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EDITORIAL

Repeated intermittent administration of a ubiquitous proteasome inhibitor leads to restrictive cardiomyopathy

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This editorial refers to 'Primary proteasome inhibition results in cardiac dysfunction', by J. Herrmann *et al.* doi.1093/eurjhf/hft034

In the cell, protein turnover occurs in the case of nearly all proteins. This turnover, particularly that which occurs in an orderly and targeted fashion, is especially important in order for post-mitotic cells (e.g. cardiomyocytes) to stay alive and to function properly. The turnover process is highly regulated. Both targeted protein degradation and protein synthesis are known to play an equally important role in the turnover process. Targeted degradation of most cellular proteins is primarily performed by the ubiquitin–proteasome system (UPS). UPS-mediated protein degradation generally consists of two main steps: (i) the covalent attachment of a chain of ubiquitin proteins to a target protein molecule via a highly regulated process known as ubiquitination; and (ii) the recognition and degradation of the polyubiquitinated protein by the proteasome. Proteins degraded by the proteasome can be classified into two main families: first, perfectly normal proteins that have fulfilled their fuctions at a given time and location in the cell and are no longer needed by the cell; and secondly, terminally misfolded or permanently damaged proteins. By degrading the former, the UPS participates in the regulation of virtually all cellular processes; meanwhile, degradation of the latter by the proteasome constitutes arguably the final line of defence of intracellular protein quality control (PQC).[1] PQC acts to minimize the level and toxicity of misfolded proteins in the cell, playing a pivotal role in maintaining protein homeostasis in the cell. Hence, normal proteasome function is essential to the functioning of all organs, especially those post-mitotic organs such as the heart. This notion is reinforced by the findings of a study published in this issue.[2] In this study, Herrmann *et al.* found that long-term, intermittent, ubiquitous proteasome inhibition (PSMI) is sufficient to cause a phenotype resembling restrictive cardiomyopathy in otherwise healthy domestic pigs.[2] They reported previously that chronic PSMI could result in early atherosclerosis changes in coronary vessels.[3] Their further investigation into the same cohort of animals reveals cardiac hypertrophy, apoptosis, fibrosis, and diastolic malfunction in pigs receiving twice-weekly subcutaneous injections of the proteasome inhibitor MLN-273 (0.08 mg/kg) for 11 weeks.[2] This is not the first study to show that PSMI can cause cardiac dysfunction and cardiomyopathy, as Tang *et al.* reported that PSMI activates the calcineurin–NFAT (nuclear factor of activated T cells) pathway and cardiac hypertrophy in mice;[4] however, the use of large animals and more sensitive heart function assessments confers a higher degree of clinical relevance to this study by Herrmann and his colleagues.

Since UPS-mediated protein degradation is crucial to cell cycle control, perturbation of the UPS, including proteasome inhibition, has been explored for and, in some cases, used as a strategy to treat cancers. For example, bortezomib, a ubiquitous proteasome inhibitor, is clinically used to treat multiple myeloma.[5] Several other drugs in the same family either have been approved by the Food and Drug Administration (FDA) or are in clinical trials as a cancer treatment. It is not surprising that adverse effects,[5,6] including cardiac dysfunction or even heart failure,[7,8] have been reported for patients receiving bortezomib. A large clinical trial of 315 patients with relapsed multiple myeloma receiving bortezomib (Valcade) revealed that the incidence of cardiac adverse effects was 15%.[5,6] Although this rate is not considerably higher than that of other very effective pharmacological therapies (e.g. high-dose dexamethasone) for relapsed multiple myeloma,[6] it indicates that proteasome functional insufficiency (PFI) is detrimental to the heart. Later clinical reports show that the cardiac adverse effects of clinical use of Valcade can be further exacerbated by pre-existing cardiac conditions.[6–8] Indeed, decreased proteasome activities were observed in the hearts of humans with hypertrophic cardiomyopathy, and PFI has been implicated in an even larger subset of human hearts with congestive heart failure.[9,10] Cardiac PFI has been unravelled in experimental cardiomyopathies including desmin-related cardiomyopathy and ischaemia/reperfusion (I/R) in injury.[10,11] Moreover, proteasomal enhancement by overexpression of proteasome activator 28

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alpha (PA28α) can protect against oxidative stress in cultured cardiomyocytes,[12] slow down the progression of desmin-related cardiomyopathy, and reduce myocardial I/R injury,[13] demonstrating for the first time that PFI plays an important pathogenic role in not only proteinopathy but also I/R injury, both conditions with increased demand on PQC.

Contradictory to a pivotal role for the proteasome in PQC, pharmacologically induced short-term ubiquitous PSMI was shown in several studies to be beneficial in treating experimental I/R injury.[14] Genetically induced cardiomyocyte-restricted chronic moderate inhibition of the 20S proteasome via overexpression of the peptidase-disabled β5 subunit (PSMB5) of the 20S proteasome appears to be well tolerated by mice under baseline conditions but exacerbates acute myocardial I/R injury in mice,[11] suggesting that pharmacological PSMI may protect the heart by acting on the non-cardiomyocyte compartment. The anti-inflammatory actions of ubiquitous PSMI may have benefited the hearts with acute I/R injury.[14] Interestingly, both short-term and long-term PSMI were shown to suppress or even reverse pressure-overloaded cardiac hypertrophy and remodelling without impairing heart function in rodents.[15] The mechanism by which PSMI suppresses pressure-overloaded cardiac hypertrophy remains elusive. Inhibition of the nuclear factor (NF)-κB signalling pathway and reduction of protein synthesis are suspected contributing factors.[15] These reported cardioprotective effects of PSMI advocate that PSMI should be pursued as a new therapeutic strategy to treat heart diseases. However, as suggested by this most recent study by Harrmann and his colleague,[2] long-term constitutive PSMI at least does not seem to be suitable for treating human heart disease. This study also provides additional support from a large animal model for the notion that PFI plays an important role in cardiac pathogenesis.[10]

Given that an anti-inflammatory effect of PSMI is suggested to contribute to the protective effects of PSMI that were observed in some of the studies,[11,14,15] it is tempting to propose that measures to target the subpopulation of proteasomes (e.g. immunoproteasomes) that are more intimately involved in the propagation of inflammation might be able to protect the heart under certain pathological conditions.

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