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It TAK(es) 1 to prevent steatohepatitis and tumorigenesis

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Article commented:

TAK1-mediated autophagy and fatty acid oxidation prevent hepatosteatosis and tumorigenesis. Inokuchi-Shimizu S, Park EJ, Roh YS, Yang L, Zhang B, Song J, Liang S, Pimienta M, Taniguchi K, Wu X, Asahina K, Lagakos W, Mackey MR, Akira S, Ellisman MH, Sears DD, Olefsky JM, Karin M, Brenner DA, Seki E. *J Clin Invest 2014*; 124(8): 3566-78.

Comment:

TAK1 (TGF-β activated kinase 1) is activated by TLRs, IL-1, TNF, and TGF-β, and in turn, regulates two main transcription factors, IKK/NF- κB and JNK, which control a plethora of essential cellular functions such as cell proliferation, survival, growth, inflammation, tumorigenesis, insulin sensitivity and lipid metabolism.[1] While sustained JNK signaling has been known to exert pathophysiological effects on the liver by causing inflammation, cell death, reactive oxygen species (ROS) generation, lipid accumulation and hepatocellular carcinoma (HCC),[2] IKK/NF- κB signaling has been shown to prevent TNF- and ROS-mediated cell death, steatosis and HCC.[3] Since TAK1 regulates both IKK/NF- κB and JNK pathways with seemingly contrasting effects,[2,3] its role in liver has been difficult to envisage. These authors previously showed that hepatocyte-specific ablation of TAK1 led to spontaneous liver inflammation, apoptosis, fibrosis and HCC development, mediated through TNF- and TGF-β signaling.[4]

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In addition to regulating IKK/NF- κB and JNK, TAK1 signaling is also believed to enhance AMPK-mediated autophagy.[5] Since AMPK is a metabolic sensor, it is activated upon nutrient deprivation, and in turn suppresses mTORC1 complex, a regulator of lipid metabolism and autophagy.[6] Under of nutrient excess, conditions, when ATP levels are high, AMPK activity is suppressed leading to activation of mTORC1, and thereby increased lipid biosynthesis via upregulation of ppar γ and SREBP1c.[7] In addition, mTORC1 is also known to inhibit ppar alpha, which regulates hepatic fatty acid oxidation (FAO).[8] AMPK activation and mTORC1 inhibition regulate autophagy, to remove and recycle cellular components, during a phase with limited nutrients. Autophagy promotes lipid breakdown and inhibits lipid storage.[9]

In this elegant work, the authors have expanded our understanding of this enigmatic and important regulator by clarifying the metabolic function of TAK1, and the pathophysiological relevance of TAK1 regulating autophagy and lipid metabolism through AMPK/mTORC1, and therefore, its effect on liver metabolism and liver tumorigenesis.[9]

To address the physiological role of TAK1 in the liver, the authors first assessed the effect of acute fasting on 1 month old WT (wild type) mice, and mice carrying a hepatocyte-specific deletion of TAK1. After 12 hours of fasting, they found that the livers of Δhep TAK1 mice showed hepatic steatosis and had significantly elevated hepatic triglycerides. Hepatocytes isolated from such mice showed lipid accumulation, relative to their WT counterparts. Furthermore, liver lysates from fasted Δhep TAK1 mice showed overactivation of S6, a marker of mTORC1 activity, whereas WT livers showed an inhibition of mTORC1 activation, consistent with nutrient deficiency. Thus, lipid deposition in the liver is TAK1 dependent, and absence of TAK1 causes excessive mTORC1 activation.

Next, the authors assessed AMPK activation and autophagy under fasting conditions in WT and Δhep TAK1 livers. They observed that AMPK activation was reduced in the livers of Δhep TAK1 mice, rela-

tive to WT livers. Furthermore, autophagy was reduced in the livers of Δhep TAK1 mice, assessed by the increased expression of p62, relative to fasted WT livers, which showed reduced p62 expression (a marker of autophagy induction). In addition, an AMPK activator such as metformin increased TAK1 kinase activity and overexpression of AMPK could stimulate autophagy in livers of Δhep TAK1 mice, indicating that AMPK is a downstream effector of TAK1, which mediates its effect on autophagy.

The authors next wanted to address the cause of steatosis in the livers of Δhep TAK1 mice. On examining the expression of hepatic fatty acid oxidation (FAO) genes, they found that ppar alpha target genes and FAO genes (Cpt1a, Acox) were downregulated in the livers of Δhep TAK 1 mice relative to WT livers, indicating that TAK1 deficiency suppresses ppar alpha activity and the induction of its target genes, thus enhancing lipid accumulation in their livers.

Since TAK1 deficiency causes overstimulation of mTORC1, the authors next asked if rapamycin (an established inhibitor of mTORC1) could restore autophagy in the livers of Δhep TAK mice, and ppar alpha function, reducing lipid accumulation in Δhep TAK1 livers. They found that autophagy was restored, and so was ppar alpha-induced FAO. This salutary effect of mTORC1 inhibition was due to restoration of autophagy, indicating that a defect in autophagy was responsible for the hepatic steatosis in the Δhep TAK1 livers. Furthermore, this rescue establishes that TAK1 acts upstream of mTORC1.

Since TAK1 expression levels are lower in experimental fatty liver disease and in obese mice,[9] the authors wished to test the response of liver-specific TAK1 ablation to a High Fat Diet (HFD) challenge. After 12 weeks on a HFD, relative to WT mice, TAK1 deficient livers showed increased steatosis, increased hepatic TG, FFA, serum ALT and impaired autophagy (increased p62 accumulation). They showed elevated expression of lipid synthesis genes (SREBP1C, DGAT1), inflammatory genes (TNF-α, IL-6), fibrogenic markers (collagen1a1,TGF-β) and also showed significantly enhanced expression of Afp, a HCC marker. Thus, TAK1 deficiency exacerbates a HFD- induced steatohepatitis, as a result of impaired lipid metabolism and autophagy, and also accelerates liver tumorigenesis. Notably, there was no difference in blood glucose levels and body weighs between HFD-fed WT and Δhep TAK1 mice, despite liver pathophysiology.

Finally, the authors wanted to test if rapamycin would protect livers of Δhep TAK1 mice from hepatocellular carcinoma (HCC), since these mice spontaneously develop HCC with expression of typical HCC markers such as alpha fetoprotein, glypican3 and others, relative to WT mice. The authors tested if restoration of autophagy and inactivation of mTORC1 could block HCC development. They found that rapamycin is effective in reducing the number of tumors in an early treatment regimen (2 -10 weeks from birth) and a late therapy with rapamycin (7-9 months of age) reduced the number and size of tumors and fibrosis.

In summary, in this work the authors have shed light on yet another critical role of TAK1: as a regulator of AMPK, an inhibitor of mTORC1 and as a mediator of autophagy; serving as a master regulator of lipid metabolism in the liver. While there is still no evidence showing TAK1 deficiency in human HCC; TAK1 deletion is observed in human prostate cancers.[9] Based on the important findings in this study, it is conceivable that inhibition of mTORC1 activity could become a useful therapy for HCC.

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