ABSTRACT (EN)

Tumours are heterogeneous and consist of multiple populations of cells. The population of cells with tumour-initiating capability is known as cancer stem cells (CSC). Cells with increased stemness properties and elevated resistance to anti-cancer treatment have been shown to be highly affected upon decline of mitochondrial respiration, linking the concept of CSCs to deregulated bioenergetics. Consistently, functional electron transport chain (ETC) is crucial in tumorigenesis. Expression of *HER2* oncogene, associated with resistance to treatment in breast cancer, has been connected with regulation of mitochondrial function. We therefore investigated the possibility that manipulation of mitochondrial bioenergetics via disruption of ETC eliminates the conventional therapy-resistant populations of tumour, such as CSCs and $HER2^{high}$ cells.

We demonstrate that $HER2^{high}$ cells and tumours have increased complex I-driven respiration and increased assembly of respiratory supercomplexes (SC). These cells are highly sensitive to MitoTam, a novel mitochondria-targeted derivative of tamoxifen, acting as a CI inhibitor and SC disruptor. MitoTam was able to overcome resistance to tamoxifen, and to reduce the metastatic potential of $HER2^{high}$ cells. Higher sensitivity of $HER2^{high}$ cells to MitoTam is dependent on the mitochondrial fraction of HER2. Another ETC disrupting anti-cancer agent MitoVES efficiently eliminates breast CSCs and, via suppression of tryptophan uptake machinery in CSC, exposes CSCs to the immune system.

In summary, we show that mitochondrially targeted agents directed at ETC act by several mechanisms that in combination are able to overcome resistance of breast cancer to therapy.