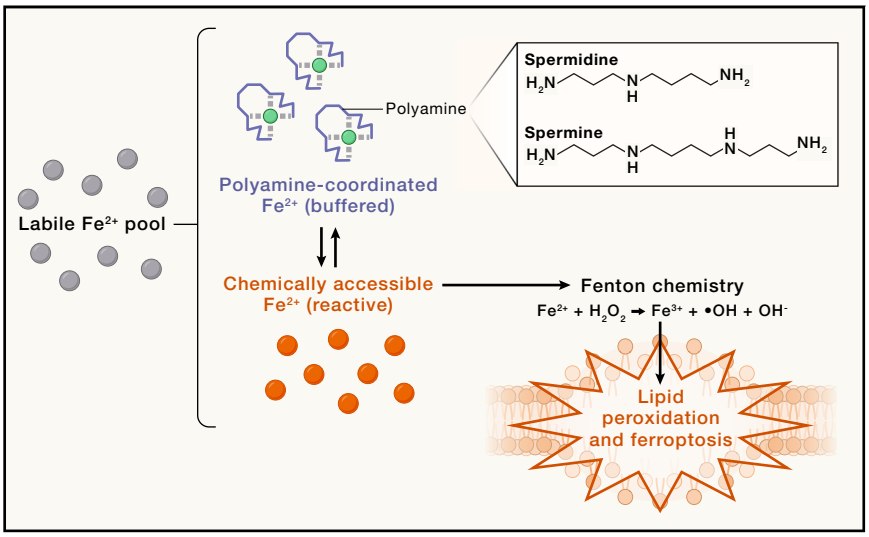

Figure 1. Polyamines buffer the labile iron pool to prevent lipid peroxidation and ferroptosis

Polyamines, such as spermine and spermidine, are proposed to reversibly coordinate a fraction of the intracellular labile Fe^{2+} pool, reducing the amount of chemically accessible iron available to participate in Fenton chemistry and initiate lipid peroxidation. By buffering the redox-active fraction of the labile iron pool, polyamines may suppress ferroptosis while preserving iron availability for essential cellular metabolism.

combining this reporter with a previously developed fluorescent sensor of intracellular polyamines, Sharma and colleagues demonstrate a striking inverse relationship between polyamine abundance and redox-active iron at the single-cell level. Beyond ferroptosis, the genetically encoded fluorescent reporters should prove valuable for studying iron metabolism in diverse biological contexts and allow genetic screens for identifying regulators of the iron redox state.

A key unanswered question concerns the organization of the intracellular iron pools and the role of polyamines in their regulation. Iron continuously exchanges among metabolites, storage proteins, and biosynthetic pathways that support ferritin loading, heme synthesis, Fe–S cluster assembly, and numerous iron-dependent enzymes.[1] How polyamine buffering interfaces with these established pathways remains unclear. Does polyamine-bound iron simply represent one coordination state within a rapidly exchanging labile iron pool, alongside complexes with ATP, citrate, and other metabolites? Or do polyamines participate more directly in intracellular iron trafficking and distribution? Likewise, ferritin accumulation following polyamine depletion suggests activation of iron-dependent homeostatic responses,[5] yet the relationship between ferritin storage and polyamine buffering remains to be determined. Addressing these questions will be essential for understanding how cells regulate not only the amount of labile iron but also its chemical accessibility for competing metabolic and oxidative reactions.

More broadly, the findings prompt a reconsideration of why cells contain millimolar concentrations of polyamines and tightly regulate their metabolism.[7,8] While polyamines have long been recognized for their roles in translation, chromatin organization, and proliferation, these functions alone do not readily explain their abundance. Iron buffering offers an explanation that links polyamine homeostasis to oxidative stress while providing a unifying framework for many of the diverse phenotypes associated with altered polyamine metabolism.

Together, the emerging findings broaden the framework of ferroptosis regulation. Established defense pathways, including GPX4, FSP1, and GCH1, operate downstream of iron by detoxifying lipid peroxides or regenerating lipophilic radical-trapping antioxidants.[4] In contrast, polyamines function upstream by limiting the iron-dependent reactions that initiate lipid peroxidation, providing an additional metabolic layer of ferroptosis control. These studies support the idea that ferroptosis sensitivity depends not simply on the abundance of intracellular iron but also on its chemical accessibility. By reversibly buffering the labile iron pool, polyamines appear to limit the fraction of iron available for oxidative chemistry while preserving iron for essential metabolic processes. Beyond expanding the network of ferroptosis defense mechanisms, these findings reveal an unexpected function for a highly abundant metabolite class and reshape our understanding of how metabolism regulates intracellular iron chemistry.

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DECLARATION OF INTERESTS

J.A.O. has patent applications related to ferroptosis and consults for Dojindo Laboratories.

REFERENCES

1. Jain, C., and Shah, Y.M. (2025). Iron: Regulation, redox homeostasis, and ferroptosis in cancer. Ferroptosis Oxid. Stress *2*, 202526. https://doi.org/10.70401/fos.2026.0022.
2. Sies, H., Belousov, V.V., Chandel, N.S., Davies, M.J., Jones, D.P., Mann, G.E., Murphy, M.P., Yamamoto, M., and Winterbourn, C. (2022). Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology.

Nat. Rev. Mol. Cell Biol. *23*, 499–515. https://doi.org/10.1038/s41580-022-00456-z.

3. 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. https://doi.org/10.1016/j.cell.2012.03.042.
4. Dixon, S.J., and Olzmann, J.A. (2024). The cell biology of ferroptosis. Nat. Rev. Mol. Cell Biol. *25*, 424–442. https://doi.org/10.1038/s41580-024-00703-5.
5. Sharma, P., Keys, H.R., Mansell, R.P., Stark, J., Girard, L., Ausler, C., Anderson, R., Müller, S., Imada, S., Pires, I.S., et al. (2026). Polyamines buffer labile iron to suppress ferroptosis. Cell *189*, 5571–5589.e10. https://doi.org/10.1016/j.cell.2026.07.040.
6. Li, M., Yu, X., Ouyang, S., Chen, X., Yu, H., Liu, Y., Li, Z., Yu, C., Kang, R., Gaillet, C., et al. (2026). Spermine is an endogenous iron chelator that inhibits ferroptosis. Nature *655*, 240–250. https://doi.org/10.1038/s41586-026-10597-2.
7. Casero, R.A., Murray Stewart, T., and Pegg, A.E. (2018). Polyamine metabolism and cancer: treatments, challenges and opportunities. Nat. Rev. Cancer *18*, 681–695. https://doi.org/10.1038/s41568-018-0050-3.
8. Pegg, A.E. (2016). Functions of Polyamines in Mammals. J. Biol. Chem. *291*, 14904–14912. https://doi.org/10.1074/jbc.R116.731661.