The role of the ubiquitin-proteasome pathway in cardiovascular disease

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Whereas the mechanisms controlling cellular growth through protein synthesis have been investigated extensively in the cardiovascular system, especially in terms of cardiac cell hypertrophy and vascular smooth muscle cell proliferation, the processes by which endogenous proteins are degraded in these cells have received much less attention and have only begun to be revealed. The ubiquitin-proteasome system (UPS) is responsible for the degradation of 70–90% of intracellular proteins. The fundamental importance of the UPS in these degradation mechanisms was highlighted when Rose, Hershko, and Ciechanover were awarded the 2004 Nobel Prize in Chemistry for their seminal contributions in that field, i.e. the discovery of both ubiquitin1 and the proteasome.2 As illustrated in this Spotlight Issue, protein degradation by the UPS plays a central role in cardiovascular physiology and disease: from endothelial function, the cell cycle, and atherosclerosis to myocardial ischaemia, cardiac hypertrophy, inherited cardiomyopathies, and heart failure.

Investigations on the role of the UPS in the cardiovascular system started about 15 years ago and have since increased exponentially. In the heart, the first reports demonstrated that the proteasome is responsible for the degradation of specific, stress-sensitive transcriptional regulators, such as NF-κB, HIF-1α, or inducible cAMP early repressor.3,4 It was subsequently shown that the UPS also degrades contractile proteins and components of the sarcomere.5,6 The development of several categories of proteasome-specific inhibitors further delineated a role for the UPS in multiple forms of heart disease, such as ischaemia/reperfusion, cardiac hypertrophy, cardiomyopathies, and heart failure. In the vasculature, it was initially shown that proteasome activity affects angiogenesis7 and, subsequently, that the proteasome participates in nitric oxide metabolism, oxidative stress, and atherosclerosis. Descriptions of a dysfunction of the UPS in human heart disease also began to emerge in the literature.8–10 Recently, several clinical case reports have mentioned potentially cardiotoxic side effects of proteasome inhibitors, for example, in patients treated for solid tumours and haematological malignancies.11,12 All these advances have been reviewed in the current Spotlight Issue dedicated to the role of the ubiquitin-proteasome pathway in cardiovascular disease. This issue covers three main aspects of the UPS in the cardiovascular system: protein quality control, the role of the UPS in vascular function, and the role of the UPS in heart disease. Throughout the issue, we have tried to emphasize the paradoxes and controversies that still characterize this field of investigation, in particular in terms of the physiological consequences of UPS activation vs. inhibition.

In the first two articles, Su and Wang13 as well as Dantuma and Lindsten,14 review the importance of the UPS in quality control mechanisms of protein production. These control mechanisms include minimizing the production of non-functional proteins and degrading misfolded and denatured proteins. It is estimated that under normal conditions up to 50% of nascent proteins will be degraded by the proteasome even before peptide elongation is achieved.15 The authors emphasize how this crucial function of the UPS can be perturbed by cytotoxic stress14 and how proteasome insufficiency may lead to heart failure.13 A key concept is that UPS insufficiency will permit aberrant protein aggregation and will lead to the accumulation of unwanted proteins in cardiomyocytes. This ‘cardiac proteinopathy’ may in the long run contribute to ventricular dysfunction and failure. Su and Wang also highlight the emerging importance of functional interplay between the UPS and autophagy, another mechanism of protein degradation.13 It is noteworthy that, as for the UPS, it remains controversial whether activation or inhibition of autophagy may prove beneficial for cardiac cell survival.

The next few articles address different roles of the UPS in vascular function and disease. Fasanaro et al.16 explain how the UPS controls the endothelial cell cycle through ubiquitination of specific protein complexes controlling the transition through the cell cycle and the exit from mitosis. In particular, the authors detail the central role played by specific and cooperative E3 ubiquitin ligases (SCF and APC/C) in this cellular mechanism and how it can be affected by oxidative stress. Stangl and Stangl17 further
develop the mechanisms by which oxidative stress-induced dys-
function of the UPS disturbs endothelial function. These authors
also review the mechanisms by which nitric oxide (NO) may
affect proteasome function and, reciprocally, the mechanisms tar-
getting NO synthase isoforms to the proteasome. In another
article, Herrmann et al.\textsuperscript{18} expand further on the importance
of oxidative stress in endothelial proteasome dysfunction and show
how it participates in the early stages of atherosclerosis, such as
the formation and survival of foam cells or the phenotypic
switch and proliferation of vascular smooth muscle cells.

The second half of this Spotlight Issue is devoted to the con-
tribution of UPS function and dysfunction to heart disease in
terms of cardiac cell survival and growth. The reviews by Powell
and Divald\textsuperscript{19} and by Yu and Kem\textsuperscript{20} describe the role of the UPS
in ischaemic heart disease and paradoxically demonstrate that UPS
activation as well as inhibition may be beneficial in that context.
Whereas Powell describes the different mechanisms leading to a
dysfunction of the UPS in the setting of myocardial ischaemia,\textsuperscript{19}
Yu highlights the beneficial effects of proteasome inhibition in the
ischaemic heart.\textsuperscript{20} Powell’s review also addresses the important
and emerging concept of alteration of cardiac proteasome activity
by post-translational modifications and, in particular, by oxidation.

The last four reviews explore the importance of the UPS in
cardiac hypertrophy and failure. As reviewed by Hedhli and
Depre,\textsuperscript{21} several reports have now shown that proteasome inhibi-
tion can prevent or reverse stress-induced as well as adaptive
hypertrophy without impairing cardiac function, thereby demon-
strating a necessary role for the UPS in cardiac cell growth.\textsuperscript{21–24}
The potential mechanisms by which the UPS could interfere with
protein synthesis are described in their review. Carrier et al.\textsuperscript{25}
develop the pathogenic role of UPS dysfunction in inherited hyper-
rophic cardiomyopathy. The authors show that the UPS is criti-
cally involved in the degradation of mutant or truncated proteins,
together with the degradation of the corresponding mes-
senger RNAs by nonsense-mediated mRNA decay. Tsukamoto
et al.\textsuperscript{26} and Luo et al.\textsuperscript{27} review the consequences of UPS dysfunc-
tion in the transition into heart failure. In particular, Tsukamoto’s
contribution covers the still controversial effects of proteasome
activation vs. inhibition in the context of cardiac hypertrophy
and failure, whereas Luo’s review addresses the very intriguing
and emerging role of an immunoproteasome in the heart.

Altogether, the reviews presented in this Spotlight Issue offer a
far-reaching view of the multiple functions of the UPS in the car-
diovascular system. They also emphasize its causal role in different
forms of cardiovascular disease, and the potential of harnessing
proteasome activity as a new therapeutic avenue. Although still
in its infancy, this field of research is rapidly expanding; however,
multiple controversies remain. Therefore, the authors also single
out the important issues that remain underrated at this point
and which will have to be addressed in the future: the
tissue-specific composition of the proteasome, its regulation by
post-translational modifications, the expression of the immunoprote-
asome, the interference of the UPS with protein translation, the
cooperation between UPS and autophagy, or the mechanisms con-
trolling substrate specificity. It is likely that answering these
questions will change our conception of the pathophysiology and
of the treatment of cardiovascular diseases.

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