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EDITORIAL

Linking of Senescence to Autophagy Deficiency in Chronic Liver Disease

Cellular senescence is a state of irreversible cell-cycle arrest while cells still maintain metabolic activity. Senescence generally is activated as an adaptive response to stresses, such as oxidative stress, oncogene activation, and DNA damage. Morphologically, senescent cells have an enlarged size and flattened morphology with nuclear accumulation of senescence-associated heterochromatic foci and senescence-associated DNA damage foci. Although there are no universal biomarkers for senescence, senescent cells generally have increased β-galactosidase activity; increased cell-cycle inhibitory proteins; such as p21/CDKN1A, p16/CDKN2A, and TP53; as well as increased secretion of a variety of factors, collectively termed as *senescence-associated secretory phenotype* (SASP).[1] Autophagy is a catabolic pathway in which the cellular contents are wrapped in the double-membrane autophagosomes and delivered to lysosomes for degradation.[2] Interestingly, stresses such as oxidative stress and DNA damage that trigger senescence also can activate autophagy or apoptosis. It is conceivable that the magnitude of the stresses may decide a cell should undergo autophagy, senescence, or apoptosis. Although both senescence and autophagy have been implicated in chronic liver diseases,[1,2] the inter-relationship of autophagy and senescence in liver pathogenesis of autophagy-defective livers has not been studied.

Mice with genetic deletion of autophagy-related genes, such as *Atg5* or *Atg7*, develop liver injury, inflammation, fibrosis, and spontaneous adenoma.[3,4] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Huda et al[5] investigated the temporal changes, possible mechanisms, and role of senescence in the pathogenesis of mouse livers with defective hepatic autophagy. They found that senescence markers, including β-galactosidase activity, *p15/Cdkn2b*, *p21/Cdkn1a*, and *Cdkn3*, as well as senescence-associated DNA damage, senescence-associated heterochromatic foci, and SASP, all were increased in liver-specific *Atg7* knockout (L-*Atg7* KO) mice in an age-dependent manner. Because L-*Atg5* or L-*Atg7* KO mice develop liver injury at 2 months old,[3,4,6] senescence could be secondary to hepatocyte damage. However, using an elegant tamoxifen-inducible *Atg7* deletion approach in adult mice, Huda et al[5] showed that some of the senescent markers were increased as early as day 5 after deletion of *Atg7*, suggesting that senescence could be triggered independently of hepatocyte damage in the absence of autophagy.

Mechanistic studies have shown that increased expression of chemokines in autophagy-defective livers likely was owing to the activation of forkhead box K1 transcription factor, but not the activation of nuclear factor-κB and GATA4, 2 well-known transcription factors that are associated with senescence and SASP.[7] Furthermore, using isolated hepatocytes and nonparenchymal cells from L-*Atg7* KO mouse livers, Huda et al[5] found that hepatocytes, but not nonparenchymal cells, were the primary source for increased chemokine production. Autophagy-deficient livers have increased inflammation, as shown by increased F4/80 or CD11b-positive macrophages, which likely is mediated by chemokine (C-C motif) ligand 2 (CCL2) family chemokines. Indeed, deletion of *Ccr2* attenuated hepatocyte senescence and SASP, suggesting C-C chemokine receptor type 2 (CCR2)-mediated signaling may form a feedback loop between senescent hepatocytes and SASP in autophagy-deficient livers. CCR2 was more critical in senescence but had no effects on ductular reactions and fibrosis. Moreover, CCR2 deletion only delayed the tumor progression that normally arises in the setting of deficient hepatocyte autophagy, but had no effects at the late stage of liver tumorigenesis.

It is well known that autophagy-defective livers have persistent nuclear factor (erythroid-derived 2)-like 2 (*Nfe2l2* or Nrf2) activation owing to Sequestosome 1/p62-mediated noncanonical Nuclear factor-erythroid factor 2-related factor 2 (Nrf2) activation.[3] Persistent Nrf2 activation is detrimental in autophagy-defective livers, which likely is owing to the impaired autophagic protein turnover and proteotoxicity.[6,8] Interestingly, deletion of *Nfe2l2* markedly reduced senescence in L-*Atg7* KO mouse livers. Senescence often is associated with increased oxidative stress, which also occurs in autophagy-defective livers that have increased lipid peroxidation and oxidative DNA damage. It remains unclear why increased Nrf2 activation paradoxically increased oxidative stress, DNA damage, and senescence in autophagy-defective livers.

Although this study has advanced our understanding on the mechanisms of senescence and convincingly showed hepatocyte senescence occurred in autophagy-defective mouse livers, several questions remained unanswered. The exact contribution of senescence in the pathogenesis of autophagy-defective livers remained unclear because the data only showed an indirect association of senescence with the pathogenesis of L-*Atg7* KO mouse livers. Future studies to generate mice with double deficiency of autophagy and senescence by crossing L-*Atg7* or L-*Atg5* KO mice with either *p15/Cdkn2b* or *p21/Cdkn1a* KO mice would help to confirm the definite role of senescence in the pathogenesis of autophagy-defective livers. Senescence may have a dual role in either suppressing or promoting liver tumorigenesis in autophagy-defective livers. Notably, Huda et al[5] did not determine senescence in tumor and nontumor cells in aged L-*Atg7* KO mouse livers. Therefore, future work is

needed to determine whether tumor cells would escape senescence to enter a proliferating cell cycle in autophagy-defective livers.

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