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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).

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