Is Mitogen-Activated Protein Kinase Phosphatase 5 a Solution to the Puzzle of the Mitogen-Activated Protein Kinase Signal in Steatohepatitis?

Mitogen-activated protein kinases (MAPKs) are a family of intracellular protein kinases that can regulate hepatic glucose and lipid metabolism. MAPKs are roughly classified into three groups, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, based on their molecular structures. Various stresses, including metabolic stress and cytokine stimulation, activate MAPK pathways to maintain cellular and tissue homeostasis. Activation of MAPKs is also negatively regulated by a group of MAPK phosphatases (MKPs), including MKP1, MKP3, and MKP5. Because MAPK signaling pathways are tightly controlled by their activators and negative regulators, disturbance of MAPK signaling may lead to metabolic dysfunctions, including nonalcoholic steatohepatitis.

While intensive investigations on MAPK signaling pathways discovered their critical functions in the development of obesity as well as steatohepatitis, the studies have also suggested their complexity. For example, (1) following deletion or inhibition of one MAPK molecule, other MAPK molecules are frequently activated that complement the native role of the deleted or inhibited MAPK molecule; (2) there are multiple isoforms in MAPK molecules, and the functions of the individual MAPK may be context dependent, such as cell type and experimental model; and (3) more than 10 negative regulators overlap their substrates.

The gene-modified mouse is an excellent tool to investigate functions of the target molecule. This is not to say that the p38-deficient mouse is the best model to investigate the functional role of p38; however, p38 deletion may cause the activation of JNK, another wing of the MAPK cascade. Also, JNK deletion often shows p38 activation. Therefore, we should carefully interpret the data from gene-modified mice. Distinct roles of MAPK isoforms raise the bar for researchers to elucidate the mechanism. For instance, JNKs have three isoforms: JNK1, JNK2, and JNK3. By hepatic deletions of JNK1 and JNK2, which are major isoforms in the liver, the mice are protected from insulin resistance induced by a high-fat diet. In contrast, hepatic JNK1-deleted mice are prone to insulin resistance in response to a high-fat diet. p38 has four isoforms, comprising p38α, p38β, p38δ, and p38γ, and these show different tissue distributions. Activation of p38α in the liver improves hyperglycemia by reducing...
endoplasmic reticulum stress, whereas p38α/γ in neutrophils promotes inflammation by producing tumor necrosis factor α.(1) JNK1 depletion in hepatocytes promotes insulin resistance,(4) whereas JNK1 depletion in hematopoietic cells protects from insulin resistance induced by a high-fat diet.(5) These findings reflect the distinct and cell-specific roles of individual isoforms even though they share similar substrates. In addition, there are at least 10 different MKPs that negatively regulate MAPK activities.(2) These MKPs possess specific as well as multiple substrates. For instance, MKP1 can inhibit p38, JNK, and ERK, whereas MKP3 inhibits ERKs. Therefore, we are struggling to understand the roles of MAPKs and MKPs in the development of obesity and hepatic steatosis.

In the present issue, Tang et al.(6) elegantly demonstrated the roles of MKP5, a negative regulator of the MAPK signal, in the development of steatohepatitis. MKP5 deficiency exacerbated a high-fat diet-induced steatohepatitis in which aging also affects the metabolic disturbance in mice. Deletion of MKP5 highly activated p38, which induced two targets: activating transcription factor 2 (ATF2) and peroxisome proliferation-activated receptor gamma (PPARγ). ATF2 and PPARγ then elicited an activation of cell death-inducing DNA fragmentation factor-α like effectors (CIDEs), which are associated with the accumulation of lipid droplets in the cytoplasm of hepatocytes. Thus, MKP5 protects from steatosis under physiological and pathologic conditions.

Although MKP5 is likely to regulate MAPK signaling in tissue- and cell-specific manners, little information is available on the roles of MKP5 in the liver. Tang et al. demonstrated that MKP5 specifically inhibited p38 in the steatotic liver without alterations of JNK and ERK activities. This finding is in accordance with MKP5 in neutrophils but in contrast to T cells and skeletal muscle in which MKP5 deficiency induces JNK and ERK activation, respectively. MKP1 and MKP5 have been reported to share the same substrates, including p38, JNK, and ERK. In contrast to MKP5-deficient mice, MKP1 depletion protects against the development of steatohepatitis in leptin receptor-deficient mice, which show an obese phenotype.(7) MKP1 is ubiquitously expressed, and its deficiency induces activation of multiple MAPK signaling pathways, including p38, JNK, and ERK. The cellular localization of MPKs may also affect the activity of MAPK signaling. MKP1 is located in the nucleus, whereas MKP5 exists in both cytoplasm and the nucleus. Interestingly, MKP1 increases JNK activation in the nucleus but not in cytoplasm, which may be associated with different actions between MKP1 and MKP5.

Tang et al. also clearly demonstrated the downstream target of p38 in hepatocytes. There are at least three isoforms in CIDEs, including CIDEa, CIDEb, and CIDEc. These CIDEs, located on the surface of lipid droplets, contribute to the fusion of lipid droplets and promote fat storage. Insulin is a well-known regulator for CIDEs, including CIDEa and CIDEc. In human adipocytes, expression of CIDEa and CIDEc is regulated by protein kinase B2 (Akt2) and JNK2, respectively. Interestingly, the p38 inhibitor SB203580 did not affect the expression of these CIDEs.(8) On the other hand, Tang and colleagues discovered that p38 regulated CIDEa and CIDEc in mouse liver cells. Thus, the regulatory mechanism of CIDEs may differ among cell/organ types or animal species.

Although an understanding of MAPK signals has been progressed by the study of Tang and colleagues, a number of questions on MAPK signaling in the development of steatohepatitis have been raised. First, the presence of MKP5 and its target p38 in human steatohepatitis have not been determined despite genetically modified mice revealing the important role of MKP5 in the development of steatohepatitis. Second, little information is available on the isoforms of p38 in steatohepatitis. In the present study, Tang et al. focused on p38 as a target of MKP5 in hepatocytes, in which p38α and p38β are the major forms. Their research group also showed the crucial role of MKP5 in macrophages,(9) in which other isoforms of p38 may play a role. Third, the functions of CIDEs are not simple. Although CIDEc-deficient mice showed healthy metabolic profiles under a chow diet, the high-fat diet exacerbated hepatic steatosis and insulin resistance. (10)

The actions of MAPK molecules can be compared to pieces of a jigsaw puzzle in the development of steatohepatitis (Fig. 1). Tang and colleagues have fit several pieces related to p38 molecules into the holes of the mouse liver. However, because MAPK signaling differs among cells/organs as well as species, it is unknown if these pieces also fit into humans. Nonetheless, Tang and colleagues unveiled a missing link between MAPK signaling and hepatic steatosis in mice. These data attracted our attention in the role of MKP5 and MAPK signaling. Further investigations are required to elucidate the detailed MAPK signaling in the development of steatohepatitis.
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** REFERENCES **

1) Lawan A, Bennett AM. Mitogen-activated protein kinase regulation in hepatic metabolism. Trends Endocrinol Metab 2017;28:868-878.
2) Caunt CJ, Keyse SM. Dual-specificity MAP kinase phosphatases (MKPs): shaping the outcome of MAP kinase signalling. FEBS J 2013;280:489-504.
3) Vernia S, Cavanagh-Kyros J, Garcia-Haro L, Sabio G, Barrett T, Jung DY, et al. The PPARα-FGF21 hormone axis contributes to metabolic regulation by the hepatic JNK signaling pathway. Cell Metab 2014;20:512-525.
4) Sabio G, Cavanagh-Kyros J, Ko HJ, Jung DY, Gray S, Jun JY, et al. Prevention of steatosis by hepatic JNK1. Cell Metab 2009;10:491-498.
5) Solinas G, Vilcu C, Neels JG, Bandyopadhyay GK, Luo JL, Naugler W, et al. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. Cell Metab 2007;6:386-397.
6) Tang P, Low HB, Png CW, Torta F, Kumar JK, Lim HY, et al. Protective function of mitogen-activated protein kinase phosphatase 5 in aging- and diet-induced hepatic steatosis and steatohepatitis. Hepatol Commun 2019;3:748-762.
7) Flach RJ, Qin H, Zhang L, Bennett AM. Loss of mitogen-activated protein kinase phosphatase-1 protects from hepatic steatosis by repression of cell death-inducing DNA fragmentation factor A (DFFA)-like effector C (CIDEC)/fat-specific protein 27. J Biol Chem 2011;286:22195-22202.
8) Ito M, Nagasawa M, Omac T, Ide T, Akasaka Y, Murakami K. Differential regulation of CIDEA and CIDEC expression by insulin via Akt1/2- and JNK2-dependent pathways in human adipocytes. J Lipid Res 2011;52:1450-1460.
9) Zhang Y, Nguyen T, Tang P, Kennedy NJ, Jiao H, Zhang M, et al. Regulation of adipose tissue inflammation and insulin resistance by MAPK phosphatase 5. J Biol Chem 2015;290:14875-14883.
10) Zhou L, Park SY, Xu L, Xia X, Ye J, Su L, et al. Insulin resistance and white adipose tissue inflammation are uncoupled in energetically challenged Fsp27-deficient mice. Nat Commun 2015;6:5949.

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