Metal-dependent regulated cell death: Molecular architecture and translational frontiers

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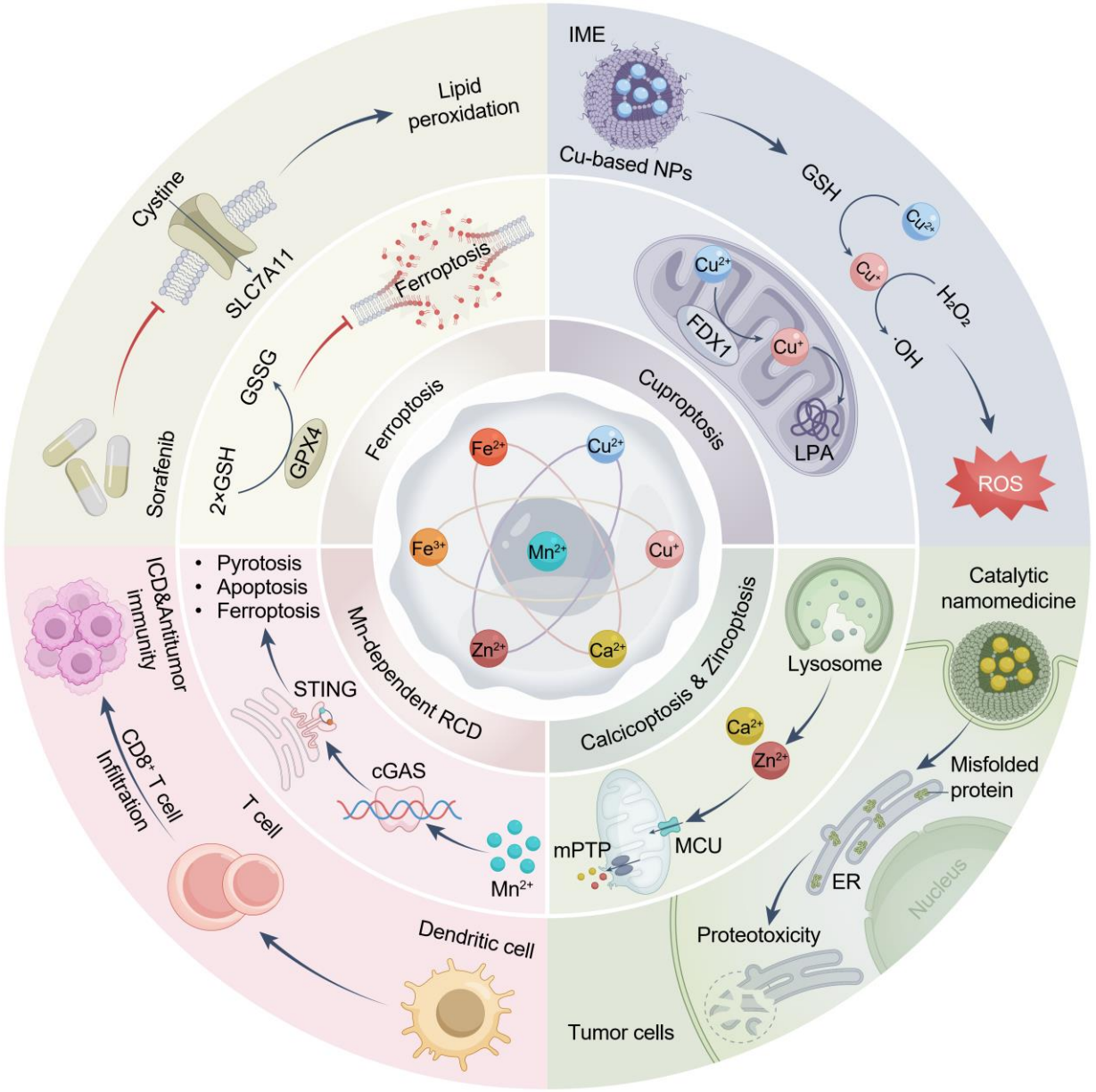
Haoliang Hu, Zhe Chen, Yaqi Li, Jiayi Peng, Jiangang Cao, Hong Zhou, Mengqi Wang, et al. 2026. Metal-dependent regulated cell death: Molecular architecture and translational frontiers. ***iMeta*** 5: e70141. https://doi.org/10.1002/imt2.70141

Graphical abstract



Molecular pathways and translational strategies of diverse metal-dependent RCD

Highlights

- Metal dyshomeostasis drives canonical and newly designated different regulated cell death programs, challenging classical views that frame necrosis as purely accidental.
- Bidirectional therapeutic strategies exploit tumor-specific synthetic lethality or apply targeted inhibitors to preserve vulnerable tissues.
- Bioresponsive nanomedicines and single-atom catalysts spatiotemporally confine oxidative flux, overcoming systemic toxicity to orchestrate interconnected PANoptosis networks.
- Metal-induced immunogenic cell death and cGAS–STING hyperactivation cooperate systemically with immune checkpoint blockade.

1. INTRODUCTION

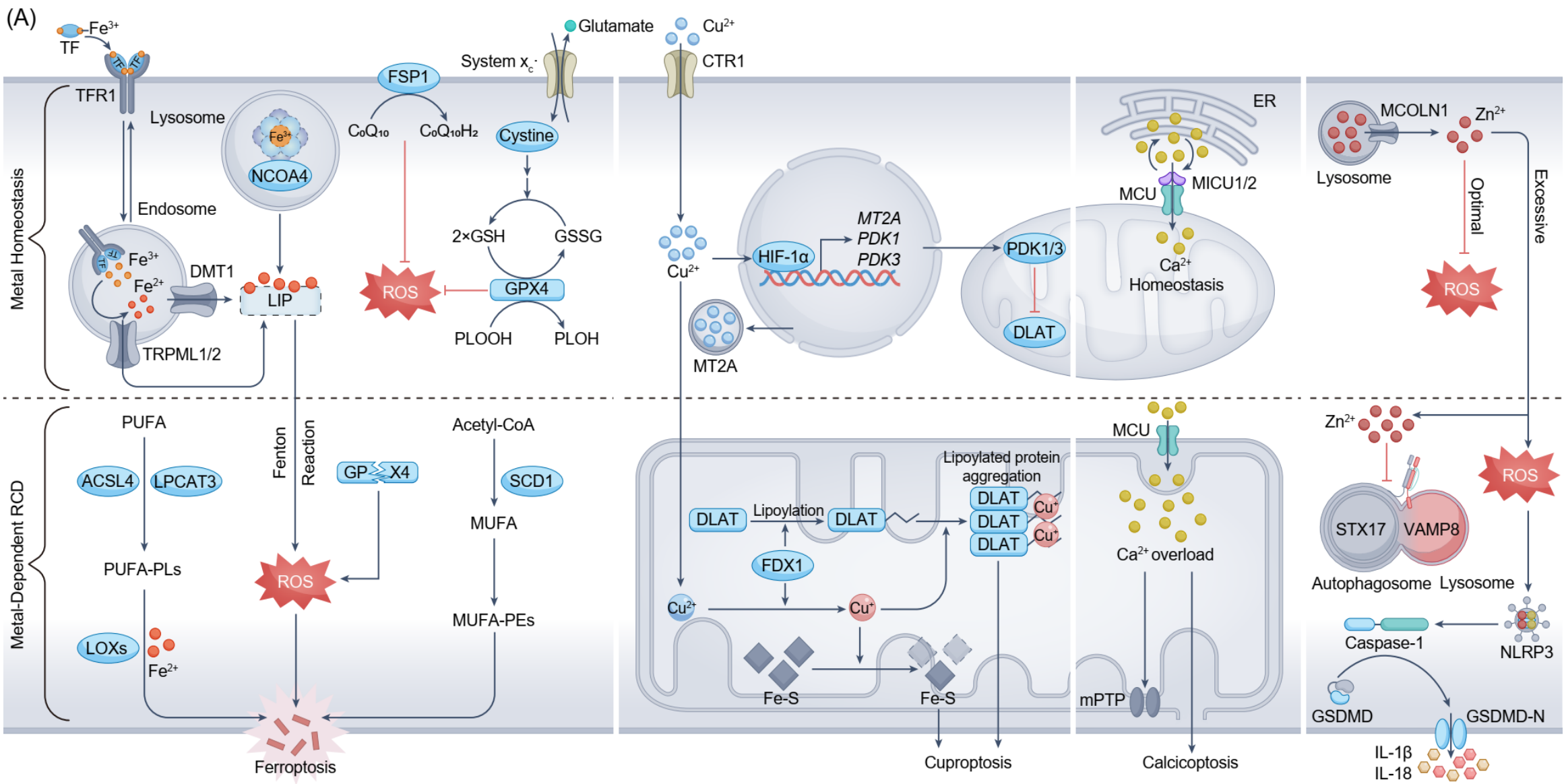


FIGURE 1A. Mechanistic transition from physiological metal homeostasis to pathological RCD.

2. CONCEPTUAL EVOLUTION OF METAL-DEPENDENT RCD

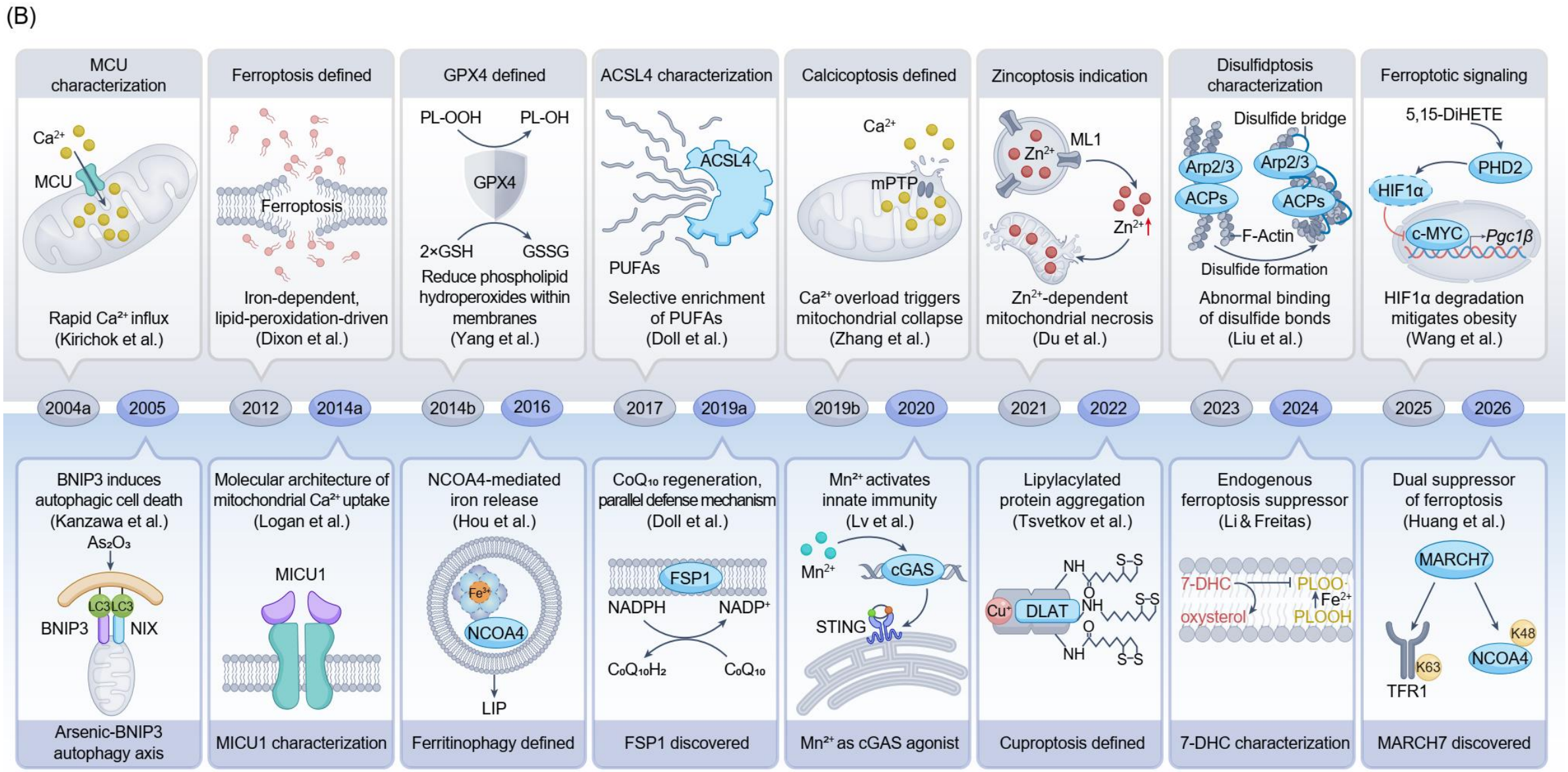


FIGURE 1B. Timeline detailing the conceptual evolution of structural advancements in metal-dependent RCD.

3. FERROPTOSIS: IRON, LIPIDS, AND REDOX

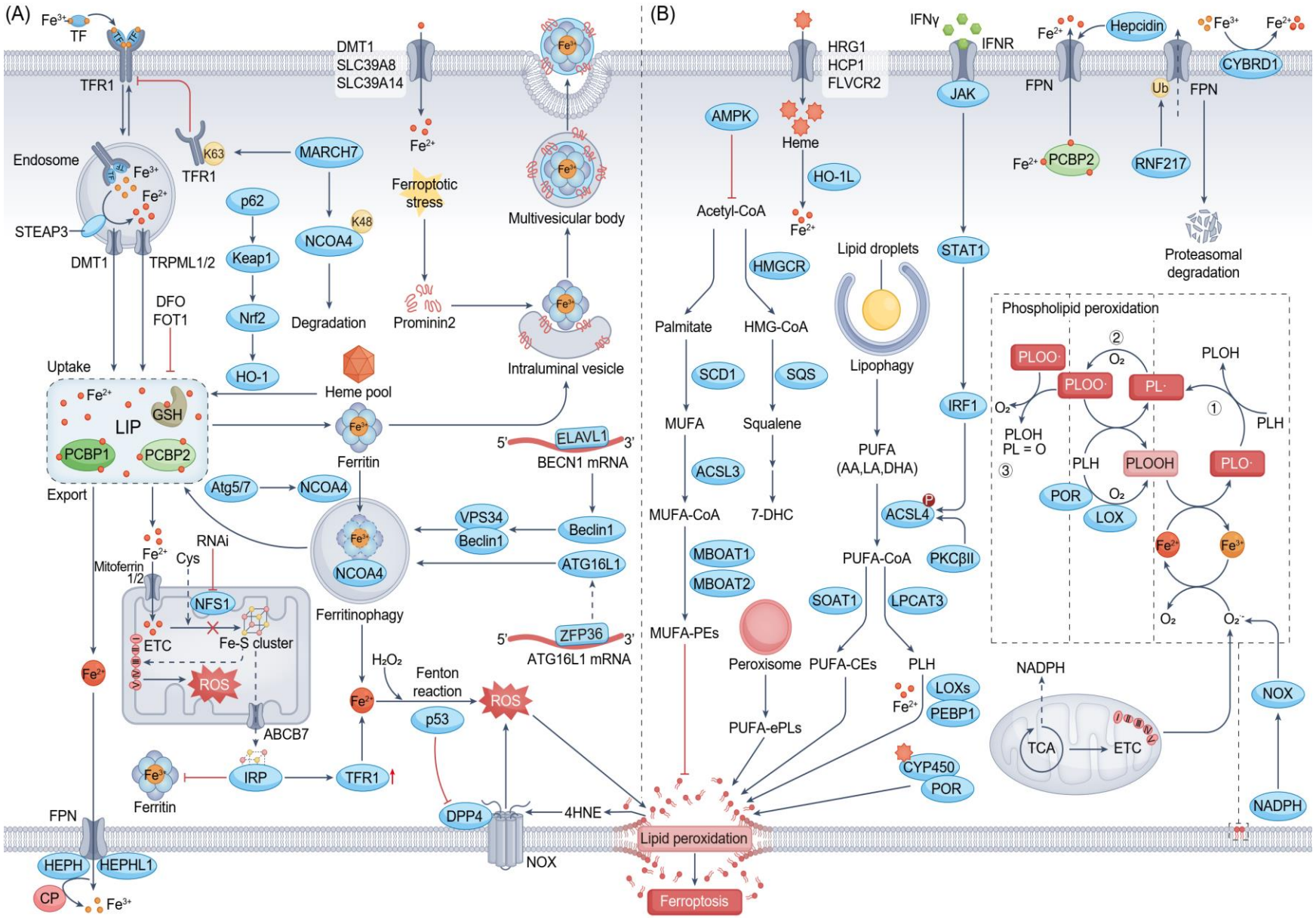


FIGURE 2. Iron metabolism and lipid peroxidation regulatory networks in ferroptosis.

3. FERROPTOSIS: IRON, LIPIDS, AND REDOX

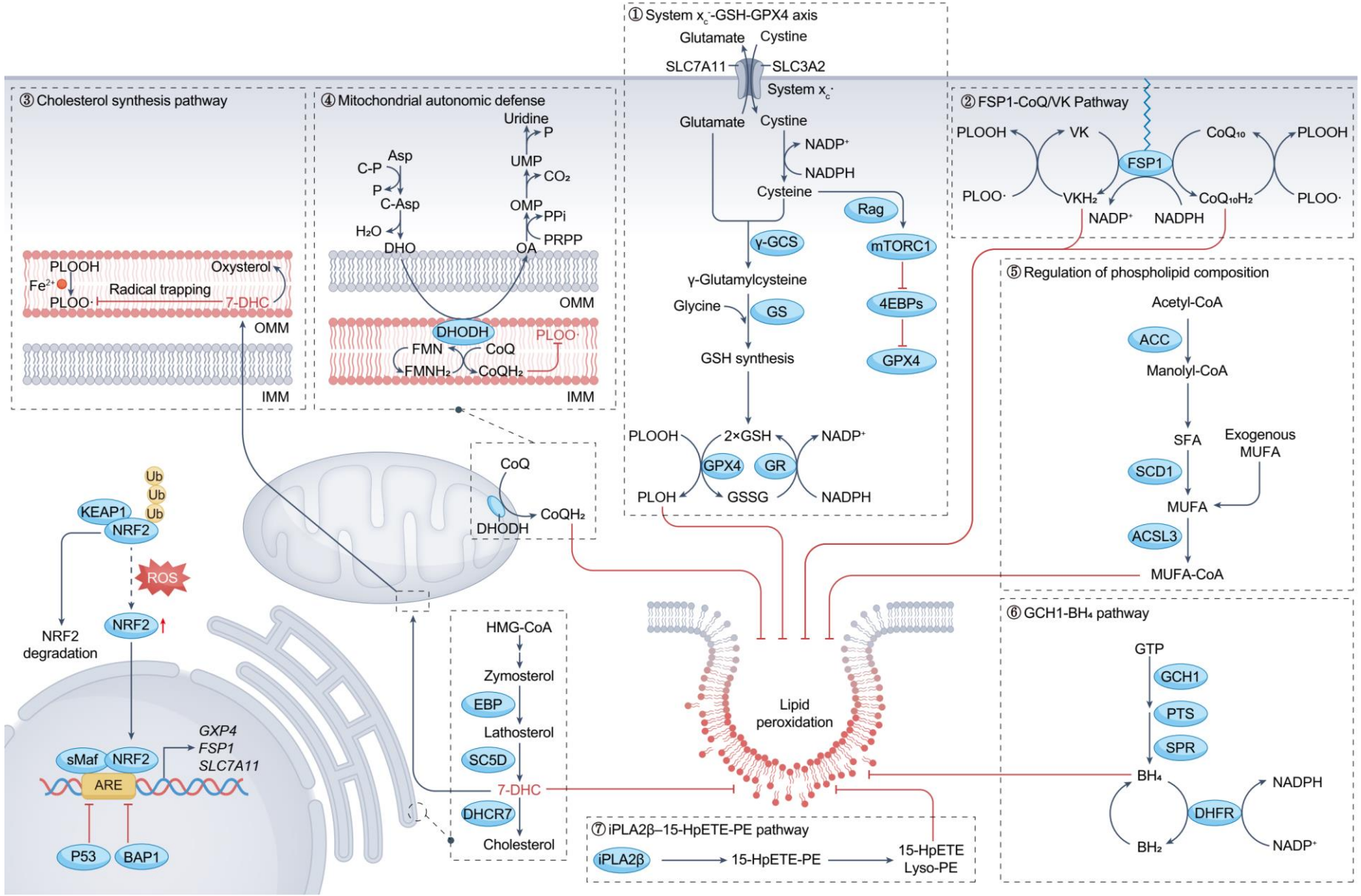


FIGURE 3. Compartmentalized redox defense network against ferroptosis.

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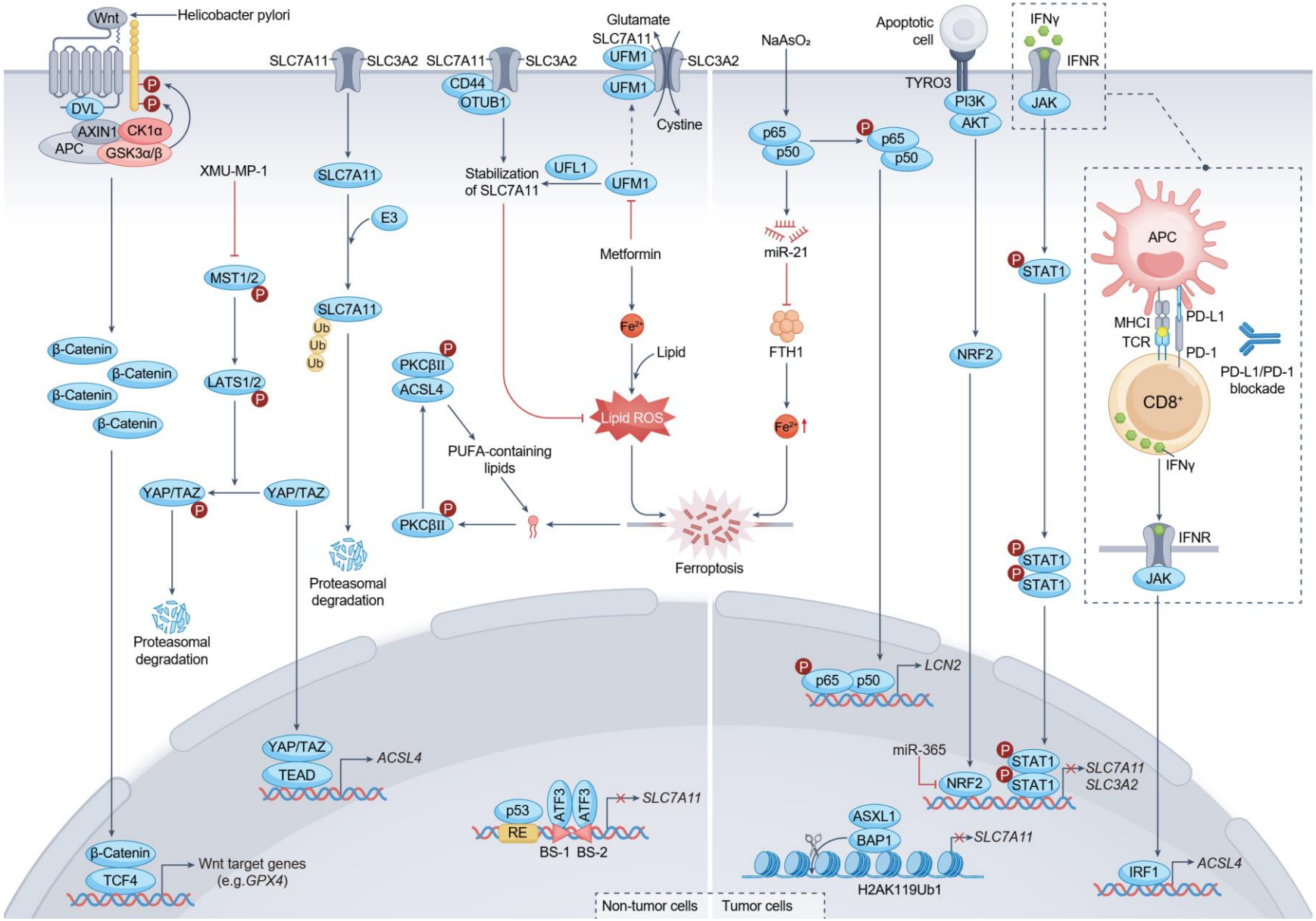

FIGURE 4. Hierarchical regulation of ferroptotic thresholds via epigenetic and post-translational modulation.

4. CUPROPTOSIS: BIOENERGETIC COLLAPSE AND PROTEOTOXICITY

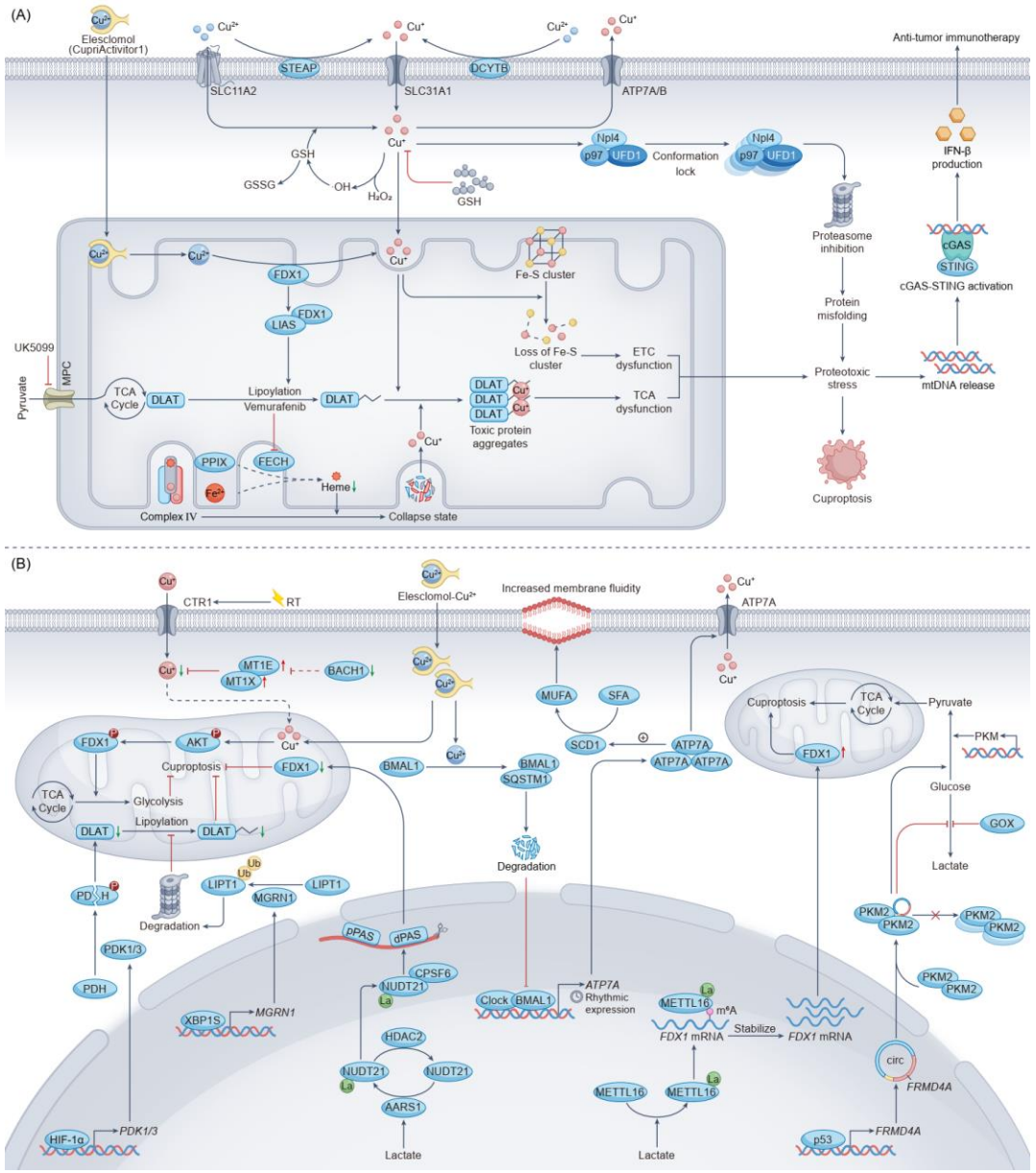

FIGURE 5. Molecular architecture and metabolic gating of cuproptosis.

4. CUPROPTOSIS: BIOENERGETIC COLLAPSE AND PROTEOTOXICITY

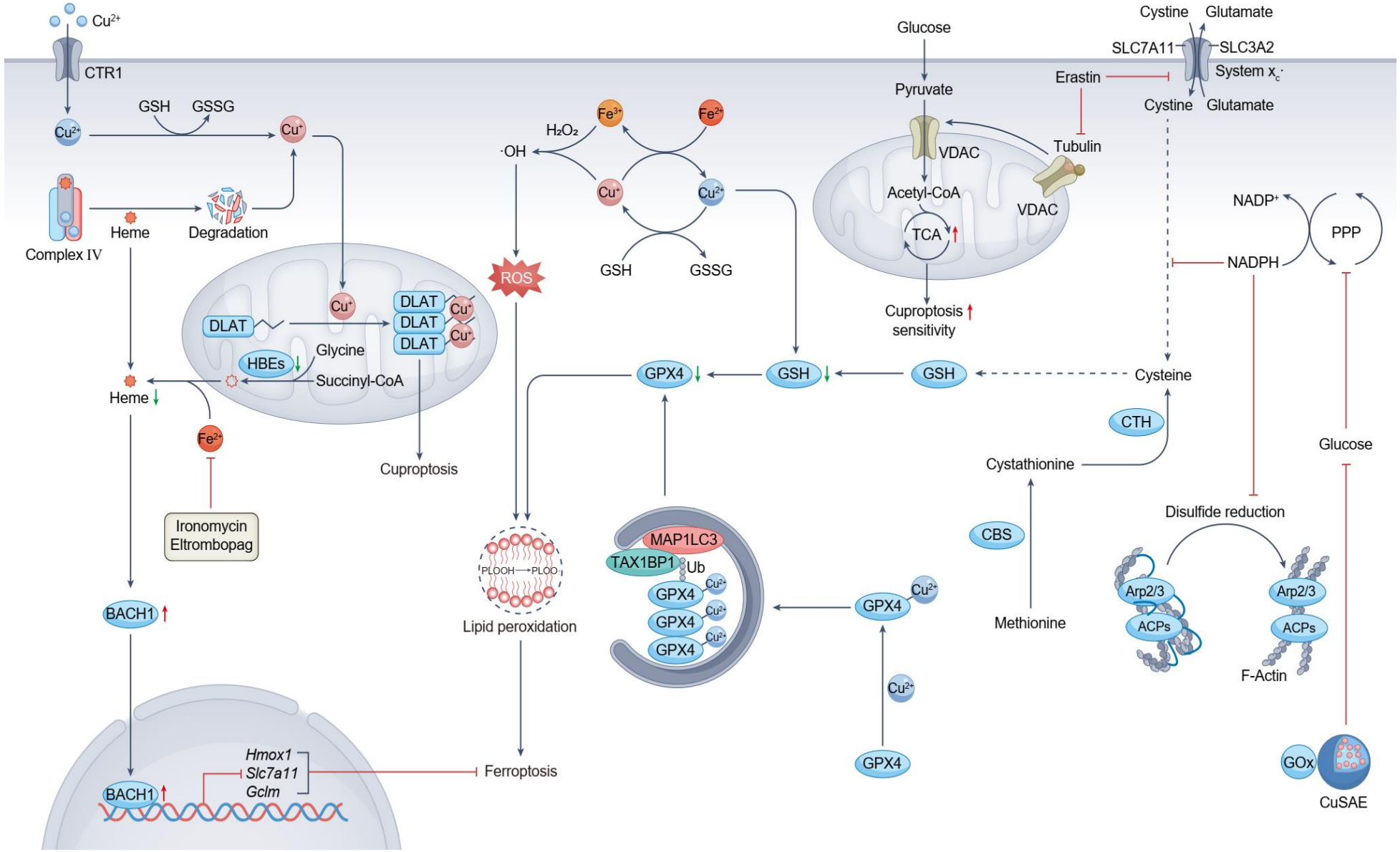

FIGURE 6. Mechanistic crosstalk among cuproptosis, ferroptosis, and metabolic regulation.

5. EMERGING METAL-DRIVEN LETHAL MODALITIES

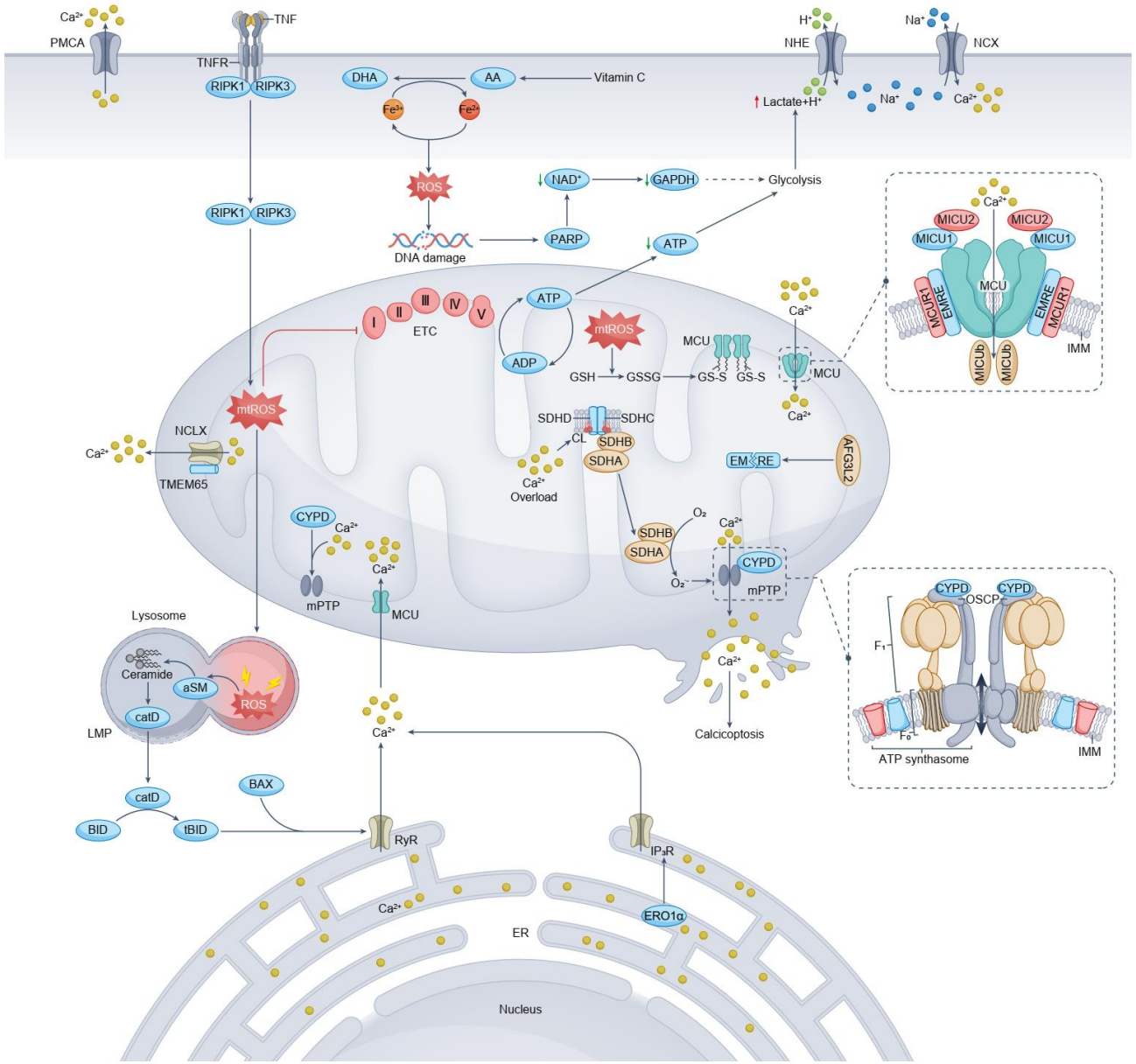

FIGURE 7. Molecular architecture of calcicoptosis driven by calcium dysregulation.

5. EMERGING METAL-DRIVEN LETHAL MODALITIES

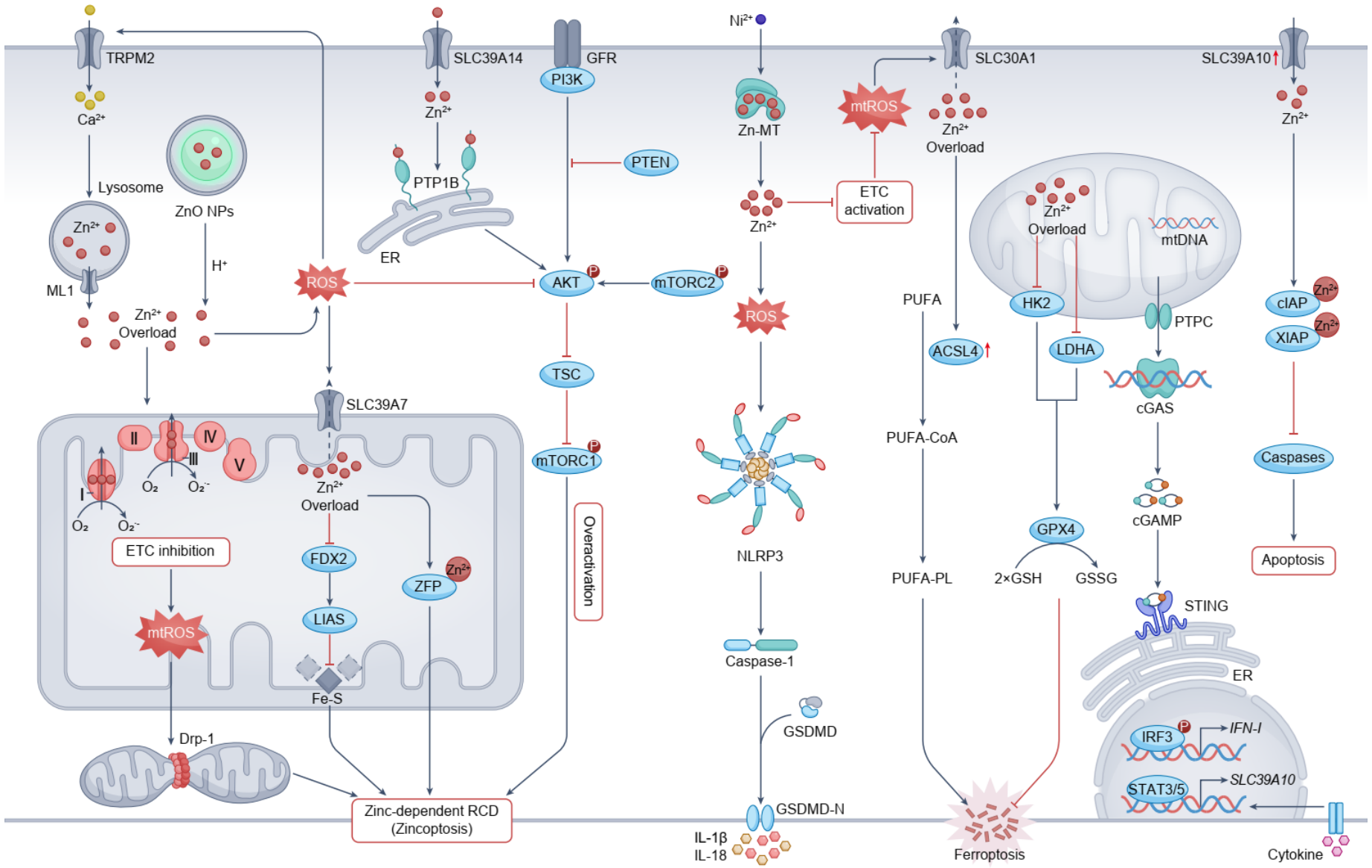

FIGURE 8. Molecular architecture of zinc-mediated cytotoxicity and zincoptosis-liked cell death.

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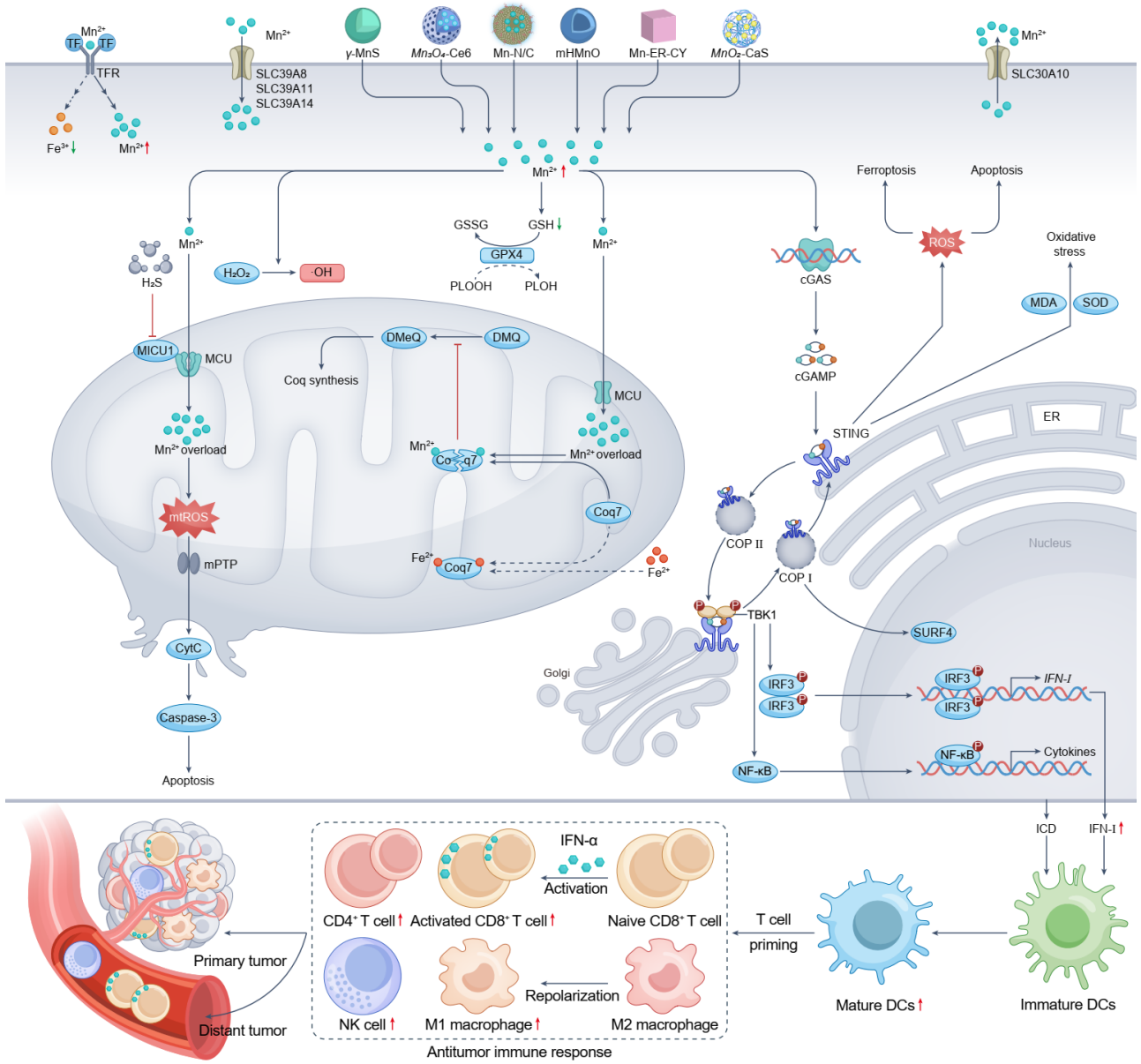

FIGURE 9. Mechanisms of manganese-triggered cytotoxicity and systemic immunomodulation.

5. EMERGING METAL-DRIVEN LETHAL MODALITIES

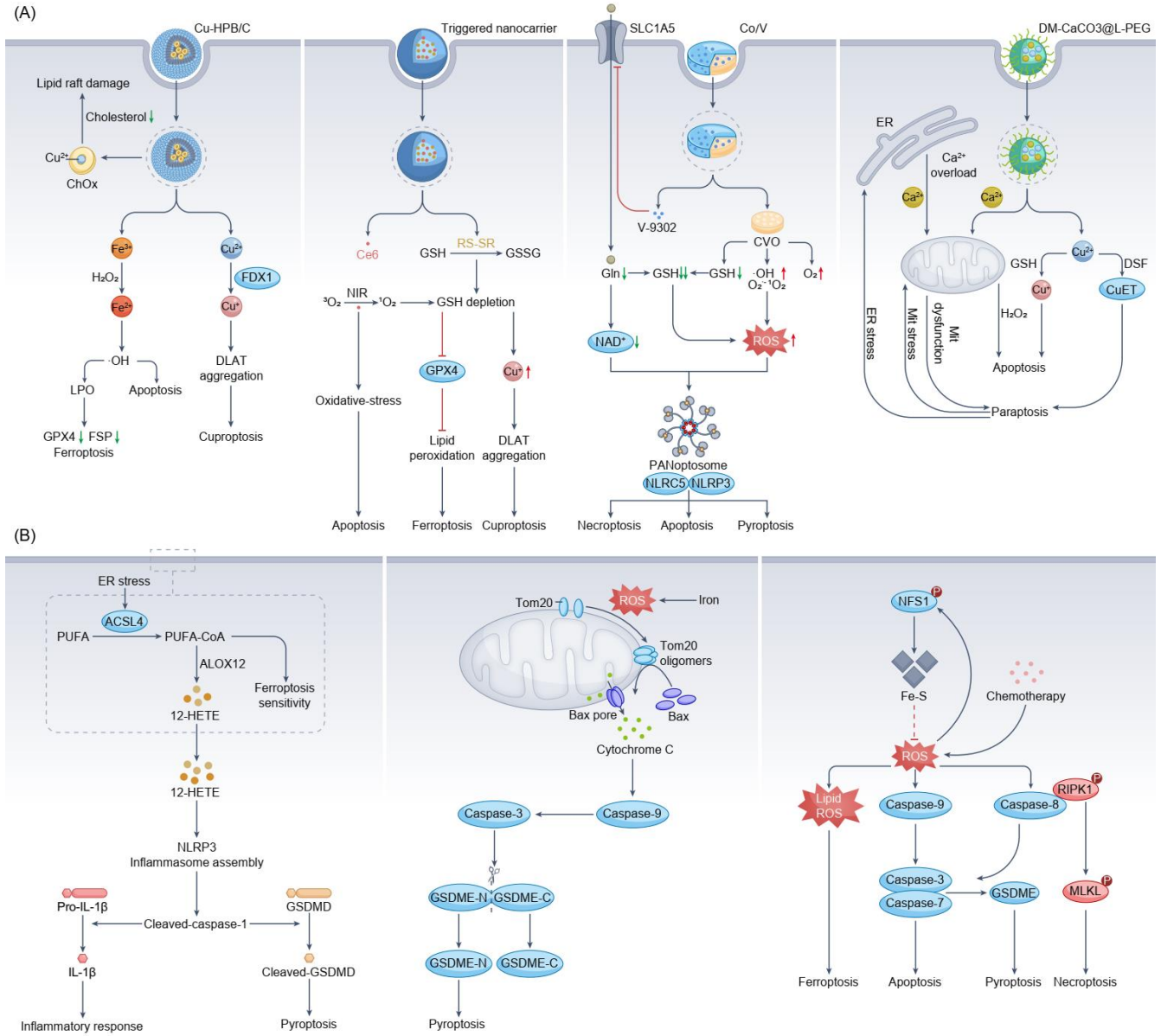

FIGURE 10. *In vivo* crosstalk and metal-dependent PANoptosis.

6. BIDIRECTIONAL THERAPEUTICS AND CLINICAL TRANSLATION

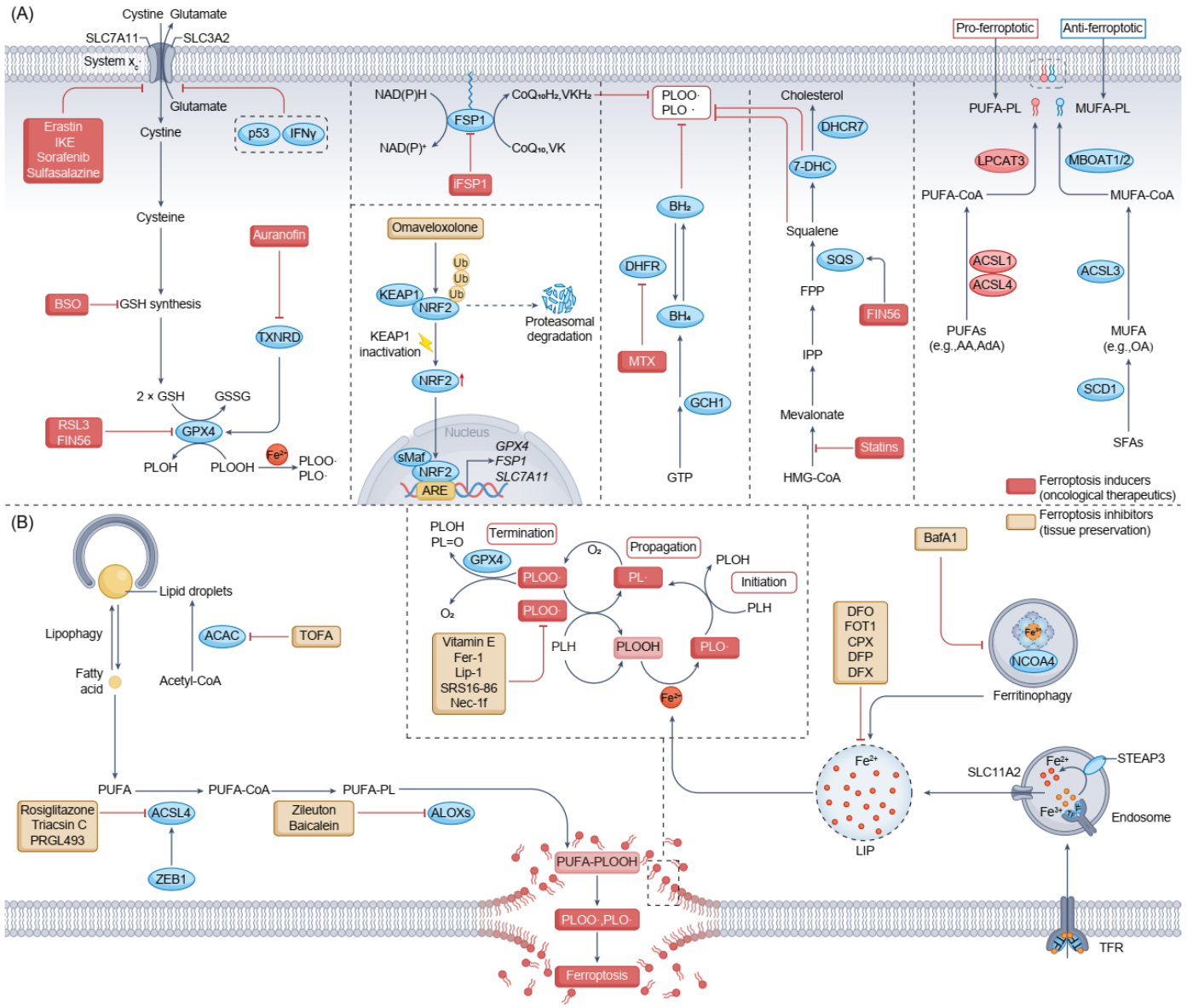

FIGURE 11. Therapeutic modulation of ferroptosis for oncological synthetic lethality and tissue preservation.

7. BIORESPONSIVE NANOMEDICINE AND SPATIOTEMPORAL DELIVERY

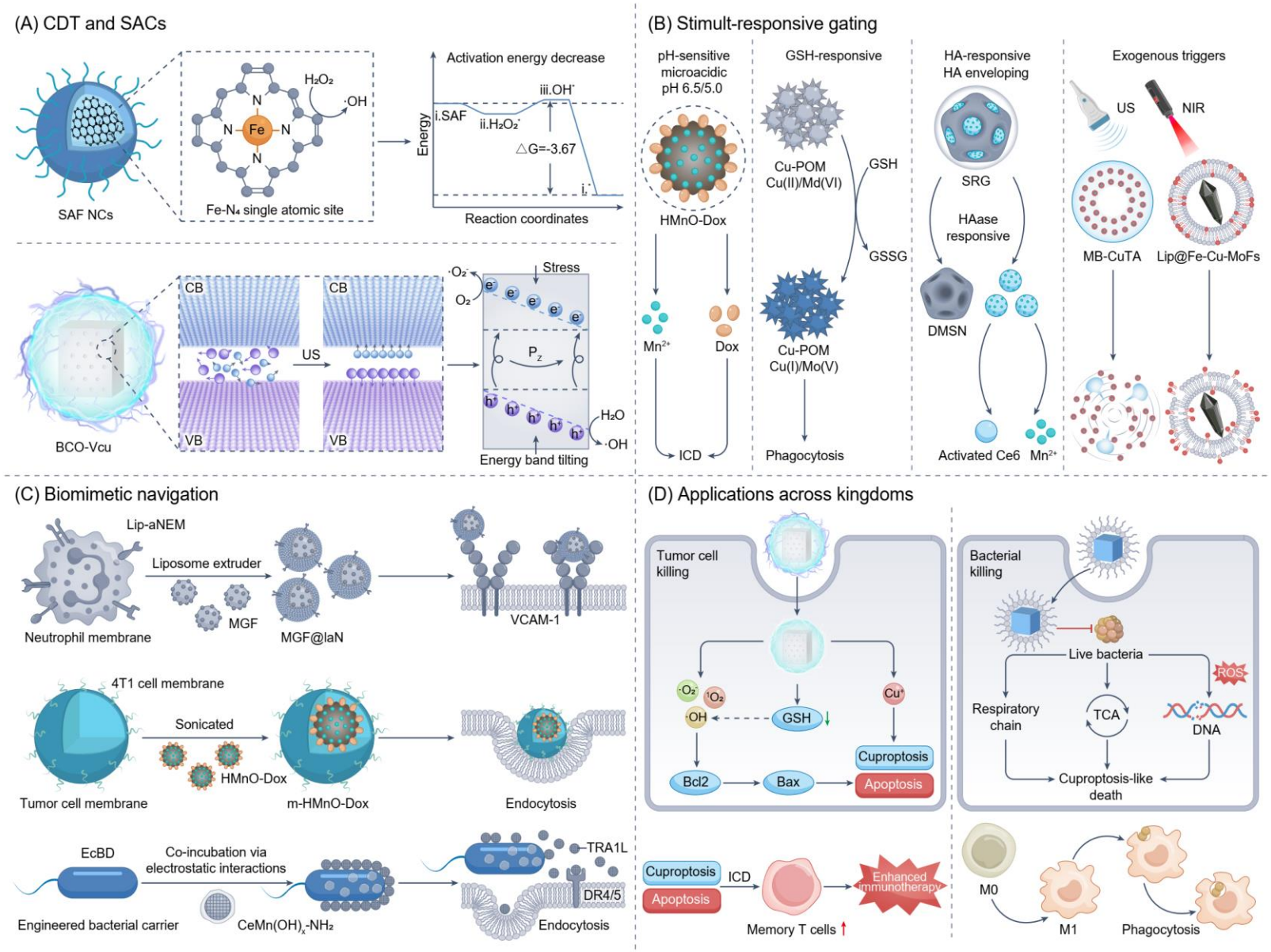

FIGURE 12. Bioresponsive nanomedicine and spatiotemporal delivery.

8. SYSTEMIC IMMUNE REMODELING IN METALLOIMMUNOTHERAPY

❑ Immunogenic cell death and sterile inflammation

Metals promote the release of damage-associated molecular patterns (DAMPs), exerting a dual effect that drives both local anti-tumor immunity and systemic pathogenic sterile inflammation.

❑ Manganese-driven cGAS-STING activation

Manganese activates the cGAS-STING pathway to enhance anti-tumor immunity; however, manganese overload can lead to pathological neurotoxicity.

❑ Synergizing ICB and modulating systemic autoimmunity

Metals remodel the tumor microenvironment to synergize with immune checkpoint blockade (ICB) therapies, aiming to strike a balance between anti-tumor efficacy and systemic immune tolerance.

9. CRITICAL ANALYSIS AND FUTURE PERSPECTIVES

❑ The challenge of systemic toxicity and selectivity

Narrow therapeutic window: Targeting conserved mechanisms frequently leads to severe off-target toxicity in normal organs.

Biomarker dependency: The precise screening and stratification of patients who will benefit from treatment strictly relies on specific biomarkers.

Targeted delivery: There is an urgent need for nanotechnological breakthroughs to overcome microenvironmental barriers and achieve precise targeted delivery.

❑ Pharmacological, manufacturing, and diagnostic hurdles

Druggability challenges: Small-molecule probes often exhibit poor pharmacokinetics, while smart nanomedicines face significant bottlenecks in scale-up manufacturing.
Lack of *in vivo* diagnostics: There is a critical shortage of validated, non-invasive, and highly specific biomarkers for *in vivo* applications.
***In vitro-in vivo* translational disparities:** The complex metabolic environment *in vivo* frequently induces therapeutic tolerance, a phenomenon that is highly challenging to recapitulate in *in vitro* models.

10. CONCLUSION

Metal-dependent RCD reveals complex mechanistic networks spanning from lipid peroxidation to bioenergetic collapse, providing bidirectional translational strategies for targeted tumor eradication and the protection of vulnerable tissues. Building upon this, this review proposes a novel interdisciplinary theoretical framework encompassing Ferrology, Zincology, and Cuprology. By systematically integrating elemental metabolic biology with programmed cell death research, this framework aims to overcome current translational bottlenecks and propel elemental science fully into the era of precision medicine.

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