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## The interplay between apoptosis and ferroptosis mediated by ER stress

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### Reply

In our recent article (1), we report that ER stress response plays a pivotal role in the crosstalk between ferroptosis and apoptosis. Dr. Yoshida constructively criticizes that TRAIL treatment alone leads to JC-1 aggregation and combined treatment of TRAIL and erastin results in mitochondrial depolarization which is indicated by an increase in JC-1 fluorescence intensity. Since we used a sublethal dose of TRAIL, the degree of JC-1 aggregation didn't significantly change during treatment with TRAIL alone (Fig. 4C). However, the combined treatment led to significant increased membrane permeability (loss of mitochondrial membrane potential) and consequently less amount of JC-1 aggregates in the mitochondria. Thus, under this promoted apoptotic death condition, we observed an increase in JC-1 fluorescence intensity (retaining its original green fluorescence) (2).

Moreover, Dr. Yoshida suggests several possible mechanisms to maintain the balance between proapoptotic PUMA protein and anti-apoptotic Bcl-2 family proteins to prevent apoptosis during treatment with ferroptotic agent erastin. We agree with Dr. Yoshida's comment. It is possible that imbalance between them occurs during the combined treatment and results in promoting apoptosis. The imbalance is probably due to the reduction of Bcl-2 family proteins through phosphorylated JNK-mediated phosphorylation and subsequent ubiquitination during the combined treatment (3, 4). We also agree with Dr. Yoshida's comment. It is possible that Beclin-1 is a key molecule in the crosstalk between ferroptosis and apoptosis. Akt-mediated dephosphorylation of Beclin-1 at Ser 234/295 may occur and enhance Beclin-1 cleavage and enhance apoptosis during the combined treatment (5). Obviously, these possibilities need to be further examined to understand the role of PUMA in the combinatorial treatment-induced synergistic apoptosis.

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