The renin-angiotensin system (RAS) and autophagy are both essentially involved in the pathomechanisms of various cardiovascular pathologies, e.g., cardiac hypertrophy/load-induced heart disease, ischemic heart disease, or atherosclerosis.1-4 Regarding the RAS, it is commonly accepted that angiotensin II via the angiotensin II type 1 receptor (AT1R) directly and indirectly (by increasing blood pressure) contributes to, e.g., cardiomyocyte hypertrophy, interstitial fibrosis, inflammation, oxidative stress, or apoptosis in cardiac pathologies, thereby promoting disease.1,5 In contrast, regarding the angiotensin II type 2 receptor (AT2R), the majority of data points to a tissue-protective effect of this receptor in cardiac disease because of its antifibrotic, anti-inflammatory, and antiapoptotic features. However, some publications also report a prohypertrophic effect of the AT2R in the heart. Because the determination of “true” AT2R-mediated effects is still difficult and experimental approaches are often indirect (inhibition experiments using the AT2R antagonist PD123319) and/or make use of genetically altered animals or cells, the true nature of AT2R-mediated effects in cardiac diseases is probably not yet completely understood.

Autophagy represents a highly conserved process for the lysosomal degradation of cytoplasmatic long-lived proteins and organelles.6 It can result in final decomposition of proteins contributing to a certain form of programmed cell death (autophagic cell death), but it may also serve as a survival mechanism by intracellular clearance of toxic or damaged proteins and organelles or, in times of starvation, through protein recycling and maintenance of intermediary metabolism.6 During autophagy, autophagosomes are built from so-called isolated membranes to sequestrate cytosolic constituents for later degradation (Figure). The whole process of autophagy is controlled by a set of autophagy-related genes (Atgs). One of these, Beclin-1 (Atg6), together with class III phosphoinositide 3-kinase, is needed for the vesicle nucleation of autophagosomes. Vesicle elongation requires 2 conjugation pathways, one of them involving microtubule-associated protein 1 light chain 3, which, during the process of elongation, is converted from its soluble form into a vesicle associated form. Both, vesicle-associated microtubule-associated protein 1 light chain 3 and Beclin-1 are main experimental markers for autophagy. After compartmentalization of proteins into autophagosomes, the autophagosomes fuse with lysosomes to form autolysosomes in which the phagosomal cargo is eventually degraded (Figure).

Although in the heart autophagy is part of the physiological turnover of organelles at low basal levels, autophagic processes in cardiomyocytes are clearly upregulated in response to stresses, e.g., cardiac remodeling/hypertrophy or ischemic disease.2-4 However, for a long time it was not clear whether this increased autophagic response is a sign of failed cardiomyocyte repair or a suicide pathway for failing cardiomyocytes and whether autophagy should be regarded as a protective mechanism or a process contributing to disease progression. Current evidence supports the view that a physiological baseline autophagic activity is important for cellular homeostasis, whereas excessive autophagy is rather detrimental and to be eliminated in the clinical setting.4

Taking into account that the RAS and autophagy have both been clearly identified to be of major importance in cardiovascular pathologies, it seems only logical to look for an interaction between these 2 mechanisms. However, because scientists nowadays are usually very much specialized in a certain, defined area of research (which is a necessity because of the enormous amount of data), it needs people who look beyond the horizon of their daily, defined field of research to reveal connections and relationships between seemingly unrelated biological systems. The main achievement of the article by Porrello et al7 published in this issue of Hypertension is that it bridges the gap between the 2 biological systems of RAS and autophagy and provides first evidence for an interplay between these 2 systems in cardiomyocytes. Porrello et al7 report that neonatal rat cardiomyocytes overexpressing either the AT1R or the AT2R or both after adenoviral transfection present with either an augmented (via the AT1R) or inhibited (via the AT2R) autophagic response on stimulation by angiotensin II (Figure). Their finding is based on the determination of the number of autophagosomes labeled by fluorescent HcRed microtubule-associated protein 1 light chain 3. Cardiomyocytes derived from a genetic model of disturbed heart growth in rats (hypertrophic heart rat) were more susceptible to AT1R-induced autophagy but also showed a strong reduction of autophagic activity via the AT1R. The authors concluded that autophagy in cardiomyocytes is reciprocally regulated by AT1R and AT2R and suggested that the AT2R may be a novel therapeutic target in autophagic cardiomyopathies.

The results by Porrello et al7 open a completely new field of angiotensin research and will certainly stimulate many
other researchers to look into interactions between autophagy and the RAS in various cardiovascular diseases. Presumably, it will not take long until the major findings by Porrello et al., a stimulatory effect on autophagy by the AT1R and inhibition of autophagy via the AT2R, will be validated by other groups. Confirmation of these data will be important in particular in experiments using primary (not genetically altered) cells, because artificially modified receptor expression levels may have an impact on receptor heterodimerization or other receptor-protein interactions resulting in altered receptor signaling. Further in vivo studies to corroborate an interaction between RAS and autophagy are needed even more, because although the study by Porrello et al. is composed of some in vivo data, conclusive insights into the interaction between RAS and autophagy are solely derived from in vitro experiments in cardiomyocytes. For example, although the authors confirmed an increased autophagic response in cardiac ischemia reperfusion (increase in Beclin-1 and microtubule-associated protein 1 light chain 3, which was more pronounced in the hypertrophic heart rat compared with the normal heart rat), the impact of the RAS in this setting remains unclear and needs further investigation.

Nevertheless, this first description of a regulation of autophagic activity by angiotensin II with reciprocal effects depending on the angiotensin receptor subtype involved is an observation of absolute novelty and importance. Given the fact that autophagy and RAS are both involved in many physiological and pathophysiological processes as divergent as fetal development, neurodegeneration, ischemic tissue damage, aging, cancer, or keratinocyte differentiation, understanding the interaction between RAS and autophagy may be a key to improved understanding not just of hypertrophic or ischemic cardiac disease but also of many more pathological conditions.

Disclosures

None.

References


Figure. The process of autophagy and its modulation by AT1R and AT2R. Autophagy is initiated by formation of so-called isolation membranes, which sequestrate large proteins or organelles for later degradation. Expansion of the isolation membrane and enclosure of the cytoplasmic cargo lead to formation of autophagic vacuoles, the autophagosomes. Autophagosomes dock and fuse to lysosomes to form autolysosomes in which the cargo is eventually degraded. Porrello et al. report in this issue of *Hypertension* that autophagy is promoted by angiotensin via the AT1R but is diminished via the AT2R. Adapted from Reference 6.