Mechanisms of cell death induced by proteostasis disruptors in Multiple myeloma cells: Ferroptosis and immunogenic cell death

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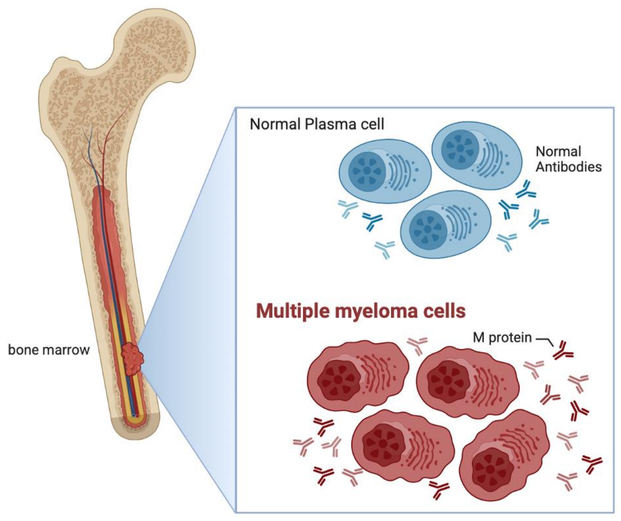
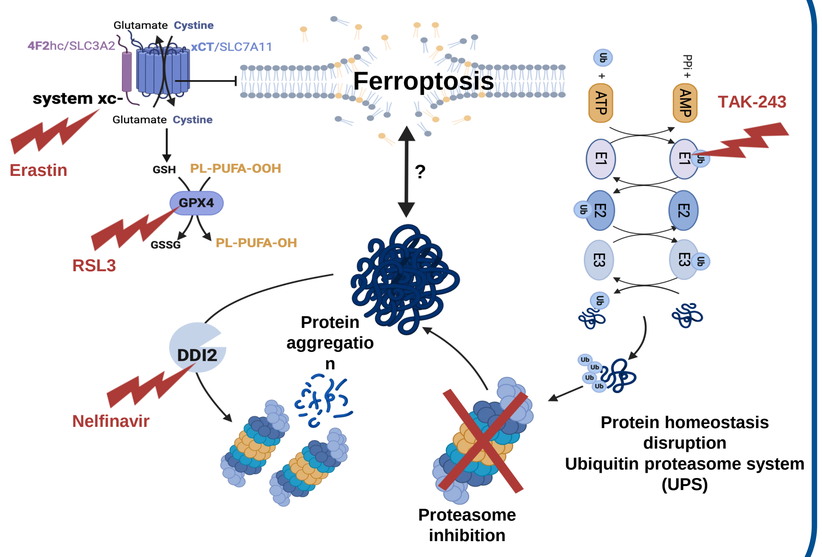
BACKGROUND



Most multiple myeloma (MM) patients develop resistance under proteasome inhibitor treatment.

New therapeutic targets: Induction of ferroptosis as an alternative cell death mechanism.

Can proteotoxic stress trigger ferroptosis and kill MM cells?

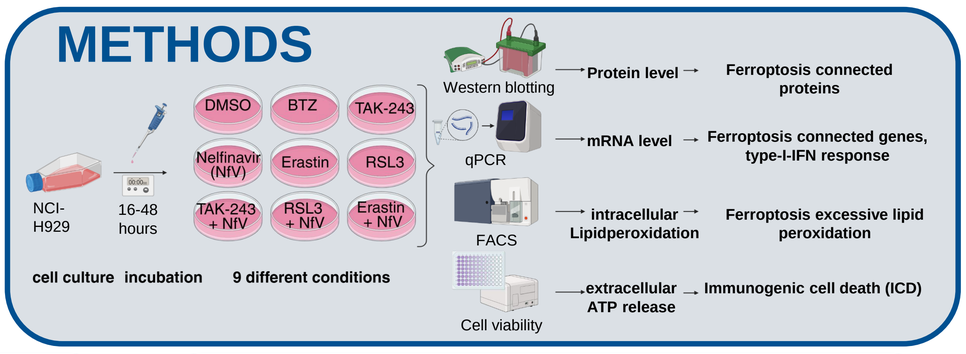


HYPOTHESIS & AIMS

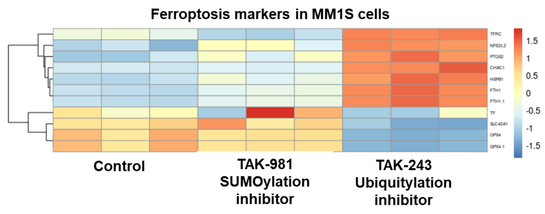
What has been published: The inhibition of DDI2 by Nelfinavir sensitizes cells to ferroptosis and induces immunogenic cell death (ICD) in MM cells.

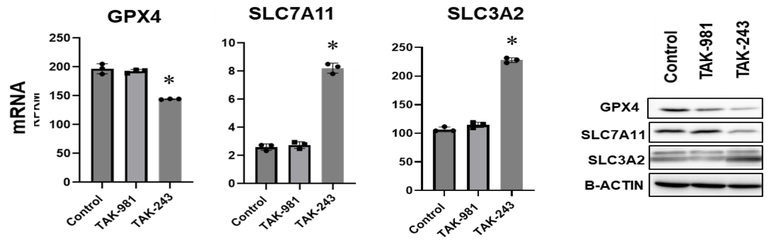
We investigated the effect of proteostasis disruptors (TAK-243 and Nelfinavir) on **ferroptosis, type-I-interferon-(IFN) response and ICD.**

METHODS

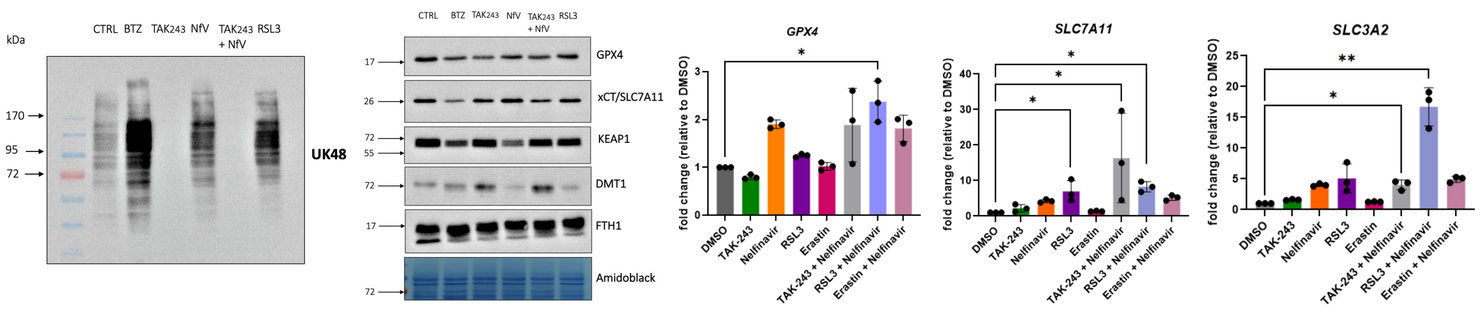


Crosstalk – ferroptosis and proteostasis



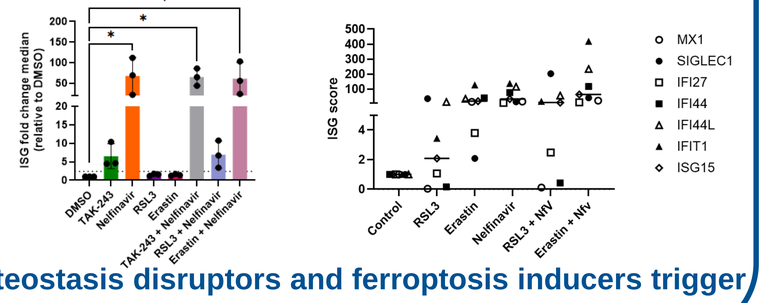


Inhibition of Ubiquitylation but not SUMOylation disturbs ferroptosis markers.



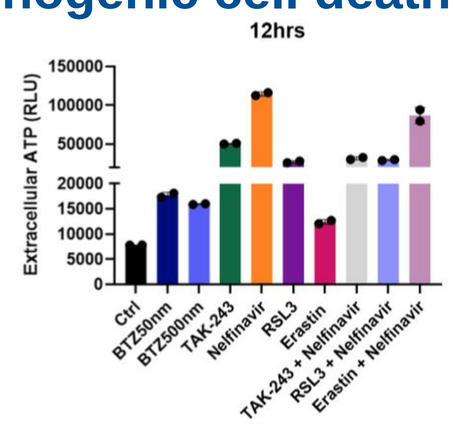
Ferroptosis inducers (RSL3) can induce protetoxic stress. Proteostasis disruptors (TAK-243 and Nelfinavir) affect ferroptosis connected proteins. Combination treatments activate a compensating mechanism.

Type-I-IFN response



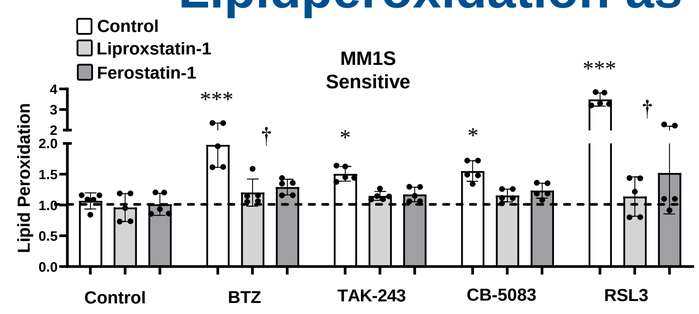
Proteostasis disruptors and ferroptosis inducers trigger type-I-IFN response.

Immunogenic cell death (ICD)

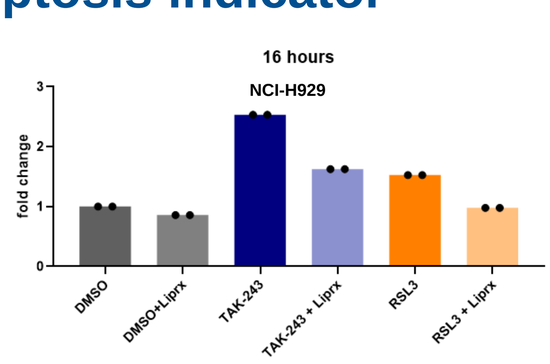


ATP release is time and compound dependent.

Lipidperoxidation as ferroptosis indicator

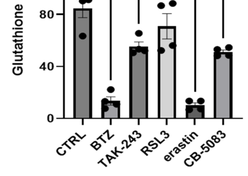


Lipidperoxidation is induced in MM1S cells treated with proteostasis disruptors (BTZ, TAK-243, and CB-5083 (p97/VCP inhibitor). This effect is reversed by ferroptosis inhibitors.



TAK-243 and the combination RSL3+NfV can induce ferroptosis

Intracellular Glutathion



Intracellular glutathione is reduced after exposure to proteostasis disruptors in MM1S.

- The role of ISR kinases in the crosstalk between ferroptosis and protein homeostasis disruptors.
- Time-dependent determination of the effect of RSL3 and Erastin on type-I-IFN response.
- CRISPR/Cas9 screening is planned to unveil the crosstalk between ubiquitin proteasome system (UPS) and ferroptosis.

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