Proteasome inhibition and stress compromise the heart in chemotherapy

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This editorial refers to ‘Overexpression of endoplasmic reticulum-resident chaperone attenuates cardiomyocyte death induced by proteasome inhibition’ by H.Y. Fu et al., ⁶ pp. 600–610, this issue.

Several new therapeutic options are opening up for the treatment of haematological and solid malignancies. Although the effects on the malignancies can be dramatic, the collateral damage can be devastating as well. The concept of gene therapy was to develop cell-type-specific techniques, and similar expectations were raised with the concept of targeting cells specifically by binding selected receptors or other proteins. Yet, most therapies that have reached the clinic are not specific and will therefore influence all tissues and organs. This will make the heart a vulnerable organ, as it has limited or no regenerative capacity. The best known and most frequently used therapy in cancer are drugs from the anthracycline family, including doxorubicin. The exact mechanism of cardiotoxicity is still not completely clear, but one prevailing hypothesis involves oxidative stress and the production of free radicals, interference with the sodium–potassium pump of the sarcolemma, and interference with the mitochondrial electron-transport chain. This latter may explain the severe cardiotoxic effect of doxorubicin as the heart is a mitochondria-rich organ.¹ Of patients treated with anthracyclines, nearly 17% develop cardiomyopathy, as reported for a group of sarcoma patients.²

An unexpected surprise came with the introduction of monoclonal antibodies (MAb) to treat solid tumours. MAb against the human epidermal growth factor (EGF) receptor (HER2/ErbB2), Trastuzumab, have also shown cardiotoxicity. Trastuzumab treatment is used in the presence of ErbB2-positive cells in breast cancer. The EGF receptor (or ErbB1) and the related ErbB4 are transmembrane receptor protein tyrosine kinases that bind extracellular ligands of the EGF family. ErbB2 is considered an orphan or co-receptor. In the heart, targeted deletion of ErbB2, ErbB3, or ErbB4 leads to embryonic lethality resulting from cardiovascular defects. Ligand binding leads to activation of the extracellular signal-regulated kinase 1/2 (ERK) pathway and Akt (protein kinase B), inducing cardiomyocyte survival. The toxic effect of ErbB2 appeared to be potentiated when used together with anthracyclines.³ The toxic effect of anthracyclines may be counteracted by ErbB-receptor ligands.⁴ Therefore, blocking ErbB2 activity in the presence of doxorubicin hits the heart twice as hard. In contrast with anthracycline-induced cardiomyopathy, the cardiac dysfunction induced by Trastuzumab appears to be at least partially reversible and not related to the cumulative dose, and a re-challenge is generally well tolerated.⁵

In this issue of Cardiovascular Research, Fu et al.⁶ show the effect of two proteasome inhibitors (MG132 and epoxomicin) on cardiomyocyte apoptosis. The data suggest that proteasome inhibition could trigger apoptosis through the induction of endoplasmic reticulum (ER) stress and the activation of CHOP [CCAATenhancer-binding protein (C/EBP) homologous protein]. They provide convincing data that show that CHOP can be added to the list of ER stress-initiated apoptosis signalling molecules in addition to Bax and p53. Knock-down of these proteins showed a partial protection and improved cell survival in the presence of ER stress. Inhibition of c-Jun N-terminal kinases (JNK) and Caspase 12 had no effect.⁷ The experiments are also interesting in which the protective effect of adenoviral-mediated overexpression of glucose-regulated protein-78 (GRP78, an ER chaperone protein) is demonstrated. The ER responds to stress by increasing the expression of chaperones, but persistent stimuli can induce apoptosis. The rationale behind specifically addressing the role of GRP78 is based on the molecular analysis of tissue from failing human hearts and is supported by findings in hypertrophic and failing murine hearts following aortic banding.⁸

In the previous work, the overexpression of ER chaperones, including GRP78, was considered unfavourable and could be blocked by interfering with the activation of the angiotensin II type 1 receptor, which is a strategy commonly used in patients. The currently presented data would indicate that a more specific interference with ER chaperones is required, as blocking the upregulation of GRP78 seems...
to be unfavourable. Most likely, also with respect to ER stress, the balance of protein expression is crucial for the functional effects and more important than changes in the expression of a single player. The paper by Fu et al. represents excellent experimental work. However, the authors suggest that the induction of GRP78 or blocking CHOP could be a mechanism for cardioprotection. Yet, they provide no hints on how to proceed in the clinical setting. A few crucial issues remain, such as the suggestion made by Fu et al. concerning a role for dimerized cleaved activating transcription factor (ATF 6) and spliced XBP1 in the regulation of transcription of GRP78. In the current paper, the level of transcriptional modulation was not evaluated. Also, the authors suggest that the data obtained in this study can be extrapolated to all proteasome inhibitors, including Bortezomib. This assumption could turn out to be one step too far.

The induction of cardiac failure in man and mouse was previously also reported for a small molecule inhibitor Imatinib mesylate, which blocks the Bcr-Abl fusion protein. An important role is described in murine models after treatment for 3–6 weeks, apparently due to mitochondrial functional loss and cytochrome C release. ER stress also is considered to play a central role here in the activation of cardiomyocyte apoptosis. However, Kerkela et al. showed a crucial role in mice for JNK in relation to ER stress, and blocking JNK protected mitochondrial function and improved cardiomyocyte survival. The difference in response to Imatinib and the proteasome inhibitors is yet unexplained.

It is exciting to observe the major steps forward that are being made in chemotherapy. The efficacy and success rate of modern treatment are unprecedented. Despite the molecular knowledge and more specific design of therapy, the susceptibility of organs cannot be predicted. The brain appears to have some protection, but not the peripheral neural cells and cardiomyocytes. Therefore, the search for improvement of therapy or combination therapy to protect non-dividing cells and organs with limited regenerative capacity is still a key research issue.

References