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Editorial

Autophagy protects from liver injury

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Autophagy is understood as a mechanism by which subcellular debris are recycled and metabolic intermediates produced for maintaining cellular homeostasis. Moreover, autophagy can be induced under stress conditions with the goal of cell survival. On the other hand, autophagy also has a role in the cell death pathways, and the existence of a complex cross-talk between autophagy and apoptosis has recently emerged.[1] For instance, key proteins originally thought to be apoptosis-specific inhibitors are also able to block autophagy,[2] while some proteases involved in apoptosis block autophagy by cleaving autophagy-regulating proteins.[3] In still other cases, the autophagy-related (ATG) proteins can be converted into a pro-apoptotic factor[4] or can directly bind FAS-associated protein with death domain to support apoptosis.[5] Unfortunately, all these findings currently fail to provide a consistent interpretation for the general function of autophagy in the apoptosis pathways. Nonetheless, an understanding of the molecular mechanisms regulating the interplay between autophagy and apoptosis promises to provide new hints on how to modulate the cell death pathways under pathological conditions such as cancer, neurodegenerative, or chronic inflammatory disorders.

In this issue of the Journal, Amir *et al.*[6] report the development of a mouse line exhibiting an inducible, hepatocyte-specific lack of the key ATG gene *atg7*. These mice have been challenged with D-galactosamine (GalN) and lipopolysaccharide (LPS), both of which are stimuli commonly used to study tumor necrosis factor (TNF)-dependent liver injury. With the purpose of studying autophagy in TNF-induced cytotoxicity in the liver, these investigators found that autophagy protects the hepatocytes from TNF-dependent cell death. Mice with *atg7*-deficient hepatocytes showed a higher rate of hepatocytic apoptosis, liver injury, and mortality as compared with the wild-type mice following combined GalN and LPS treatment. Interestingly, these effects were not due to altered, LPS-induced cytokine production by macrophages in the liver, because TNF-α, IFN-γ, IL-6, and IL-1β levels were not altered as a consequence of the ATG7 deficiency. This suggests that the accelerated TNF-induced toxicity in such knockout mice resulted from an inhibition of autophagy.

Furthermore, *atg7*$^{-/-}$ mice showed features of an accelerated extrinsic apoptotic pathway in liver cells, including caspase-8 activation, increased expression of truncated Bid,

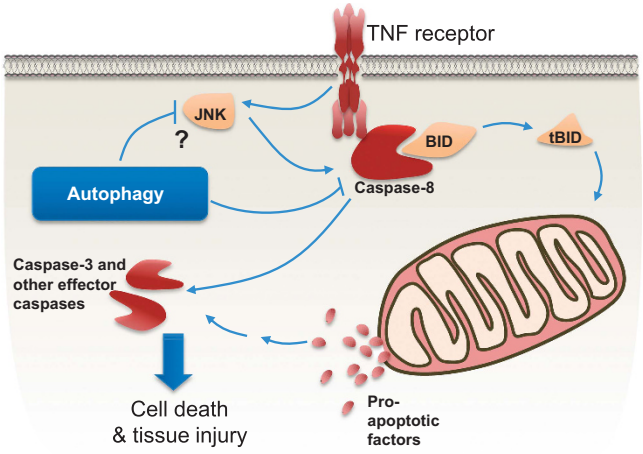

Figure 1 Autophagy overlaps with the extrinsic apoptosis pathway in liver cells. Deficient autophagy results in overactivation of JNK, which increases caspase-8 activation and allows the induction of TNF-dependent apoptosis. How autophagy regulates JNK activity remains still unknown. In addition, several canonical pro-apoptotic molecules, such as caspase-8, can be degraded by autophagy

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and cytochrome-*c* release, as well as caspase-3, caspase-7, and poly (ADP-ribose) polymerase cleavage. It had previously been shown that overactivation of c-Jun N-terminal kinase (JNK) can activate caspase-8, resulting in increased TNF-dependent cell death.[7] Amir *et al.*[6] observed increased phosphorylated JNK and its downstream target c-Jun in the *atg7*$^{-/-}$ mice upon GalN/LPS stimulation, indicating that autophagy protects TNF toxicity by blocking JNK activity (Figure 1).

Interestingly, this study also showed that GalN can inhibit LPS-induced autophagy by blocking the activation of adenosine monophosphate-activated protein kinase, which in turn positively regulates autophagy. Increased autophagy resulting from Beclin 1 overexpression prevented GalN/LPS-induced liver injury. This suggests that the toxicity caused by GalN is at least partially dependent on the inhibition of autophagy. Because autophagy is crucial for the survival of the GalN/LPS-sensitized hepatocytes, its inhibition leads to extra cell death and tissue injury in the knockout mice. Therefore, it seems likely that it is the autophagic suppression of apoptosis that helps the liver cells to survive by delaying the onset of death signals under toxic conditions. Hence, upregulating the autophagic pathway might be an attractive therapeutic strategy in several inflammatory liver diseases.

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