Autophagy is an adaptive mechanism against endoplasmic reticulum stress

Sir,
Kawakami et al. recently demonstrated that endoplasmic reticulum (ER) stress induces autophagy in renal proximal tubular cells [1]. We believe that this paper is of importance because it underscores the emerging roles of ER stress and autophagy in nephrological pathophysiology and brings out new information on the activation of autophagy during ER stress. There is no doubt that ER stress play important roles in renal pathology since it is activated during nephrotoxicity, ischaemia-reperfusion injury, viral infections, glomerulonephritis, podocytopathies, albuminuria and kidney ageing [2].

Cells subjected to ER stress activate the unfolded protein response to reduce the amount of accumulated proteins. Recent evidence suggests that ER stress drives autophagy [3] and this self-digestion can rid cells of superfluous or misfolded protein accumulation. Thus, it is suggested that autophagy alleviates the deleterious effects of ER stress by eliminating misfolded proteins and prolongs cell survival. We have demonstrated that cyclosporine-induced autophagy is triggered by ER stress and protects cells against death [4]. Thus, our findings are complementary to the paper of Kawakami showing that autophagy could constitute an adaptive mechanism to kidney injuries far more common than previously thought.

This paper is also important because the authors demonstrate for the first time that ERK activity, a prosurvival pathway, is activated during ER stress and autophagy. Until now, it has been demonstrated that JNK and p38 MAPK were the main regulators of autophagy during ER stress. These MAP kinases are activated during ER stress by the IRE1/TRAF2 signalling and induce autophagy through dissociation of the BCL-2–Beclin complex and activation of the powerful autophagy inducer Beclin [3]. Here, the authors show that an alternative pathway may exist. Although the precise mechanisms of ERK-activated autophagy during ER stress remain to be determined (role during autophagosome maturation?), these findings open the door to further existing investigations.

Thus, deciphering new biological pathways that induce autophagy in kidney diseases is of great importance because they may lead to the development of early biomarkers of kidney injury and to new therapeutic options.

Conflict of interest statement. None declared.

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Reply

Sir,
We agree with Dr Pallet et al. that deciphering new biological pathways to induce autophagy is important and may lead to the development of new therapeutic approaches. Their findings that cyclosporine-induced autophagy is triggered by ER stress and protects cells against death are relevant and further emphasize biological significance of autophagy associated with ER stress. We appreciate their encouraging comments.

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