Published in final edited form as:

Gut. 2017 April ; 66(4): 567–568. doi:10.1136/gutjnl-2016-312775.

PGAM5: A new player in immune-mediated liver injury

Anup Ramachandran¹ and Hartmut Jaeschke¹

¹Department of Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center, Kansas City, Kansas, USA

Keywords

necroptosis; programmed necrosis; autoimmune hepatitis; concanavalin A-induced liver injury

Mechanisms of cell death are critical in any pathophysiology and hence have been extensively investigated in a number of different organ systems. Initially, the term “programmed cell death” was exclusively applied to apoptosis, where molecular mediators and signaling pathways involved in the process were relatively well characterized. The other form of cell death, namely necrosis, was considered to be an uncontrolled process, where catastrophic events within the cell resulted in a rupture of the plasma membrane with release of cell contents. However, this paradigm has been rapidly evolving as new pathways and mediators, which control necrotic cell death, are discovered. It is now clear that whenever cells die by necrosis, they do so in an ordered systematic manner, which, not surprisingly, shares some components with the apoptotic pathway. This is especially relevant in the liver, where apoptosis was considered to be the main form of cell death in a large number of contexts. These concepts are now changing based on the identification of specific mediators involved in programmed necrosis in response to a number of insults in the liver. The new study from He et al in this issue now identifies mitochondrial phosphoglycerate mutase/protein phosphatase 5 (PGAM5) as another key mediator in physiologically relevant cell death in the liver,¹ reiterating that necrosis is a pathophysiologically relevant form of cell death in the liver.

The initial signaling mediators identified as playing a role in programmed necrosis were induced by Fas Ligand and TNF- α , which along with the receptor-interacting serine-threonine protein kinase 1 (RIP1) induced necrotic cell death (necroptosis) in apoptosis-deficient conditions. The two members of the RIP family, RIP1 and RIP3, were suggested to control the switch between apoptotic and necrotic cell death and a central role for the mitochondria in programmed necrosis is also now recognized.² PGAM5 was identified as a component of the RIP1 and RIP3 containing complexes formed in response to necrosis induction, where it recruited the mitochondrial fission protein dynamin-related protein (Drp1) and induced mitochondrial fragmentation. Knockdown of PGAM5 in either HeLa or

Correspondence: Dr. Hartmut Jaeschke, Department of Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center, 3901 Rainbow Blvd, MS 1018, Kansas City, Kansas, 66169, USA, Tel. +1 913 588 7969, Fax +1 913 588 7501, hjaeschke@kumc.edu.

Competing interests: None declared.

HT29 cells attenuated necrotic cell death and a critical role for this protein in necrosis induced by TNF- α , reactive oxygen species or calcium ionophores implicated it as a convergent point for multiple necrosis pathways.³ PGAM5 is anchored in the mitochondrial membrane and has been shown to associate with and activate apoptosis signal-regulating kinase 1 (ASK1) by dephosphorylation of inhibitory sites.⁴

The role of PGAM5 in necroptosis may be cell and organ specific, since it was found that PGAM5-deficiency surprisingly exacerbated, rather than reduced necroptosis in response to multiple *in vitro* and *in vivo* necroptotic stimuli, including ischemic reperfusion injury in the heart and brain. In these tissues, the loss of PGAM5/PINK1 (PTEN-induced putative kinase 1) mediated mitophagy caused the accumulation of abnormal mitochondria, leading to the overproduction of reactive oxygen species and worsened necroptosis.⁵ PGAM5 was also found to be dispensable for necroptosis in mouse embryonic fibroblasts and bone marrow-derived macrophages, where PGAM5 seems to function independent of RIP3 to promote inflammasome activation.⁶

In the liver, PGAM5 has been shown to be involved in immune signaling by being activated by RIP3, which promotes cytokine expression through facilitating nuclear translocation of nuclear factor of activated T-cells (NFAT) and dephosphorylation of Drp1. This suggests that RIP3-PGAM5 signaling may mediate crosstalk between mitochondrial function and immune signaling in the organ.⁷ In the work by He et al, the investigators first showed that PGAM5 expression and Drp1-mediated mitochondrial fission are activated in hepatocytes from humans and mice with autoimmune hepatitis.¹ Using PGAM5-deficient mice, they then demonstrated that PGAM5 is strictly required for concanavalin A-induced hepatic necrosis and liver damage, which was used as an experimental model of autoimmune hepatitis. Mechanistically, they showed that Drp1-mediated mitochondrial fission is a critical step downstream of PGAM5 in hepatocellular necrosis since a Drp1 inhibitor (Mdivi; mitochondrial division inhibitor 1) blocked mitochondrial fission and attenuated liver damage induced by concanavalin A.¹ However, the investigators have not differentiated between the two forms of PGAM5 (the long and short form) and it would be interesting to determine if both forms function similarly in the liver. This is relevant, since a comparison of phosphatase activity between short and long PGAM5 isoforms in HEK 293 cells suggested that only the long isoform is catalytically competent, a property which correlated with an increased ability of PGAM5L to form dimers and/or higher order oligomers in intact cells compared to PGAM5S.⁸ Also, of relevance to the metabolic role of the liver is the fact that PGAM5 may be involved in the whole-body metabolism in response to stresses that impose metabolic challenges on mitochondria. Pgam5-deficient mice better maintained body temperature than wild-type animals and showed an extended survival rate under cold stress with fasting and were also resistant to high-fat-diet-induced obesity.⁹ In addition, it was recently shown that apoptosis inducing factor (AIF), which has a role in maintaining mitochondrial energy homeostasis, binds both the short and long isoforms of PGAM5 and can reduce the ability of PGAM5 to control antioxidant responses in HEK293 cells, suggesting the existence of an AIF/PGAM5/XIAP (X-linked inhibitor of apoptosis) axis that can regulate PGAM5 activities related to the antioxidant response and mitophagy.⁸ Since the RIP-Drp1 axis as well as AIF play key mechanistic roles in signaling cascades responsible for necrosis and liver injury in other clinically relevant models (such as acetaminophen

hepatotoxicity) as well,¹⁰ it is possible that PGAM5 has a role in programmed necrosis in this context as well. Though shRNA-mediated knockdown of PGAM5 did not protect HepG2 cells from acetaminophen-induced cell death,⁶ the results may be confounded by the fact that HepG2 cells lack the metabolic competence to initiate acetaminophen hepatotoxicity. Hence, further studies would be needed to confirm the broad relevance of PGAM5 in liver injury induced by a wide variety of insults.

Acknowledgments

Work in this laboratory was supported in part by the National Institutes of Health grants R01 DK102142 and R01 AA12916, and by grants from the National Institute of General Medical Sciences (8 P20 GM103549-09 and 1P30 GM118247-01) from the National Institutes of Health.

Abbreviations

AIF	apoptosis inducing factor
ASK1	apoptosis signal-regulating kinase 1
Drp1	dynammin-related protein
Mdivi	mitochondrial division inhibitor 1
NFAT	nuclear factor of activated T-cells
PGAM5	phosphoglycerate mutase/protein phosphatase 5
PINK1	PTEN-induced putative kinase 1
XIAP	X-linked inhibitor of apoptosis

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