Mechanisms of resistance to ferroptotic cell death : the impact of bioenergetic pathways

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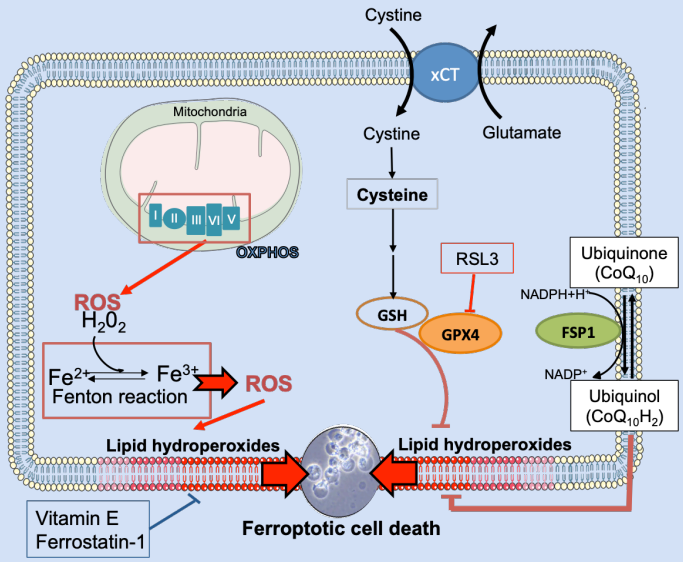
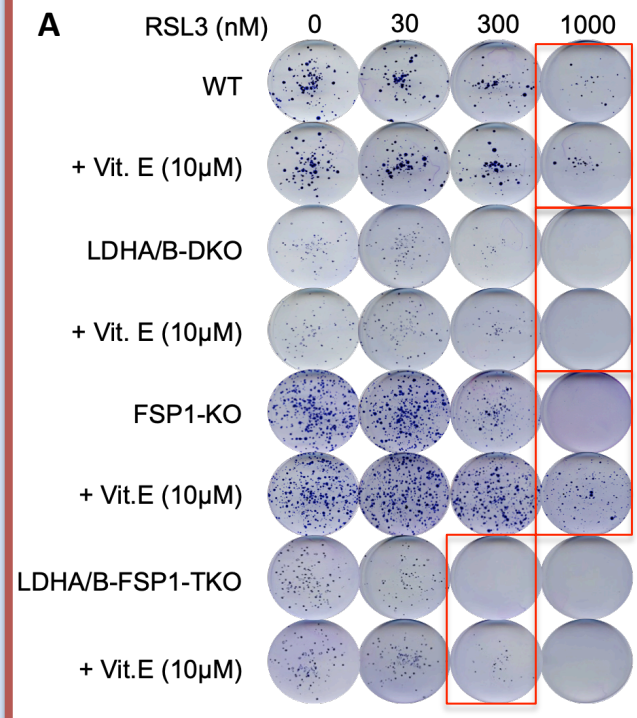
Introduction

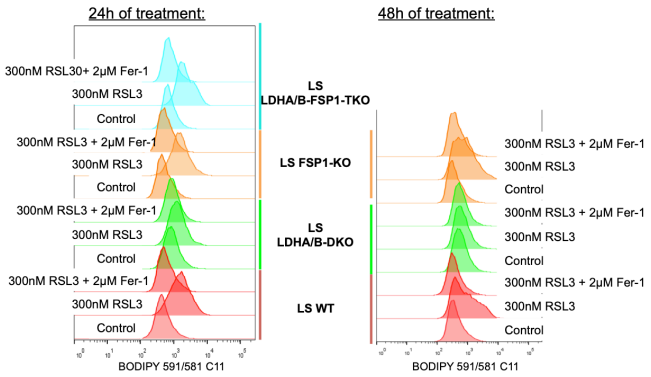
Ferroptotic-cell death is an iron-dependent hydroperoxidation of polyunsaturated membrane Phospholipids (PUFA). It is prevented by two enzymes : the glutathione peroxidase 4 (GPX4) and the Ubiquinol (CoQ_{10}) reductase re-named FSP1 for Ferroptosis Supressor Protein 1 (FSP1).

Although ferroptosis seems to be general mechanisms of all mammalian cells, the sensitivity toward this type of cell death varies significantly between different cell lines. Considering redox nature of the ferroptotic process as well as the effect that energy metabolism, oxidative metabolism (OXPHOS) in the first place, has on the redox homeostasis of the cell; we wanted to investigate if and how manipulation of the major energy-producing metabolic pathways is connected with the sensitivity to ferroptosis using the CRISPR/Cas9 technique to switch the fermentative glycolysis to the OXPHOS metabolism (lactate dehydrogenase A and B knock out; LDHA/B-DKO) in ferroptosis resistant colon adenocarcinoma cells, LS174T.



Cumulative LDHA/B and FSP1 deletion induce ferroptosis sensitivity in LS174T cells





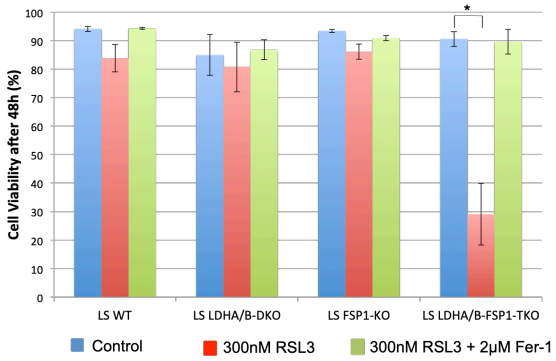


Figure 1: (A) Sensitivity of the LS174T WT, LDHA/B-DKO, FSP1-KO and LDHA/B-FSP1-TKO cells toward GPX4 inhibition with different concentration of RSL3. **(B)** Lipid hydroperoxide accumulation is detected in all the cell lines upon treatment with 300nM RSL3 for 24h, and rescued by 2µM Ferostatin-1 (Fer-1). Interestingly, after 48h of treatment, lipid hydroperoxide accumulation was not detected in none of the cell lines except LDHA/B-FSP1-TKO, **(C)** which succumbed to ferroptotic cell death at this time point.

Conclusion

- FSP1 plays a key role in ferroptosis resistance of the cancer line LS174T
- Bioenergetic switch to OXPHOS and FSP1-KO show cumulative effect on sensitivity of LS 174 cells to ferroptosis