News Release

Title

Lysosomal nitric oxide determines transition from autophagy to ferroptosis after exposure to plasma-activated Ringer's lactate

Key Points

- **Non-thermal plasma is a novel technology to load oxidative stress**
- **Plasma activated Ringer's lactate specifically kills malignant mesothelioma cells via ferroptosis**
- **Lysosomal nitric oxide determines transition from autophagy to ferroptosis**

Summary

Non-thermal plasma (NTP), an engineered technology to generate reactive species, induces ferroptosis and/or apoptosis specifically in various-type cancer cells. NTP-activated Ringer's lactate (PAL) is another modality for cancer therapy at preclinical stage. Here we found that PAL induces selective ferroptosis of malignant mesothelioma (MM) cells, where non-targeted metabolome screening identified upregulated citrulline-nitric oxide (.NO) cycle as a PAL target. .NO probe detected biphasic peaks transiently at PAL exposure with time-dependent increase, which was responsible for inducible .NO synthase (iNOS) overexpression through NF-κB activation. .NO and lipid peroxidation occupied lysosomes as a major compartment with increased TFEB expression. Not only ferrostatin-1 but inhibitors for .NO and/or iNOS could suppress this ferroptosis. PAL-induced ferroptosis accompanied autophagic process in the early phase, as demonstrated by an increase in essential amino acids, LC3B-II, p62 and LAMP1, transforming into the later phase with boosted lipid peroxidation. Therefore, .NO-mediated lysosomal impairment is central in PAL-induced ferroptosis.

Research Background

Recently, ferroptosis is considered as a biomarker of effectiveness in cancer therapy. Cancer cells are intrinsically rich in catalytic Fe(II) for proliferation, which is now targeted to specifically kill them. Ferroptosis is catalytic Fe(II)-dependent regulated necrosis and immunogenic in comparison to apoptosis. Malignant mesothelioma (MM) is an aggressive cancer of somatic cavities in association with asbestos exposure. Current standard therapeutic regimens for MM have been dismal due to the difficulty in early diagnosis and operational access. Non-thermal plasma (NTP) is an engineered technology to generate various reactive species at near body temperature. Here we used NTP-activated Ringer's lactate (PAL) to MM cells, considering flexible clinical applications in somatic cavities, and performed comprehensive metabolomic screening in search of the responsible chemical reactions.

Research Results

NTP-activated Ringer's lactate (PAL) induces ferroptosis selectively in MM cells. Metabolome analysis identified both similarities to and differences from erastin-induced ferroptosis. PAL supplies exogenous nitric oxide (.NO) at first and later endogenous .NO in MM cells. .NO plays a major role in PAL-induced ferroptosis. .NO induces lysosome-dependent autophagy at the early phase after PAL exposure. P62-regulated lipid peroxidation leads to ferroptosis at the late phase after PAL exposure.

Research Summary and Future Perspective

we demonstrated for the first time that PAL induces ferroptosis in MM cells via lysosomal .NO-derived oxidants-mediated lipid peroxidation. Our results point to an important scenario that .NO is a potential regulator of ferroptosis through autophagic processes, which may be interpreted as lysophagy failure. Moreover, the presence of a threshold from the early autophagic phase into the late ferroptotic phase elicited by PAL exposure provides us with a novel understanding toward oxidative stress-dependent cancer therapies. PAL can be a burgeoning ferroptosis-directed cancer therapy, flexibly combined with other modalities.

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