The anticancer compounds auranofin, TRi-1 and TRi-2 have distinct cytotoxicity profiles with regards to thioredoxin reductase inhibition

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Cancer cells' reliance on the thioredoxin (Trx) and thioredoxin reductase (TrxR) system for sustained proliferation has led to the development of TrxR inhibitors, such as auranofin, TRi-1 and TRi-2, with pronounced anticancer effects and varying target specificity (1). TRi-1 and auranofin additionally create prooxidant TrxR forms known as SecTRAPs, which potentiates their effects. The cellular signaling programs triggered by these inhibitors, however, are still poorly understood. We report three observations regarding the kinetics of intracellular TrxR inhibition, the compounds' cytotoxicity relative to cellular uptake and their broad effects on proteostasis.

Whereas cell death following auranofin treatment is swift, TRi-1 and TRi-2 treatment produces distinctly delayed cytotoxicity (2). Nevertheless, TRi-1 produces the fastest and most pronounced inhibition of TrxR activity which returns to pretreatment levels well before the onset of cell death, likely through Nrf2-mediated compensatory mechanisms. All three compounds deplete TrxR activity but not protein abundance, creating a window for additional cell damage via potential SecTRAPs.

The molecular mechanisms governing the inhibitors' cellular uptake are not known but we have found dose-dependent delayed cytotoxicity seen even with 5-10 min treatment and subsequent compound removal. This suggests rapid uptake before cytotoxicity can be detected. These effects are more prominent for TRi-1, suggesting the importance of distinct uptake and signaling pathways for these inhibitors' activity.

Outlining the differences in the specificity, speed, and uptake of TrxR inhibitors is crucial towards understanding the effects of antioxidant system inhibition and furthering its therapeutic potential.

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