# Letter to the editor: "Doxorubicin and ErbB2 overexpression: another piece in the mitochondrial jigsaw"

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**Doxorubicin and ErbB2 overexpression: another piece in the mitochondrial jigsaw**

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We read with great interest the article published by Belmonte et al (1) which results were discussed by P. Rocic in an Editorial focus (2). The authors highlight for the first time the key-role of ErbB2 upregulation on the redox dysregulation involved in doxorubicin (DOX) cardiotoxicity. Interestingly, mice overexpressing ErbB2 displayed a « cardioprotected » phenotype with lower mitochondrial reactive oxygen species (ROS) levels and increased expression/activity of cardiac anti-oxidant enzymes, probably through c-Abl and Arg nonreceptor tyrosine kinases overexpression.

These results add another piece in the complex jigsaw of mitochondrial interactions between anthracyclines and trastuzumab (TRZ). Indeed, TRZ, a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER 2 or ErbB2) protein, has been reported to induce an unexpected incidence of cardiac side-effects (3), especially when administrated following anthracyclines treatment. Therefore, TRZ is now believed to potentiate the cardiotoxic effects of anthracyclines (4). In *in vivo* murine models that combined DOX with TRZ, a synergetic interaction was reported, leading to increased deterioration in cardiac function and cardiomyocyte apoptosis (5). In addition, *in vitro* in cardiomyocytes, HER2 blockage was accompanied by apoptotic processes and by an increase in oxidative stress level (4).

In the light of these findings, the authors may have performed an *in vivo* model of DOX cardiotoxicity in order to confirm that the cardioprotection afforded by selective cardiac ErbB2 overexpression through ROS production decrease. Moreover, evaluating the effects of the administration of TRZ (6) or of a distinct ErbB2 blocker (7) could have confirmed this hypothesis, if the benefits of the knockout phenotype had been reversed by ErbB2 inhibitors.

The second part of our reflexion is related to the crucial role of a transition metal, iron, in the ROS production following anthracyclines administration (8, 9). Thomas and Aust showed that DOX-induced superoxide anion may increase the amount of free, redox-active, iron through the slow reductive release of iron from ferritin (10). However, the localization of iron inside the mitochondria seems to be a key event in DOX-induced cardiotoxicity since it was observed recently that mice lacking mitochondrial ferritin are more sensitive to doxorubicin-mediated cardiotoxicity (11). The authors demonstrate convincingly that mitochondria are at the crossroads of all the modifications in the cell redox potential

induced by ErbB2 overexpression. Ichikawa *et al* have shown that DOX-induced cardiotoxicity originates from the specific mitochondrial accumulation of iron, which leads to increased ROS production in this organelle, but also that DOX represses the expression of ATP-binding cassette subfamily B transporter-8 (ABCB8), a protein that exports iron out of the mitochondria (12). However, such findings have not been described with TRZ, although that a mitochondrial-ErbB2 (mtErbB2) has been described recently as a key regulator of cell metabolism (13). Interestingly, breast cancer cells with higher levels of mtErbB2 were found more resistant to TRZ; the translocation of membrane ErbB2 into mitochondria is now considered as novel mechanism for TRZ resistance.

These findings also raise important questions concerning the interactions between TRZ and other chemotherapeutic agents on ABCB transporters (14), which are involved in iron distribution into the cell (9, 15). Consequently, it would be of interest to elucidate if ErbB2 could be directly involved in mitochondrial iron regulation, thus being the missing link between increased ROS production and neuregulin overexpression following DOX administration (4).

1. Belmonte F, Das S, Sysa-Shah P, Sivakumaran V, Stanley B, Guo X, et al. ErbB2 overexpression upregulates antioxidant enzymes, reduces basal levels of reactive oxygen species, and protects against doxorubicin cardiotoxicity. Am J Physiol Heart Circ Physiol. 2015;309(8):H1271-80.
2. Rocic P. Can ErbB2 overexpression protect against doxorubicin cardiotoxicity? Am J Physiol Heart Circ Physiol. 2015;309(8):H1235-6.
3. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20(5):1215-21.
4. Rochette L, Guenancia C, Gudjoncik A, Hachet O, Zeller M, Cottin Y, et al. Anthracyclines/trastuzumab: new aspects of cardiotoxicity and molecular mechanisms. Trends Pharmacol Sci. 2015;36(6):326-48.
5. Fedele C, Riccio G, Coppola C, Barbieri A, Monti MG, Arra C, et al. Comparison of preclinical cardiotoxic effects of different ErbB2 inhibitors. Breast Cancer Res Treat. 2012;133(2):511-21.
6. Walker JR, Sharma A, Lytwyn M, Bohonis S, Thliveris J, Singal PK, et al. The cardioprotective role of probucol against anthracycline and trastuzumab-mediated cardiotoxicity. J Am Soc Echocardiogr. 2011;24(6):699-705.
7. Gordon LI, Burke MA, Singh ATK, Prachand S, Lieberman ED, Sun L, et al. Blockade of the erbB2 Receptor Induces Cardiomyocyte Death through Mitochondrial and Reactive Oxygen Species-dependent Pathways. J Biol Chem. 2009;284(4):2080-7.
8. Guenancia C, Li N, Hachet O, Rigal E, Cottin Y, Dutartre P, et al. Paradoxically, iron overload does not potentiate doxorubicin-induced cardiotoxicity in vitro in cardiomyocytes and in vivo in mice. Toxicol Appl Pharmacol. 2015;284(2):152-62.
9. Gudjoncik A, Guenancia C, Zeller M, Cottin Y, Vergely C, Rochette L. Iron, oxidative stress, and redox signaling in the cardiovascular system. Mol Nutr Food Res. 2014;58(8):1721-38.
10. Thomas CE, Aust SD. Release of iron from ferritin by cardiotoxic anthracycline antibiotics. Arch Biochem Biophys. 1986;248(2):684-9.
11. Maccarinelli F, Gammella E, Asperti M, Regoni M, Biasiotto G, Turco E, et al. Mice lacking mitochondrial ferritin are more sensitive to doxorubicin-mediated cardiotoxicity. J Mol Med (Berl). 2014;92(8):859-69.
12. Ichikawa Y, Ghanefar M, Bayeva M, Wu R, Khechaduri A, Naga Prasad SV, et al. Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. J Clin Invest. 2014;124(2):617-30.
13. Ding Y, Liu Z, Desai S, Zhao Y, Liu H, Pannell LK, et al. Receptor tyrosine kinase ErbB2 translocates into mitochondria and regulates cellular metabolism. Nat Commun. 2012;3:1271.
14. Alakhova DY, Kabanov AV. Pluronics and MDR reversal: an update. Mol Pharm. 2014;11(8):2566-78.
15. Lane DJ, Merlot AM, Huang ML, Bae DH, Jansson PJ, Sahni S, et al. Cellular iron uptake, trafficking and metabolism: Key molecules and mechanisms and their roles in disease. Biochim Biophys Acta. 2015;1853(5):1130-44.