mTOR: good, bad, or ugly?

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This editorial refers to 'Inhibition of AMPK signalling by doxorubicin: at the crossroads of the cardiac responses to energetic, oxidative, and genotoxic stress' by S. Gratia et al., pp. 290–299, this issue.

Doxorubicin (DXR) is one of the most widely used chemotherapeutics in the treatment of a variety of cancers, including breast, prostate, stomach and liver tumours, soft tissue sarcomas, leukaemias, and lymphomas.⁰ The anti-malignancy effects of DXR are attributed to its interaction with the DNA helix and proteins involved in DNA replication and transcription, resulting in the inhibition of synthesis of DNA, RNA, and proteins and ultimately cell death. However, DXR causes severe cardiomyopathy and resultant congestive heart failure, especially in patients treated with a high dose or in high-risk populations such as children, adolescents, or patients with predisposed cardiac problems. DXR-induced cardiac injury is manifested as acute or chronic cardiomyopathy, and both can eventually develop into severe congestive heart failure.

Over the past few decades, extensive studies have been focused on the mechanisms underlying DXR-induced cardiotoxicity. Although multiple mechanisms have been implicated, oxidative-stress-mediated death of cardiac myocytes has been identified as one of the most important. It is now well established that DXR-induced cardiomyopathy is associated with myocyte energetic stress, oxidative stress, and genotoxic stress.⁰–⁵ In particular, in vitro and in vivo studies have shown that DXR treatment causes a marked energetic deficit in the cardiomyocytes as a consequence of impaired mitochondrial function, altered energy substrate utilization, deficient high-energy phosphate storage and transfer, and a disturbed regulatory system of the cellular energy state.⁶–⁸ Under these conditions, energy deficiency would be expected to induce the activation of AMP-activated protein kinase (AMPK), a primary energy sensor in most cells. Surprisingly, in several previous studies it was shown that instead of being up-regulated, AMPK activity is depressed in cardiomyocytes in response to DXR treatment.⁹,¹⁰ which exaggerates the cardiac injury through enhanced myocyte energy stress and increased cardiac vulnerability in response to both physiological and pathological insulting stimuli. In the current issue, Gratia et al.¹¹ have further demonstrated that DXR-induced energy stress is paradoxically accompanied by the inhibition of AMPK and the activation of mammalian target of rapamycin (mTOR), a conserved Ser/Thr kinase that promotes protein synthesis and cell growth. In searching for the mechanism underlying DXR-induced inhibition of AMPK, the authors have revealed that DXR-evoked DNA damage activates DNA-dependent protein kinase (DNA-PK) and subsequently activates Akt and ERK pathways, which not only suppress AMPK but also activate mTOR. The suppression of AMPK and the concurrent activation of mTOR lead to a strong reinforcement of the DXR-induced energetic stress and myocardial damage (Figure 1).

Multiple lines of evidence show that AMPK is also a cellular redox modulator. The activation of AMPK has been reported to reduce reactive oxygen species (ROS) levels by increasing the expression of the antioxidant thioredoxin (Trx).¹² On the contrary, the silencing of AMPK can suppress a panel of genes involved in antioxidant defence, including manganese superoxide dismutase (Mn-SOD), catalase, γ-glutamylcysteine synthase, and Trx in endothelial cells.¹³ Thus, it is possible that the down-regulation of AMPK in cardiomyocytes will exaggerate not only the energy stress, but also oxidative stress, which will together lead to further cell injury induced by DXR treatment. In addition, p53 is an essential component of cellular stress response pathways and regulates diverse cellular processes including the cell cycle, apoptosis, and genomic stability.¹⁴⁻¹⁵ Recent studies have established a causal relation between DXR-induced suppression of AMPK and accumulation of p53 in fibroblasts and cardiomyocytes.¹⁰

It is noteworthy that mTOR senses the energy status of a cell also through AMPK, which is activated in response to low cellular energy. Activated mTOR down-regulates energetically demanding processes such as protein synthesis and stimulates ATP-generating processes such as fatty acid oxidation. Upon energy deprivation, the activation of AMPK inhibits mTOR, thus turning down energy-demanding processes and arresting growth. mTOR controls many aspects of cellular metabolism including amino acid biosynthesis, glucose homeostasis, and fat metabolism. Aberrant mTOR signalling has been implicated in tumourigenesis, cardiac hypertrophy, and various metabolic disorders including type 2 diabetes and obesity, whereas the suppression of mTOR activity by inhibitors has been indicated as a promising treatment of metabolic disorders by improving insulin sensitivity and...
The role of AMPK in doxorubicin (DXR)-induced cardiomyocyte injury. In cardiomyocytes, DXR mainly induces three forms of stress, i.e. energetic, oxidative, and genotoxic stress, all of which contribute to DXR-induced cardiotoxicity. It is genotoxic stress, but not energetic or oxidative stress, that induces the down-regulation of AMPK activity via a DNA-PK-Akt/ERK-dependent pathway. Depressed AMPK activity will exaggerate all three forms of stress; for genotoxic stress, this is possibly through increased p53 abundance. DXR can further up-regulate another important energy sensor, mTOR, via AMPK inhibition and DNA-PK-Akt/ERK activation, which further exaggerate the energetic stress induced by DXR. The elevation of all these three forms of stress will further deteriorate DXR-induced cardiomyocyte injury. AMPK, AMP-activated protein kinase; DNA-PK, DNA-dependent protein kinase; mTOR, mammalian target of rapamycin.

How does the DNA-PK/Akt pathway inhibit AMPK and activate mTOR? Can mTOR inhibitors prevent the DXR-induced cardiac toxic effects? These important questions merit further basic and translational research.

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References