Abstract

Breast cancer is a common malignant disease affecting millions of women worldwide. Amplification of HER2 oncogene, a tyrosine kinase receptor, in breast cancer allows application of targeted therapy, but approximately one third of patients develop resistance to treatment. Relocalization of HER2 from the plasma membrane into the mitochondria was found and suggested as one of the potential causes of such resistance. Here we document that the function of mitochondrial HER2 is distinct from that of HER2 in the plasma membrane. Mitochondrial HER2 enhances cancer cell energetic metabolism, proliferation and migration *in vitro*, and tumour formation *in vivo* in mice correlating with elevated level of ROS signalling. The kinase activity of mitochondrial HER2 is unaffected, therefore I investigated its role in mitochondrial HER2 function. Moderate, endogenous levels of the kinase activity of mitochondrial HER2 drive pro-tumorigenic properties of breast cancer cells, while constitutive kinase activity sensitizes these cells to cell death and attenuates tumour formation in animal models. On the other hand, impairment of kinase activity due to mutation in the ATP binding site of mitochondrial HER2 supports adherence-independent growth *in vitro* and tumor growth *in vivo*. We propose that HER2 function in mitochondria is partially kinase-dependent, but mitochondrial HER2 also contributes by an additional unidentified mechanism that provides advantage for kinase dead mutants in tumour formation. Last but not least, the kinase activity of mitochondrial HER2 sensitizes breast cancer cells to novel anti-cancer agent MitoTam that is now in clinical trials.