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Recombinant lactaptin analogon RL2 inhibits TRAIL-induced cell death in breast cancer cell lines by mitophagy

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The recombinant analogon of lactaptin (RL2) induces cell death of breast cancer cells, however, the molecular mechanism of RL2 action in breast cancer cells remains unknown. RL2 presents a promising therapeutic for treating breast cancer as a single drug or in a co-treatment with well-known therapeutics. In this study, we have investigated the effects of RL2 on cell death in a co-treatment with TRAIL in MDA-MB 231 and MCF-7 breast carcinoma cells. We have found that RL2 inhibits TRAIL-induced caspase-3/7 and caspase-8 activity as well as cell death upon short-term treatment. Further, RL2 reduced TRAIL-induced DISC (death-inducing signaling complex) formation. Moreover, administration of RL2 resulted in mitophagy induction at the early time intervals as well as the upregulation of anti-apoptotic proteins Bcl-2 and Bcl-xL. Additionally, RL2 treatment led to downregulation of the pro-apoptotic protein Bax and components of the TRAIL DISC, in particular procaspase-8 and FADD. Observed effects might contribute to down modulation of the TRAIL response upon the short-term treatment. Furthermore, our study has demonstrated two opposite effects of TRAIL and RL2 co-treatment: it blocks cell death upon short-term co-stimulation and increases cell death upon long-term treatment. Our findings have important implications for cancer therapy, especially for combinatorial treatments.