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Journal

Molecular & Cellular Oncology, 1(4)

ISSN

2372-3548

Author

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Publication Date

2014-12-08

DOI

10.4161/23723548.2014.968507

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TAK1-dependent autophagy: A suppressor of fatty liver disease and hepatic oncogenesis

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Keywords: AMPK, HCC, mTORC1, NASH, PPAR α

Abbreviations: AMPK, AMP-activated protein kinase; FAO, fatty acid oxidation; IKK, I κ B kinase; JNK, c-Jun N-terminal kinase (JNK); LC3B, microtubule-associated protein 1 light chain 3 b; LKB1, liver kinase B1; NF- κ B, nuclear factor κ B; mTORC1, mechanistic target of rapamycin complex 1; HFD, high-fat diet; PPAR, peroxisome proliferator-activated receptor; TAK1, TGF- β activated kinase 1; Tak1 Δ HEP mice, hepatocyte-specific Tak1-deficient mice; TLR, Toll-like receptor; ULK1, unc-51 like autophagy activating kinase; WT, wild-type

In addition to regulating the activation of nuclear factor (NF)- κ B and c-Jun N-terminal kinase (JNK), TGF- β activated kinase 1 (TAK1) also upregulates the activation of AMP-activated protein kinase (AMPK) and autophagy. In the liver, TAK1-mediated autophagy plays a role in preventing excessive lipid accumulation induced by starvation and fat overload. TAK1-mediated autophagy and inhibition of mechanistic target of rapamycin complex 1 (mTORC1) prevent liver fibrosis and tumor development.

Main Text

TGF- β activated kinase 1 (TAK1), also known as MAP3K7, is a serine/threonine kinase that belongs to the MAP3K family. In the signaling pathways of IL-1 β , toll-like receptors (TLRs), TNF α , and TGF- β , TAK1 regulates the activation of nuclear factor (NF)- κ B and c-Jun N-terminal kinase (JNK).¹ To examine the physiological role of TAK1 in the liver, we generated hepatocyte-specific Tak1-deficient (Tak1 Δ HEP) mice. Surprisingly, these mice develop spontaneous liver damage that leads to chronic liver inflammation, fibrosis, and carcinogenesis.² The ablation of Tak1 in hepatocytes promotes hepatocyte apoptosis and compensatory hepatocyte proliferation due to failure to activate the survival function of NF- κ B. This aberrant hepatocyte regeneration, in combination with chronic liver inflammation, ultimately results in the development of hepatocellular carcinoma in TAK1 Δ HEP mice. However, another group reported that additional deletion of *Ikkbg* (also

known as *Nemo*), an essential modulator of I κ B kinase (IKK) and NF- κ B activation, reduces the spontaneous liver damage, inflammation, fibrosis, and cancer in Tak1 Δ HEP mice.³ This suggests that mechanisms regulated by TAK1 other than the NF- κ B pathway are responsible for the regulation of the liver pathology that develops in Tak1 Δ HEP mice.

Several studies have reported that TAK1 also activates AMP-activated protein kinase (AMPK) and autophagy.⁴ Our recent work demonstrates the pathophysiological role of TAK1-mediated autophagy in the liver. Fasting is a physiological inducer of autophagy in the liver. Fasted wild-type (WT) mice show induction of hepatic autophagy accompanied by decreased expression of p62 (also known as sequestosome or SQSTM1¹) and activity of mechanistic target of rapamycin complex 1 (mTORC1). To our surprise, hepatic Tak1 deficiency suppressed autophagy induction and rescued the decrease in p62 expression and mTORC1 activity upon fasting.⁵ Nutrient deprivation or sensing an increased AMP/

ATP ratio activates AMPK through liver kinase B 1 (LKB1), which directly and indirectly phosphorylates unc-51 like autophagy activating kinase (ULK1) and subsequently induces autophagy. We found that starvation-induced phosphorylation of LKB1, AMPK, and ULK1 and autophagy are TAK1-dependent in hepatocytes. Using microtubule-associated protein 1 light chain 3 β (LC3B)-GFP transgenic mice, we found that basal levels of conversion of LC3BI to LC3BII protein, free GFP generation from the LC3B-GFP fusion protein, and mRNA levels of autophagy-related genes (e.g., *Atg3*, *Atg5*, and *Ulk1*) are downregulated in Tak1-deficient livers.⁵ This indicates that TAK1 regulates not only autophagy induced through AMPK activation, but also basal autophagy through transcriptional control of the expression of autophagy-related genes. A recent report demonstrated that TAK1 also mediates autophagy through S6K1 independently of AMPK, which may be another mechanism for the regulation of basal autophagy through TAK1.⁶

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Submitted: 08/19/2014; Revised: 08/20/2014; Accepted: 08/20/2014

<http://dx.doi.org/10.4161/23723548.2014.968507>

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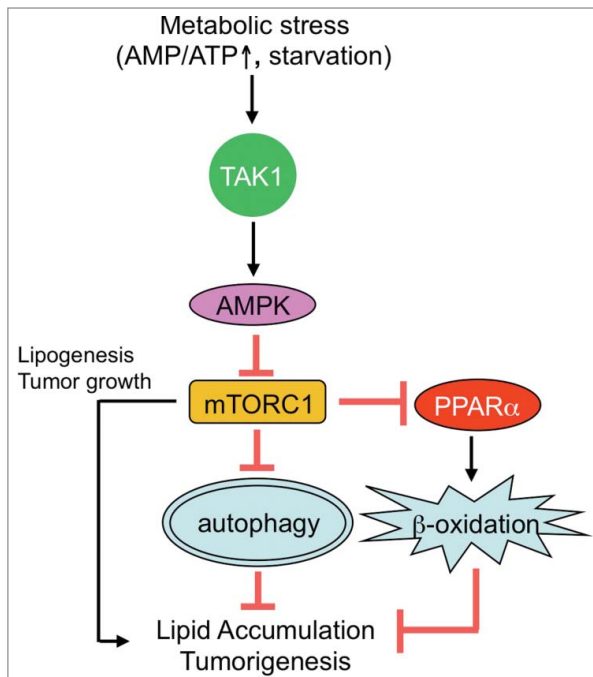


Figure 1. TAK1-mediated autophagy prevents hepatic steatosis and tumorigenesis. Upon nutrition deprivation, TGF- β activated kinase 1 (TAK1) mediates autophagy through activation of AMP-activated protein kinase (AMPK) and inhibition of mechanistic target of rapamycin complex 1 (mTORC1). TAK1 is also associated with induction of peroxisome proliferator-activated receptor (PPAR) α -mediated fatty acid oxidation (FAO) through suppression of mTORC1. Both autophagy and FAO contribute to lipid breakdown to prevent excessive lipid accumulation in hepatocytes. Autophagy prevents, and mTORC1 enhances, spontaneous tumorigenesis in the liver.

AMPK and mTORC1 are suggested to be downstream of TAK1. Indeed, overexpression of a constitutively active form of AMPK and treatment with rapamycin, an mTORC1 inhibitor, induces autophagy in Tak1-deficient hepatocytes.⁵ Rapamycin treatment of TAK1-deficient hepatocytes significantly induces autophagy, but to a lower level than that in WT cells. This suggests that the regulation of autophagy by TAK1 is modulated not only by AMPK and mTORC1, but also by other pathways such as IKK signaling, as reported previously.⁷ A physiological function of TAK1-mediated autophagy is to prevent excessive lipid accumulation through lipophagy, a type of autophagy that degrades intracellular lipid droplets. Fasting increases hepatic uptake of circulating fat released from peripheral fat tissues, but hepatic fat accumulation is tightly regulated by lipophagy to prevent excessive fat accumulation. In contrast, upon fasting the livers of Tak1 ^{Δ HEP} mice dramatically changed to a white color, reflecting excessive accumulation of fat in hepatocytes due to the lack of lipophagy.⁵

We observed autophagic vesicles attached to lipid droplets in WT livers using electron microscopy, but autophagic vesicles were rarely seen in Tak1 ^{Δ HEP} livers.

Although Ikkb ^{Δ HEP} mice have reduced autophagy induction,⁷ fasting does not cause a fatty liver appearance in these mice (Seki, unpublished observation). This suggests the existence of another mechanism in addition to autophagy that promotes hepatic lipid degradation. mTORC1 is known to negatively regulate peroxisome proliferator-activated receptor (PPAR) α -mediated functions.⁸ Given the pronounced upregulation of mTORC1 activity, hepatic PPAR α activity is suppressed in Tak1 ^{Δ HEP} livers. Expression of PPAR α -inducible genes (e.g., *Acox1*, *Cpt1*, and *Hmgcs2*) and PPAR α -mediated β -oxidation were markedly suppressed by the loss of Tak1.⁵ Suppression of lipophagy and PPAR α -mediated β -oxidation promotes lipid accumulation in the liver. Accordingly, a high-fat diet (HFD) challenge augmented hepatic steatosis and inflammation in Tak1 ^{Δ HEP} mice as a result of the strong

suppression of autophagy and β -oxidation by Tak1-deficiency.⁵ Intriguingly, insulin resistance is comparable between WT and Tak1 ^{Δ HEP} mice with high fat diet (HFD) feeding, which suggests a dissociation between hepatosteatosis/ steatohepatitis and insulin resistance.

Alternatively, the role of TAK1-mediated autophagy can be examined through forced induction of autophagy by administration of rapamycin to Tak1 ^{Δ HEP} mice. In contrast to the severe fatty liver appearance in fasted Tak1 ^{Δ HEP} mice, rapamycin treatment suppressed hepatic fat accumulation in these mice.⁵ We confirmed that the effect of rapamycin on the reduction of fat accumulation is largely dependent on autophagy using *Atg5*-silenced hepatocytes.⁵ We also found decreased hepatic expression of TAK1 in advanced fatty liver disease, suggesting a mechanism whereby a decrease in TAK1 in advanced fatty liver suppresses autophagy and increases mTORC1 activity, which further augments hepatosteatosis and liver inflammation and fibrosis, ultimately causing carcinogenesis **Figure 1**.

Since our previous study showing that autophagy defects are associated with liver tumor development,⁹ we have examined the role of autophagy defects in the development of liver fibrosis and tumorigenesis in our mouse model. Rapamycin-induced autophagy significantly suppressed spontaneous hepatocyte injury, liver fibrosis, and tumorigenesis in Tak1 ^{Δ HEP} mice.⁵ This suggests that TAK1-mediated autophagy plays a role in preventing spontaneous liver fibrosis and cancer. The clinical relevance of TAK1 in human non-alcoholic steatohepatitis (NASH) and hepatocarcinogenesis is currently unknown, but once its clinical relevance in human liver disease is understood, targeting TAK1 or TAK1-mediated autophagy could be an important option for the prevention and treatment of human liver disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed

Funding

This work is supported by NIH grants R01AA02172, R01DK085252, and P42 ES010337.

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