Too much of a good thing is bad: proteasome inhibition induces stressed hearts to fail

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This editorial refers to ‘Proteasome functional insufficiency activates the calcineurin–NFAT pathway in cardiomyocytes and promotes maladaptive remodelling of stressed mouse hearts’ by M. Tang et al., pp. 424–433, this issue.

A fine balance between protein synthesis and protein degradation regulates cellular homeostasis. Cardiac remodelling is a common response of the heart to changes in physiological or pathological demand. Hypertrophic growth is the primary mechanism through which the heart normalizes ventricular wall stress. It is characterized by an increase in the volume of individual cardiac myocytes, which can be the result of an acceleration of synthesis or a reduced degradation rate of proteins. However, while the synthesis rate has always been shown to be increased, protein degradation has been shown to be either accelerated or unchanged in hypertrophic hearts and inhibited by induction of cardiac work or high aortic pressure in Langendorff preparations.

The ubiquitin–proteasome system (UPS) is one of the two major proteolytic systems that degrade most cellular, nuclear, and myofibrillar proteins in cells, as recently reviewed in a Spotlight issue of Cardiovascular Research. A main function of the UPS is to prevent accumulation of damaged, misfolded, and mutant proteins. Over the past two decades, the UPS has been increasingly recognized as a main player in regulating a multitude of cellular processes and dynamics. Two consecutive steps characterize the UPS. The first one is ubiquitination, which consists of the addition of several ubiquitin moieties onto a target intended for degradation and which involves the concerted action of at least three different ubiquitin enzymes. The second step consists of the degradation of the target by the 26S proteolytic core. The clinical importance of the UPS is rapidly expanding. For example, a dysfunction of the UPS is involved in neurodegenerative disorders such as Huntington’s and Alzheimer’s diseases. Another potential clinical application is the regression of cancer and promotes maladaptive remodelling of stressed mouse hearts. NFATs are conversely phosphorylated by several protein kinases, including glycogen synthase kinase-3β (GSK3β), and deactivated in the cytoplasm. Phosphorylation of NFAT by GSK3β induces its ubiquitination and proteasomal degradation, reducing NFAT transcriptional activity. Moreover, calcineurin is specifically ubiquitinated by the E3 ubiquitin ligase complex SCF-atrogin-1 and degraded by the UPS (for review, see 6). Therefore, blockade of the proteasome is expected to result in accumulation of both NFAT and calcineurin, which may induce dephosphorylation of NFAT, its translocation to the nucleus, and activation of the hypertrophic gene program (Figure 1). Interestingly, the study by Tang et al.7 showed that an acute dose of the reversible proteasome inhibitor MG262 (5 μmol/kg, i.e. ~2.45 mg/kg for 24 h) was sufficient to reduce proteasomal activity by ~70% and to increase the levels of poly-ubiquitinated proteins and NFAT activity. However, the mice did not exhibit higher levels of calcineurin and left ventricular hypertrophy (LVH), which could be due to the acute application of MG262 for a period that was shorter than the estimated half-life of calcineurin (>30 h). Conversely, chronic administration of the reversible proteasome inhibitor bortezomib (1 mg/kg/2 days for 5 days) or 5 days of trans-aortic constriction (TAC) induced LVH to a similar extent, and, importantly, the administration of bortezomib and TAC for 5 days resulted in heart failure and premature death in mice. Although the authors did not show that chronic bortezomib administration is associated with higher levels of calcineurin and activation of NFAT, it was indirectly supported in a mouse model of desmin-related cardiomyopathy.

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with severe proteasome impairment. These findings substantiate an "old" hypothesis that inappropriate ubiquitination may disturb cardiac homeostasis and contribute to the transition towards failure. They also demonstrate for the first time that bortezomib induces complications in the stressed mouse heart, as has been shown in humans who received Velcade® for the treatment of multiple myeloma (reviewed in 5).

Overall, these findings are provocative in the field of cardiac UPS since they dispute several studies showing that a low dose of proteasome inhibitors could be used as a therapeutic tool. Specifically, a low dose of the irreversible inhibitor epoxomicin (0.5 mg/kg/day for 5 days) prevents TAC-induced LVH in mice. Similarly, treatment of hypertensive Dahl salt-sensitive rats with a low, non-toxic dose of bortezomib (50 μg/kg twice weekly for 8 weeks) reduces LVH. Finally, others have extended these findings by showing that different proteasome inhibitors cause the regression of LVH induced by chronic isoprenaline or TAC in mice.

A definite explanation for the discrepancies between the data of Tang et al. and others is currently lacking. However, some potential reasons can be raised. First, the mouse genetic backgrounds differ between the studies (FVB/N in the current study vs. 129Sv/J or C57BI in the others). Therefore, we cannot exclude that a genetic variant could explain the differences, as recently shown for a mutation in the β5-subunit of the proteasome, which confers bortezomib resistance. Second, the bortezomib dose used by Tang et al. is slightly above the limit of the maximum-tolerated dose of 83 μg/kg and could therefore induce additional internal stress to the TAC. Third, different types of proteasome inhibitors were used, which may have differential inhibitory effects on the various cardiac proteasome subtypes, as it has been elegantly recently shown.

In conclusion, manipulation of the proteasome activities as a therapy for cardiac disease remains a subject of debate. Taken together, the different studies support the view that a low dose of proteasome inhibitor may prevent or interrupt the development of LVH, potentially by a preferential interference with the degradation of antihypertrophic factors, whereas a high dose may give additional stress to the heart and promote transition to heart failure via the activation of the calcineurin–NFAT pathway.

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**References**