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Review

Physiological and pathological roles of PGAM5: An update and future trend

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SUMMARY

PGAM5, a phosphatase found in mitochondria, is crucial for mitochondrial quality control (MQC) through its regulation on mitochondrial dynamics, biogenesis, and mitophagy. Previous studies have shown its involvement in multiple regulated cell deaths (RCDs), including apoptosis, necroptosis, and pyroptosis. The objective of this review is to enhance our comprehension of the involvement of PGAM5 in MQC and RCDs. Additionally, we summarize some novel roles of PGAM5 in cellular senescence, lipid metabolism, and immune response modulation in recent studies. Finally, we discuss PGAM5's contribution to the pathological state of cardiovascular, hepatic, neurological, and neoplastic diseases, offering potential perspectives for future research.

INTRODUCTION

Phosphoglycerate mutase 5 (PGAM5), an individual from the phosphoglycerate mutase group, is predominantly found within the mitochondria. It serves as a mitochondrial phosphatase and a reactive oxygen species (ROS) sensor, involving in mitochondrial quality control (MQC).[1] PGAM5 has two splice variants, namely PGAM5-L (long-form) and PGAM5-S (short-form), both of which contain cleavage sites of presenilin-associated rhomboid-like (PARL). It can interact with various molecules through its different regions, and its structure can switch between a dimer and a dodecamer, rendering it multifunctional in cell biology. The detailed molecular mechanisms have been well summarized in a previous review.[2] Although certain topics of PGAM5, such as MQC, have been covered in the review, recent studies have revealed some additional roles of PGAM5 in MQC and regulated cell death (RCD). More importantly, some novel functions of PGAM5 including cellular senescence, lipid metabolism, and immune response were observed in the recent studies. The present review aims to provide updates on PGAM5's canonical roles and present the latest findings on its novel functions, offering a comprehensive comprehension of the biological roles of PGAM5, while also examining its participation in various diseases (Figure 1).

Mitochondrial phosphatase PGAM5 is involved in various cellular biological process, including mitochondrial quality control, cellular senescence, lipid metabolism, immune response, and RCD. These render it significant implications in different diseases, including cardiovascular, hepatic, and neurological diseases and neoplasm.

THE INVOLVEMENT OF PGAM5 ON MITOCHONDRIAL QUALITY CONTROL

The primary components of the MQC system comprise mitochondrial biogenesis, mitochondrial dynamics, and mitophagy. These interconnected biological processes work together to maintain cellular mitochondrial homeostasis.[3,4] PGAM5, a Ser/Thr phosphatase, is mainly located within the mitochondria. By interacting with proteins involved in mitochondrial dynamics, mitophagy, and mitochondrial biogenesis, it plays vital roles in the MQC (Figure 2).

The involvement of PGAM5 in mitochondrial dynamics

Fission and fusion and are key events that regulate mitochondrial dynamics, maintaining a balance to support normal mitochondrial function.[5] PGAM5 plays a multifaceted role in both mitochondrial fusion and fission, depending on the cellular context and specific stimuli. In particular, PGAM5 is involved in mitochondrial division through its interaction with Syntaxin 17 (STX17), a protein that localizes to mitochondria-associated membranes (MAMs), known platforms for mitochondrial fission.[6,7] Under fed conditions, STX17 is essential for proper PGAM5 localization and function. In the absence of STX17, PGAM5 clusters within the mitochondria, preventing the dephosphorylation and activation of Drp1, a GTPase responsible for mitochondrial fission. This failure to activate Drp1 leads to mitochondrial elongation as fission is impaired. Thus, STX17 enables PGAM5-mediated dephosphorylation of Drp1, ensuring that mitochondrial fission can proceed as needed under normal condition. Upon starvation, STX17 translocates from MAMs to

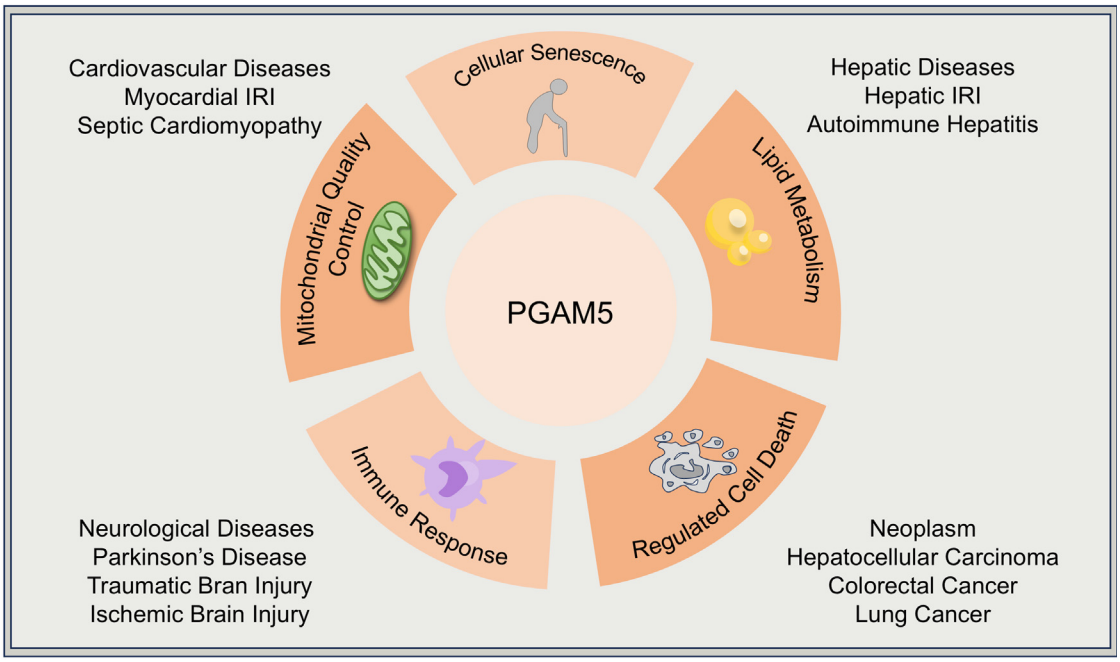

Figure 1. Physiological and pathological implication of PGAM5

autophagosomes, shifting its role from facilitating mitochondrial fission to interacting with ATG14L, a key autophagic protein. This transition indicates that the role of STX17 and PGAM5 in mitochondrial dynamics is context-dependent, switching from supporting fission in nutrient-replete states to participating in autophagy and mitophagy under stress conditions.[8] When mitophagy is induced by treatments such as CCCP, PGAM5 undergoes cleavage and is released from the mitochondria, where it binds to FUNDC1,[9] another MAM protein required for hypoxia-induced mitochondrial fission.[10] Interestingly, this interaction between PGAM5 and FUNDC1 also depends on its prior interaction with STX17, further highlighting the importance of STX17 in regulating PGAM5's roles across different mitochondrial quality control pathways.[7]

In addition to mitochondrial division, PGAM5 has recently been documented to play a significant part in mitochondrial fusion by its interaction with MFN2.[11] In particular, the interaction between PGAM5 and MFN2 safeguards MFN2 against phosphorylation, thereby increasing its stability and fusogenic capability. Interestingly, mutants of PGAM5 that lack catalytic activity can induce mitochondrial fission without the involvement of Drp1.[11] Although it may seem paradoxical that PGAM5 promotes both mitochondrial fission and fusion processes by interacting with STX17 and MFN2, respectively, it is important to recognize that mitochondrial morphology is highly dynamical. An inclination toward either mitochondrial fission or fusion may serve as a cellular mechanism for adapting to different types of stress.

The involvement of PGAM5 in mitophagy

Mitophagy is a form of selective autophagy that targets intracellular mitochondria. As we reviewed previously,[12] it is a biological process aimed at clearing dysfunctional or redundant mitochondria to maintain its quality and quantity.[12] Mitophagy can be categorized into two main types: PINK1-Parkin-mediated mitophagy and receptors-mediated mitophagy. (1) In the process of PINK1-Parkin-mediated mitophagy, PGAM5 and PINK1 serve as competitive substrates of rhomboid protease PARL, depending on the mitochondrial membrane potential (MMP).[13] Upon MMP loss, there is a cleavage switch from PINK to PGAM5, resulting in the buildup of PINK1 on the mitochondrial outer membrane (MOM) and continuous activation of PINK1-Parkin-mediated mitophagy.[13] (2) Receptors-mediated mitophagy: PGAM5 is also involved in FUNDC1-mediated mitophagy and PHB2-mediated mitophagy. Under normal conditions, FUNDC1-mediated mitophagy is inhibited by the phosphorylation of FUNDC1 at Tyr-18 (by Src kinase) and Ser-13 (by CK2 kinase). Nevertheless, when faced with hypoxia or FCCP treatments, the intensified association between FUNDC1 and PGAM5 promotes the dephosphorylation of FUNDC1 and its subsequent interaction with LC3.[9] Additionally, PGAM5 plays a role in PHB2-mediated mitophagy. Apart from functioning as a mitophagy receptor,[14] PHB2 enhances PINK1-Parkin-mediated mitophagy by ensuring the stability of PINK1, necessitating the involvement of the PARL-PGAM5 axis.[15] A recent study demonstrated that PGAM5-mediated PHB2 dephosphorylation induces its cytosolic translocation, thereby inhibiting PHB2-mediated mitophagy.[16] Overall, PGAM5 coordinates different types of mitophagy to sustain normal MQC under physiological conditions.

The involvement of PGAM5 in mitochondrial biogenesis

The process of mitochondrial biogenesis, which is tightly regulated by both the nuclear and mitochondrial genomes, entails

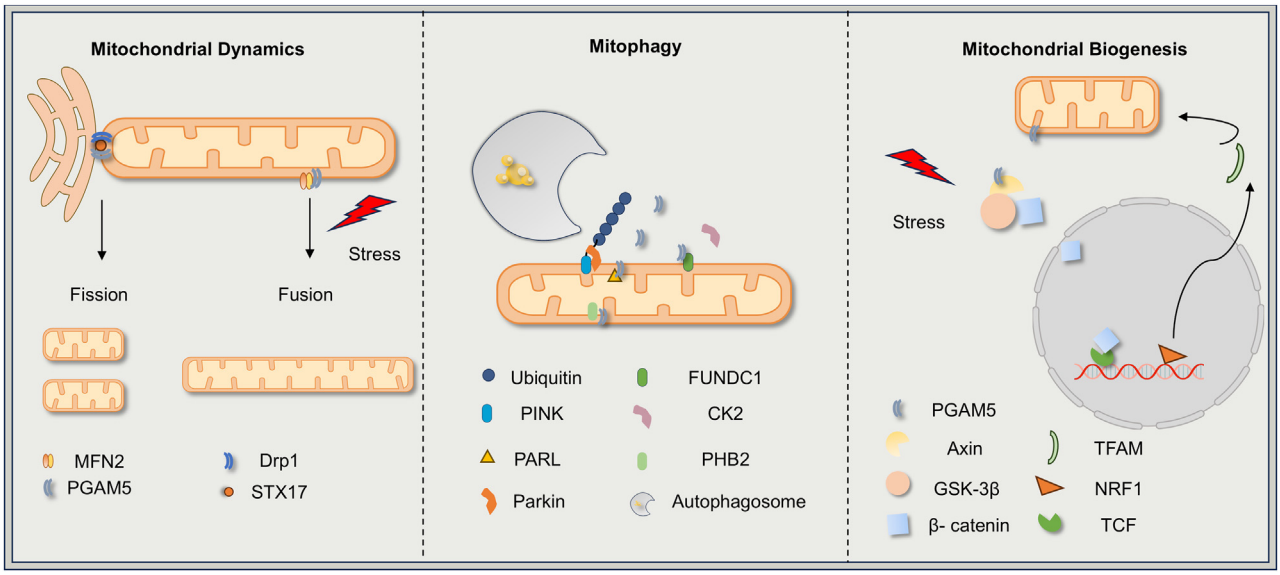

Figure 2. Role of PGAM5 in mitochondrial quality control (MQC)

PGAM5 participates in various MQC processes of MQC, including mitochondrial dynamics, mitophagy, and mitochondrial biogenesis. (1) Mitochondrial dynamics: PGAM5 can either facilitate mitochondrial fission or fusion. On the one hand, PGAM5 can promote mitochondrial fission by activating Drp1. In this process, STX17 plays a role by altering their localization. On the other hand, PGAM5 also promotes mitochondrial fusion by dephosphorylating and stabilizing MFN2 under stress conditions. (2) Mitophagy: PGAM5 is involved in both PINK-Parkin-mediated mitophagy and receptor-mediated mitophagy. Upon MMP loss, PARL tends to cleave PGAM5 rather than PINK. This leads to PINK stabilization and sustained activation of PINK-mediated mitophagy. The cleaved PGAM5 is released into cytoplasm and competes with CK2 kinase to dephosphorylate FUNDC1, thereby activating FUNDC1-mediated mitophagy. Additionally, PGAM5 is involved in the PHB2-mediated PINK1 stabilization and inhibition of PHB2-mediated mitophagy. (3) Mitochondrial biogenesis: PGAM5 promotes mitochondrial biogenesis through its interaction with AXIN and stabilization of β-catenin. Besides, NRF1-TFAM pathway may also be potentially involved in PGAM5-mediated mitochondrial biogenesis.

the increase in mitochondrial mass. PGAM5 is involved in this process, primarily via the Wnt-β-catenin pathway.[17] When mitochondrial stress is triggered by CCCP, the released cytosolic PGAM5 interacts with the AXIN, a crucial constituent of the Wnt pathway. The interaction hinders the degradation of β-catenin through AXIN, resulting in elevated β-catenin levels and β-catenin-mediated transcription.[17] This process relies on PGAM5's phosphatase activity, as the H105A mutant of PGAM5 fails to induce β-catenin dephosphorylation. Additionally, there are clues suggesting that PGAM5 is involved in NRF1-TFAM-mediated mitochondrial biogenesis.[18] PGAM5 deletion impedes heme-oxygenase-1-regulated mitochondrial biogenesis during ischemia/reperfusion injury, in which NRF1-TFAM pathway plays a role.[18] However, the detailed mechanism remains elusive. Hence, ongoing research affirms the notion that PGAM5 may function as a component of a feedback mechanism, controlling the balance of mitochondria in response to mitochondrial stress.

THE INVOLVEMENT OF PGAM5 IN REGULATED CELL DEATH

Mitochondria act as multifaceted regulators of RCD, including apoptosis, necroptosis, and pyroptosis under different types and extents of stress.[19] The mitochondrial phosphatase PGAM5, as an important regulator of MQC, has been reported to modulate multiple forms of RCDs (Figure 3).

Role of PGAM5 in apoptosis

There are two main apoptotic signaling pathways, including the extrinsic pathway of apoptosis and the intrinsic (mitochondrial) pathway of apoptosis. The extrinsic pathway includes the attachment of death receptor ligand to the family of death receptors, leading to the activation of caspase 8. On the other hand, the intrinsic pathway primarily involves MOMP and the activation of caspase 3/7.[19] The main role of PGAM5 is to control the intrinsic apoptosis process by impacting MOMP and influencing the activity of either anti-apoptotic or pro-apoptotic BCL-2 family proteins directly or indirectly. PGAM5-induced dephosphorylation of BAX facilitates MOMP and cytochrome C leakage, which further activates the downstream apoptosis pathway.[20] The ability of PGAM5 to interact with the anti-apoptotic protein BCL-xL is determined by a balance between its dimeric and multimeric states.[21] During vinblastine-induced cell death, PGAM5 binds to and dephosphorylates BCL-xL at Ser62, leading to the reestablishment of BCL-xL's ability to trap BAX and BAK. As a result, resistance to apoptosis is conferred.[21] In cells treated with selenite, PGAM5 forms additional multimers, leading to its separation from BCL-xL. This separation leads to an increase in BCL-xL phosphorylation and ultimately apoptosis.[21] Similarly, the interaction of PGAM5 with another BCL2 family protein, BCL2L13, promotes effector caspase activity and apoptosis.[22] X-linked inhibitor of apoptosis (XIAP) suppresses caspases activity by its direct interaction, functioning as protective ubiquitin ligases that regulate proapoptotic proteins. Proteins containing

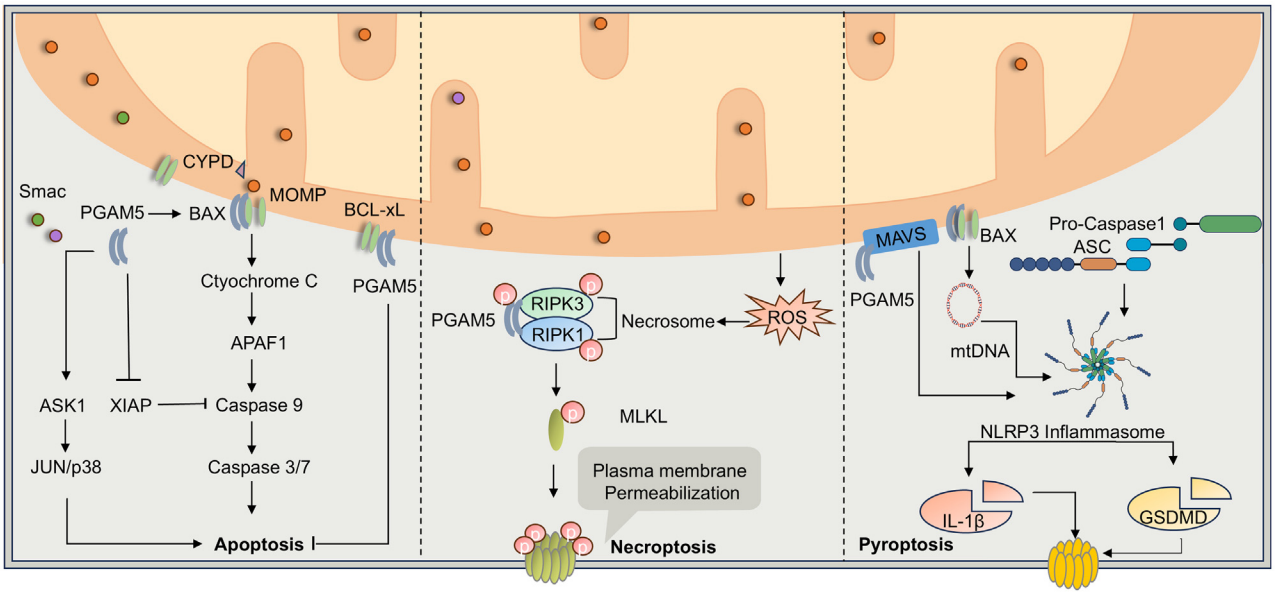

Figure 3. The involvement of PGAM5 in regulated cell death

PGAM5 participates in various forms of RCD, including apoptosis, necroptosis, and pyroptosis. PGAM5 has dual roles in apoptosis. On one side, PGAM5 enhances cell death either by aiding in the permeabilization of the outer membrane of mitochondria (MOMP) and the release of cytochrome C or by blocking XIAP through its IBM domain. Besides, PGAM5 also promotes apoptosis via the ASK1-JUN/p38 pathway. On the other side, PGAM5 prevents apoptosis by interacting with BCL-xL. Oxidative stress can induce necrosome assembly, and PGAM5 facilitates necroptosis by interacting with necrosome and activating downstream necroptosis pathways; PGAM5 promotes pyroptosis by facilitating ASC oligomerization and inflammasome activation, which may potentially be attributed to its promotion on mtDNA release.

the IAP-binding motif (IBM), such as Smac and HtrA2, prevent XIAP from binding to caspases, thereby promoting caspase activity.[23] Interestingly, an IBM was also identified in PGAM5, enabling the released cytosolic PGAM5 to bind to XIAP and sensitizes cells to apoptosis under the stress.[24,25] Moreover, PGAM5 has the ability to interact with and dephosphorylate apoptosis signal-regulating kinase 1 (ASK1),[26] leading to the activation of the downstream c-Jun N-terminal kinase (JNK)/p38 apoptosis pathway.[27] Overall, PGAM5 exhibits both an anti-apoptotic effect and a pro-apoptotic effect, which may potentially differ under mild or severe stress conditions.

Role of PGAM5 in necroptosis

Necroptosis represents a programmed, caspase-unrelated mechanism of cellular death. In the presence of caspase inhibition, the administration of tumor necrosis factor alpha (TNF-α) results in the stimulation of receptor-interacting protein kinase 1 (RIPK1) and RIPK3. As a consequence, the necrosome is formed, subsequently causing the phosphorylation of MLKL and the permeabilization of the plasma membrane.[19] PGAM5 regulates necroptosis by interacting with necrosome, which subsequently induces Drp1 activation and execution of necroptosis.[28] In addition to TNF-α, PGAM5 deletion also safeguards cells against t-butyl hydroxide (TBH), H2O2, and calcium ionophore A23187-triggered cell demise, indicating that PGAM5 could serve as the focal point for various necrosis pathways.[28] In a RIPK1-dependent and RIPK3/MLKL-independent extracellular matrix (ECM) detachment-induced cell death, PGAM5 collaborates with RIPK1 to initiate PINK-mediated mitophagy and subsequent ROS production.[29] Interestingly, the above effect of PGAM5 on necroptosis may be species-dependent, as *Pgam5* knockdown in murine cells dose not confer protection against TNF-α-induced necroptosis.[30] Neither Drp1 nor PINK1 deletion affects TNF-α-induced necroptosis.[30] The reason for this difference could be attributed to the necessity of both splice variants of PGAM5 for carrying out necrosis.[28] Specifically, the short-form PGAM5 (PGAM5-S), necessary for necroptosis execution, has only been observed in humans but not in any other species.[2] Additionally, PGAM5 has been reported to interact with cyclophilin D (CypD) to regulate the opening of mitochondrial permeability transition pore (mPTP), which is involved in cardiac microvascular ischemia-reperfusion injury and bromocriptine-induced necroptosis.[31,32] To summarize, PGAM5 meditates necroptosis downstream of the necrosome. During the process, Drp1-mediated mitochondrial fission, CypD-mediated mPTP opening, and PINK-mediated mitophagy may have a role. Of note, the aforementioned effects are not so highly conserved across species.

Role of PGAM5 in pyroptosis

Pyroptosis is an inflammatory type of RCD driven by the inflammatory caspases 1, 4, 5, and 11.[33] This condition is distinguished by the formation of inflammasomes, permeability of the plasma membrane, and the subsequent release of pro-inflammatory cytokines, such as interleukin 1β (IL-1β) and IL-18. PGAM5 plays a role in the regulation of pyroptosis. PGAM5-mediated pyroptosis is involved in the traumatic brain injury (TBI).[34] The removal of PGAM5 relieves the activation of microglia, damage to neurons, lesions in tissues, and neurological dysfunctions in mice with

TBI by decreasing molecules associated with pyroptosis. Furthermore, the inhibition of ASC-oligomerization-mediated caspase-1 activation by *Pgam5* knockdown eliminates the secretion of IL-1β induced by lipopolysaccharide (LPS)+ATP, regardless of RIPK3.[34] In the same way, PGAM5 is not necessary for necroptosis but enhances inflammasome activation in macrophages of mice.[35] The absence of PGAM5 inhibits the release of IL-1β when exposed to NLRP3/AIM2 inflammasome agonists, and this effect is independent of RIPK3.[35] Furthermore, a separate investigation indicated that PGAM5, rather than RIPK1 kinase function, is directly accountable for the release of IL-1β induced by Leishmania in macrophages derived from murine bone marrow.[36] The potential mechanism by which PGAM5 activates the inflammasome is that PGAM5 facilitates mtDNA release by dephosphorylating BAX.[37] Collectively, these investigations suggest that PGAM5 serves as a new controller of inflammasome and caspase 1 function, operating independently from RIPK1/3. However, all of the aforementioned studies were conducted in mice, so it remains unknown whether the same mechanisms apply to human.

The role of PGAM5 in the crosstalk between MQC and RCD

MQC and RCD are closely interconnected processes that maintain systemic health. The process of MQC ensures the proper function and integrity of mitochondria. When MQC mechanisms fail to restore mitochondrial function, damaged mitochondria can trigger RCD pathways, such as apoptosis and necroptosis, to eliminate dysfunctional cells and prevent harm to the organism. PGAM5 is involved in both MQC and RCD, as described earlier, and may influence RCD either by affecting MQC or through independent mechanisms. For instance, upon TNF-α treatments, PGAM5 collaborates with RIPK1/3 to induce DRP1 dephosphorylation and mitochondrial fragmentation, which ensure the necroptosis execution.[28] PGAM5 can also respond to different extent of stress by affecting the mitophagy or apoptosis.[21] Under the mild stress, PGAM5 employs FUNDC1-mediated mitophagy to eliminate the damaged mitochondria, thus promoting cell survival.[21] While upon severe stress, PGAM5 may dephosphorylate BCL-xL to inhibit BAX-BAK-mediated apoptosis.[21] However, upon lethal stress, the pro-survival effect of PGAM5 may decompensate and instead cell death is executed.[21] Upon CCCP or hypoxia treatments, PINK1-mediated mitophagy or FUNDC1-mediated mitophagy is induced to clear dysfunctional mitochondria. To compensate the mitochondria loss, PGAM5 can be cleaved and released from damaged mitochondria and activate mitochondrial biogenesis pathway,[17] which is important for determining cell fates. In tumor cells, RIPK/PGAM5 enhances anoikis by inducing PINK1-mediated mitophagy. Antagonizing RIPK1/PGAM5 inhibits mitophagy and enhances tumor formation *in vivo*.[29] In summary, PGAM5 plays a pivotal role in the interplay between MQC and RCD, influencing cellular outcomes by modulating mitochondrial quality and cell death pathways. It can mediate various responses to stress, from promoting mitophagy and cell survival under mild conditions to triggering apoptosis or necroptosis under more severe or lethal stress. Additionally, PGAM5's interactions with RIPK1/3, BCL-xL, and other key regulators highlight its dual role in maintaining mitochondrial integrity and determining cell fate, making it a critical player in both normal physiological and pathological processes.

THE INVOLVEMENT OF PGAM5 IN CELLULAR SENESCENCE

Cellular senescence and mitochondrial dysfunction are two hallmarks of aging.[38] Considering the involvement of PGAM5 in MQC, it is conceivable that it could also have a part in aging-related diseases. The activation of Wnt-β-catenin pathway has been frequently observed in age-related diseases.[39–41] Although it could be hypothesized that PGAM5 may enhance cellular senescence by stimulating the Wnt-β-catenin pathway,[17] research has demonstrated that the removal of PGAM5 expedited the senescence of retinal pigment epithelial (RPE) cells, both *in vitro* and *in vivo*. The cellular senescence caused by the deletion of PGAM5 is mechanistically linked to an increase in mitochondrial fusion and a decrease in mitochondrial turnover.[42] Additionally, the regulation of developmental mitochondrial stress by PGAM5 is necessary and sufficient to prolong the lifespan of drosophila.[43] On the other hand, another research revealed that the absence of PGAM5 can inhibit muscle degeneration and reduced lifespan caused by PINK1 inactivation in drosophila.[44] Nevertheless, the effect of PGAM5 on aging-related diseases is not always consistent. A study revealed that PGAM5 exhibits high expression and a positive correlation with ovarian aging. Furthermore, partly restoration of mitochondrial function and metabolism in aging granulosa cells is observed upon PGAM5 elimination.[45] However, the comprehensive understanding of the precise mechanism through which PGAM5 triggers aging remains unexplored. The released cytosolic mtDNA activates cGAS-STING pathway, which induces chronic senescence-associated secretory phenotype (SASP).[46] It is worth noting that PGAM5 has been found to control the MOMP and the release of mtDNA by dephosphorylating BAX, which is a constituent of macropores in the mPTP.[37] It would be interesting to investigate whether PGAM5-induced mtDNA release is involved in PGAM5-mediated aging-related diseases. In conclusion, PGAM5 might have a significant impact on age-related illnesses, primarily based on its role in MQC. However, the specific effects of PGAM5 may differ in distinct diseases, warranting further investigation.

THE INVOLVEMENT OF PGAM5 IN LIPID METABOLISM

Over the past years, researchers have observed the impact of PGAM5 on lipid metabolism. *Pgam5*-deficient mice exhibit resistance to metabolic stress such as cold stress, fasting, and high-fat-diet treatments.[47] In terms of mechanism, the removal of PGAM5 induces a dramatic increase in fibroblast growth factor 21 (FGF21), triggering diverse activities in brown adipose tissue (BAT), such as thermogenesis, despite a notable decrease in serum triglycerides and lipid content within BAT.[47] Additional research has revealed that PGAM5 inhibits the utilization of energy in mitochondria by reducing the expression of UCP1 in BAT, which depends on its phosphatase activity and intramembrane cleavage.[48] Lipin-1, a key controller of lipid balance, functions as both an enzyme and a transcription co-regulator.[49]

Table 1. Substrates of PGAM5 and biological processes involved

Substrates	Biological process	Modification site	Reference
DRP1	Mitochondrial fission	Ser 637	Wang et al.[28]
MFN2	Mitochondrial fusion	Ser 27	Nag et al.[11]
FUNDC1	Mitophagy	Ser 13	Chen et al.[9]
β-Catenin	Mitochondrial biogenesis	Unidentified	Bernkopf et al.[17]
BAX	Cytochrome C release	Ser 184	Li et al.[58]
	Mitochondrial DNA leakage	Ser 184	Li et al.[37]
BCL-xL	Apoptosis inhibition	Ser 62	Ma et al.[21]
ME-1	Lipid metabolism	Ser 336	Zhu et al.[51]
Lipin-1	Lipid metabolism	Central domain (AA153-623)	Okuno et al.[50]
NDPK-B	Immune response	His118	Panda et al.[55]

PGAM5 may potentially regulate lipid metabolism by modulating lipin-1 activity through its phosphatase function.[50] Apart from adipose tissue, PGAM5-regulated lipid metabolism has been mainly studied in cancers. PGAM5 is significantly increased during colorectal tumorigenesis, resulting in the dephosphorylation of malic enzyme 1 (ME1) at S336.[51] This dephosphorylation allows the formation of ME1 dimers and its activation,[51] which in turn stimulates the synthesis of nicotinamide adenine dinucleotide phosphate (NADPH) and promotes lipogenesis in colorectal cancers.[51] In the same way, the deacetylation of PGAM5 by SIRT2 triggers the activation of ME1, leading to the accumulation of lipids and the proliferation of liver cancer cells.[52] Furthermore, PGAM5 is upregulated in hepatocellular carcinoma (HCC) and plays a role in the buildup of lipid droplets by controlling the uptake of long-chain fatty acids in HCC via fatty acid binding protein 1 (FABP1).[53]

THE INVOLVEMENT OF PGAM5 IN IMMUNE RESPONSE

By influencing various immunological cells, recent studies have shown increased involvement of PGAM5 in the immune response. The RIPK3/PGAM5 pathway in natural killer T (NKT) cells enhances the production of cytokines by aiding the movement of NFAT into the nucleus and dephosphorylation of Drp1. This pathway is involved in immune responses in tumors and acute liver inflammation.[54] The modulation effect of RIPK3/PGAM5 in NKT cell activation is dependent on the T cell receptor (TCR) signal.[54] The deletion of PGAM5 in bone-marrow-derived macrophages (BMDM) significantly hampers the inflammasome activation and the process of maturation and release of IL-1β.[35] PGAM5 functions as a histidine phosphatase in CD4(+) T cells, dephosphorylating the catalytic histidine on nucleoside diphosphate kinase B (NDPK-B) and consequently disabling the K(+) channel KCa3.1.[55] PGAM5 negatively regulates CD4(+) T cells through the dephosphorylation of NDPK-B.[55] (The known identified PGAM5 substrates are summarized in Table 1). Furthermore, the activation of the PGAM5-β-catenin-mitochondrial biogenesis axis by urolithin A triggers mitophagy, resulting in the generation of T memory stem cells and providing robust immunity against tumor cells by CD8+T cells.[56] Besides, PGAM5 additionally contributes to antiviral immunity through its interaction with the mitochondrial antiviral-signaling protein (MAVs).[57] When infected with vesicular stomatitis virus (VSV), mouse embryonic fibroblasts (MEFs) lacking PGAM5 show reduced interferon β (IFN-β) production and enhanced replication of VSV.[57] Similarly, IL-1β secretion is impaired in VSV-infected BMDM upon PGAM5 deletion.[35] Taken together, PGAM5 is involved in immune response by modulating the activity of different immunological cell, rendering it potential target in antiviral immunity.

PATHOLOGICAL IMPLICATIONS OF PGAM5

The diverse functional roles of PGAM5 make it a key player in various pathophysiological conditions. Its involvement in regulating mitochondrial quality control, cell death pathways, lipid metabolism, and immune responses has been documented in numerous disease contexts, highlighting its potential contribution to the development and progression of cardiovascular, hepatic, neurological, and oncological disorders.

PGAM5 in cardiovascular diseases

In cardiovascular disease, PGAM5 is mainly involved in myocardial ischemia reperfusion injury (MIRI) and septic cardiomyopathy. The modulation of Keap1-mediated Bcl-xL degradation by PGAM5 regulates cardiomyocyte apoptosis during MIRI.[59] However, there are more evidence supporting that PGAM5-mediated necroptosis is involved in MIRI. PGAM5 deletion inhibited MIRI-induced necroptosis, but did not stop the activation of apoptosis. As a result, there was an enhancement in myocardial function and a reduction in the inflammatory response in mice.[20] The absence of PGAM5 facilitated mitochondrial biogenesis, restored normal mitochondrial respiration, suppressed the generation of reactive oxygen species, and hindered the opening of mPTP in cardiomyocytes.[20] Likewise, blocking PGAM5 can decrease necroptosis in rat hearts subjected to MIRI by inhibiting Drp1.[60] Moreover, the Langendorff-perfused rat hearts are safeguarded against MIRI and decreased necroptosis due to the promotion of Keap1-mediated degradation of PGAM5 by the AMPK agonist metformin.[61] Additionally, the repression of endothelial necroptosis to mitigate cardiac microvascular ischemia-reperfusion injury also involves the suppression of the RIPK3-PGAM5-CypD-mPTP pathway, as stated in study.[31] Apart from MIRI, there are also some studies supporting that PGAM5 has role in septic cardiomyopathy. The involvement of the RIPK3/PGAM5

signaling pathway in LPS-induced cardiomyocyte necroptosis was discovered.[62] Furthermore, an *in vivo* investigation indicated that the removal of PGAM5 specifically in cardiomyocytes reduced LPS-induced myocardial dysfunction and maintained the viability of cardiomyocytes by preventing the loss of PHB2 localized in the mitochondria and thereby activating mitophagy and the mitochondrial unfolded protein response (UPR^{mt}).[16]

PGAM5 in hepatic diseases

PGAM5 primarily contributes to acute liver injury, encompassing autoimmune hepatitis (AIH) and hepatic ischemia reperfusion injury (HIRI)[63] among various liver diseases. The expression of PGAM5 is significantly elevated in the liver cells of patients with AIH and in mice liver with experimental hepatitis induced by ConA. Inhibiting Drp1-mediated mitochondrial fission through the deletion of PGAM5 safeguards mice against hepatocellular death and liver injury caused by AIH.[54,64] In HIRI, studies indicate that PGAM5-mediated MQC and apoptosis play a more important role than necroptosis. Key necroptosis molecules, including RIPK1, RIPK3, and MLKL, are not increased in the HIRI model, and treatment against necroptosis did not provide a general protective impact on HIRI.[65] On the other hand, it has been documented that E3 ubiquitin ligase RNF5 safeguards against HIRI by degradation of PGAM5, which consequently hinders the activation of ASK1 and the subsequent JNK/p38 apoptosis signaling pathway.[27] Nevertheless, previous studies remain inconsistent regarding the effect of PGAM5-mediated MQC in HIRI. Suppression of PGAM5-mediated mitophagy by MiR-330-3p alleviates HIRI.[66] However, another study indicates that PGAM5 deletion abolishes the protective effect of heme oxygenase-1 in MQC in HepG2 cells subjected to hypoxia/reoxygenation.[18]

PGAM5 in neurological diseases

For neurological disease, PGAM5 is mainly involved in neurodegeneration-associated Parkinson disease (PD) and traumatic as well as ischemic brain injury.[67] PD is characterized by abnormal MQC.[68] PGAM5's ability to perform the MQC function allows its involvements in PD. A Parkinson-like movement phenotype is caused by a genetic deficiency in the mitochondrial protein PGAM5, and PD can be identified by the presence of plasma PGAM5 as a separate biomarker.[69,70] The absence of PGAM5 inhibits PINK1-mediated mitophagy, leading to dopaminergic neurodegeneration and dopamine loss.[69] Surprisingly, the phenotype of *Pgam5* knockout was unexpectedly more severe than that observed in *Pink1* knockout animals, suggesting that PGAM5 has additional roles besides PINK-mediated mitophagy in exerting its anti-PD effect.[69] One possible reason is that the PGAM5-KEAP1-Nrf2 complex might control the movement of mitochondria, which is a crucial aspect of neuronal function and survival.[71,72] In TBI context, *Pgam5* knockdown also alleviates neuronal injury through ameliorating Drp1-mediated mitochondrial dysfunction and inhibiting microglial inflammasome activation.[34,73] This protective effect also exists in spinal cord injury (SCI).[74] In contrast to HIRI, mitophagy appears to have a beneficial effect in cerebral ischemia. The inhibition of miR-330 leads to the activation of PGAM5-mediated mitophagy, which is linked to reduced cerebral infarction, edema, mortality, and apoptosis following 6-hour of permanent middle cerebral artery occlusion.[75] Notably, a different investigation demonstrated that PGAM5 inhibition by compound LFHP-1c effectively improved the disruption of the blood-brain barrier caused by brain ischemia, both *in vitro* and *in vivo*.[76] Therefore, PGAM5 may exert an anti-PD effect via its regulation on MQC. The effect of PGAM5 on TBI is mostly protective, whereas its role in ischemia brain injury remains inconsistent.

PGAM5 in neoplasm

Various kinds of neoplasms, such as breast, colorectal, lung, ovary, and melanoma, exhibit atypical PGAM5 expression, indicating its potential involvement in regulating neoplasia.[77] When detached from the extracellular matrix (ECM), cancer cells must overcome anoikis and correct metabolic deficiencies. During ECM detachment, RIPK3/PGAM5-induced mitophagy leads to ROS generation and cell viability reduction.[29] Therefore, antagonizing RIPK1/PGAM5 can enhance tumor formation *in vivo*.[29] In HCC, PGAM5 exhibits a substantial increase in expression and acts as a separate prognostic factor for decreased survival durations.[78,79] PGAM5-mediated lipid metabolism facilitates liver cancer proliferation.[52] Increased levels of PGAM5 lead to the development of resistance to chemotherapy by enhancing the stability of Bcl-xL.[78] Additionally, PGAM5 is involved in S100A9-induced post-transcatheter arterial chemoembolization (TACE) HCC progression.[80] Apart from HCC, PGAM5-mediated dephosphorylation of ME1 S336 promotes colorectal tumorigenesis by influencing NADPH generation and lipid metabolism.[51] Additionally, PGAM5 plays a role in the advancement of cervical cancer,[81] gastric cancer,[82,83] head and neck squamous cell,[84] and non-small cell lung cancer.[85]

CONCLUSION AND PERSPECTIVES

During normal conditions, PGAM5 is essential for preserving the balance of mitochondria by controlling the quantity and quality of mitochondria. However, under severe stress, PGAM5 becomes involved in multiple RCD pathways. The dual role of PGAM5 in apoptosis appears to be determined by the extent of stress. Despite extensive researchs, the specific molecular mechanism remains elusive. Interestingly, the regulation of necroptosis seems to be less conserved across species. It would be worthwhile to explore whether PGAM5-S contributes to this phenomenon or if other potential mechanisms are involved. Additionally, although ubiquitination and phosphorylation have been identified as post-translational modifications (PTMs) of PGAM5, it remains unknown whether other PTM of PGAM5 regulates its activity and function. Furthermore, recent studies have revealed phosphatase activity of PGAM5 on Ser/Thr/His residues, but whether other amino acids are also involved remains uncertain. Considering PGAM5's role in lipid metabolism and immune response, it would be intriguing to investigate whether it plays a role in lipid-related and inflammatory diseases, such as fatty liver disease and atherosclerosis. Given its substantial participation in both physiological and pathological contexts, a thorough investigation into the role of PGAM5 holds promise for devising approaches that aim to utilize PGAM5 for the identification and treatment of diverse diseases.

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AUTHOR CONTRIBUTIONS

Weibin He wrote the review, Wenlong He provided critical suggestions, Zhongchan Sun and Pengcheng He refined and agreed the submission of final draft of the review.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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