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Mcl-1 confers protection of Her2-positive breast cancer cells to hypoxia: Therapeutic implications

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Despite unprecedented advances in BC therapy during the last two decades it remains the most common cause of cancer-related death in women. Therefore continuous research to further enhance our knowledge of BC pathogenesis and to develop derived targeted therapies is urgently needed.

The present study conducted as part of my doctoral thesis shows for the first time that the anti-apoptotic Bcl-2 family member Mcl-1 plays a critical role in the survival of BC cells in general, and Her2-positive BC cells in particular, under hypoxic conditions.

I demonstrate for the first time a strong correlation between high Mcl-1 protein levels and hypoxia, predominantly in Her2-positive BC cells. Surprisingly, genetic depletion of Mcl-1 decreased Her2 and Hif-1α levels followed by inhibition of BC cell survival. In contrast, Mcl-1 protein levels were not downregulated after genetic depletion of Her2 indicating a regulatory role of Mcl-1 upstream of Her2. Indeed, Mcl-1 and Her2 co-localize within the mitochondrial fraction and form a Mcl-1/Her2- protein complex. Similar to genetically targeting Mcl-1 the novel small molecule Mcl-1 inhibitor EU-5346 induced cell death and decreased spheroid formation in Her2-positive BC cells. Of interest, EU-5346 induced ubiquitination of Mcl-1- bound Her2 demonstrating a previously unknown role for Mcl-1 to stabilize Her2 protein levels. Importantly, targeting Mcl-1 was also active in Her2-positive BC cells resistant to Her2 inhibitors, primary BC cells collected from a patient with resistant against Her2 inhibitor, a brain-primed Her2-positive cell line as well as in Luminal A and TNBC cells.

As conclusion, my results demonstrate for the first time a critical role of Mcl-1 in BC cell proliferation and survival in general, and Her2-positive BC cells in particular, under hypoxic conditions. Moreover, my data strongly support the therapeutic potential of targeting Mcl-1 to not only enhance antitumor activity of Her2-positive inhibitors but also to overcome resistance against these agents in Her2-positive BC cells.