Selective disruption of respiratory supercomplexes as a new strategy to eradicate Her2high breast cancer

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Expression of the Her2 oncogene in breast cancer is associated with resistance to treatment, and Her2 may regulate bioenergetics. Therefore, we investigated whether disruption of the electron transport chain is a viable strategy to eliminate $Her2^{high}$ disease. We demonstrate that $Her2^{high}$ cells and tumors have increased assembly of respiratory supercomplexes and increased complex I-driven respiration *in vitro* and *in vivo*. They are also highly sensitive to MitoTam. a novel mitochondrial-targeted derivative of tamoxifen. Unlike tamoxifen, MitoTam efficiently eradicates experimental $Her2^{high}$ tumors without systemic toxicity. Mechanistically, MitoTam inhibits complex I-driven respiration and disrupts respiratory supercomplexes in $Her2^{-high}$ background *in vitro* and *in vivo*, leading to elevated reactive oxygen species production and cell death. Intriguingly, higher sensitivity of $Her2^{high}$ cells to MitoTam is dependent on the mitochondrial fraction of Her2. This shows that oncogenes such as Her2 can restructure electron transport chain, creating a previously unrecognized therapeutic vulnerability exploitable by supercomplex-desrupting agents such as MitoTam.