Photo-enhanced delivery of synergistic ferroptosis inducers for anti-cancer immunotherapy by photoresponsive nanocomplexes

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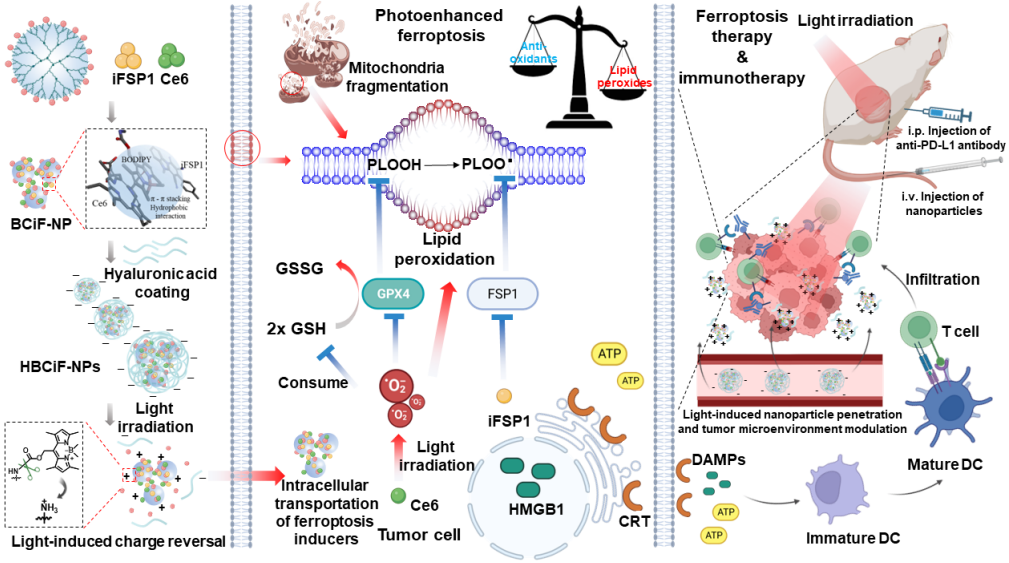
Ferroptosis showed great potential for cancer therapy. In recent years, ferroptosis is associated with photodynamic therapy (PDT) because PDT is proved to downregulate glutathione peroxidase 4 (GPX4), consume glutathione (GSH), and promote lipid peroxide accumulation. Traditionally, ferroptosis was considered to be prevented by only GPX4. Nevertheless, it is newly reported that ferroptosis suppressor protein 1 also plays an important role in lipid peroxide elimination independently. To enhance ferroptosis for anti-cancer therapy, herein, a novel strategy was put forward to inhibit GPX4 and FSP1 by the co-delivery of chlorin e6 (Ce6) and the inhibitor of FSP1 (iFSP1). For targeted delivery, a photo-responsive nanosystem, self-assembled from BODIPY-modified PAMAM (BMP), was used to encapsulate iFSP1 and Ce6. Such strategy showed high-performance ferroptosis and immunogenic cell death (ICD) induction *in vitro* and *in vivo*, thereby activating the immune system and increasing CD8+ T cell tumor infiltration. Importantly, anti-PD-L1 immunotherapy was enhanced by the nanoplatform, suggesting the great potential of photo-enhanced synergistic induction of ferroptosis by the photoresponsive nanocomplexes in cancer immunotherapy.



Scheme 1 Combination therapy of light-controlled ferroptosis and immune checkpoint blockade. Light irradiation triggers charge reversal of HBCiF-NPs, thereby promoting intracellular uptake of ferroptosis inducers. Subsequently, photodynamic therapy causes ROS accumulation and lipid peroxidation inside cells, whose protection function can be inhibited by iFSP1. Ferroptosis further promotes immunogenic cell death and activates the immune system against cancer, which is reinforced by anti-PD-L1 therapy.

References

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