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Review

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Emerging Roles of Stress Granules in Cardiac Injury Associated with Metabolic Stress

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Abstract: Metabolic diseases, mainly including obesity, diabetes, insulin resistance, and metabolic dysfunction-associated steatotic liver disease, are closely linked to cardiac remodeling and heart failure. These conditions impose a sustained cardiomyocyte stress burden, disrupting organelle homeostasis, redox balance, inflammatory tone, and proteostasis. Stress granules (SGs) are dynamic ribonucleoprotein condensates that form during stress-induced translational repression. Their transient assembly can support short-term stress tolerance. However, under chronic metabolic stress, SGs may undergo progressive remodeling, with altered composition, reduced reversibility, defective clearance, and increased potential to contribute to maladaptive cellular responses. To clarify how SGs may contribute to stress adaptation and maladaptive remodeling in metabolically stressed hearts, this review first summarizes their lifecycle and molecular organization, then discusses how chronic metabolic stress may reshape SG dynamics in cardiac cells, with the aim of identifying SG-associated pathways that may inform therapeutic development for metabolic heart disease. This review further integrates current evidence from major metabolic disease contexts and stress pathways that connect metabolic disturbance to SG remodeling, with emphasis on ER stress, oxidative-mitochondrial dysfunction, inflammatory signaling, and impaired SG clearance. SG remodeling may represent an important mechanistic framework linking chronic metabolic stress to cardiac injury and could reveal stress-responsive pathways with clinical relevance in metabolic cardiovascular disease.

Keywords: stress granules; metabolic cardiovascular disease; metabolic disease; ER stress; oxidative stress

1. Introduction

Metabolic diseases, particularly obesity and diabetes, are among the most prevalent noncommunicable diseases worldwide and represent a growing public health burden [1–3]. Beyond disrupting systemic metabolic homeostasis, these disorders exert broad pathological effects across multiple organs [4]. Of the various end-organ consequences of metabolic diseases, cardiac involvement is particularly important, as it substantially contributes to disease progression, adverse clinical outcomes, and mortality [5–7]. In patients with metabolic disease, cardiac involvement is often characterized by structural remodeling, impaired myocardial function, and an increased risk of cardiomyopathy and heart failure [8,9]. Underlying these abnormalities is a chronic stress milieu within the heart, in which persistent metabolic imbalance promotes oxidative stress, inflammation, and organelle dysfunction [10]. Sustained stress imposes broad and multifactorial effects on the heart, such that the adaptive process itself becomes maladaptive, progressively compromising proteostasis, mitochondrial integrity, and translational homeostasis in cardiomyocytes. Accordingly, the capacity of cardiac cells to dynamically reorganize RNA and protein metabolism may become a critical determinant of whether metabolic stress is transiently buffered or progressively converted into maladaptive injury [11,12].

Stress granules (SGs), dynamic regulators of translational control and stress adaptation, may provide a useful perspective for understanding how persistent metabolic stress is coupled to maladaptive cellular responses that contribute to cardiac injury [12]. SGs are biomolecular condensates enriched in translationally repressed messenger ribonucleoprotein particles (mRNPs) [13]. This view is supported by several observations: SGs typically assemble upon inhibition of translation initiation, are markedly reduced when polysomes are stabilized, and predominantly

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contain untranslated mRNAs together with translation initiation factors [14–16]. As membraneless organelles, SGs are thought to assemble through liquid–liquid phase separation (LLPS) driven by multivalent weak interactions among RNA-binding proteins and RNA [17–21]. The weak and reversible interactions that drive SG assembly endow these condensates with a highly dynamic and reversible nature, which underlies their adaptive functions during cellular stress [22]. Therefore, canonical SGs are thought to be largely absent under basal conditions and typically assemble transiently in response to stress, with their components largely remaining diffuse or returning to diffuse cytoplasmic distribution once the stress is relieved [23,24]. Under sustained or dysregulated stress, however, this normally transient behavior may be progressively distorted, allowing SGs to shift from facilitating stress adaptation to reinforcing cellular dysfunction and pathogenic signaling [25–27].

This potential transition from adaptive to maladaptive behavior is best understood in the context of the transient and reversible functions of SGs during acute stress. Under these conditions, SGs do not function in isolation, but rather as part of a broader stress-response network that coordinates translational control and organelle homeostasis [28]. One representative example of this crosstalk involves endoplasmic reticulum (ER) stress and unfolded protein response (UPR) signaling. Activation of the UPR, particularly through protein kinase R-like endoplasmic reticulum kinase (PERK; gene symbol EIF2AK3) -mediated phosphorylation of eukaryotic translation initiation factor 2 subunit alpha (eIF2α; gene symbol EIF2S1), suppresses translation initiation and promotes polysome disassembly, increasing the pool of untranslated mRNPs available for SG assembly [28–31]. Accordingly, rather than serving as primary drivers of bulk translational repression, SGs are more commonly viewed as dynamic compartments that form downstream of stress-induced translation arrest and transiently reorganize untranslated mRNPs together with RNA-binding proteins. In doing so, they may contribute to RNA triage and possibly proteostatic buffering [22,32]. Through these effects, SGs may help support adaptive responses across multiple organelles, including the ER and mitochondria, during acute or short-lived stress [33]. Such adaptive behavior may depend, at least in part, on SGs remaining transient and dynamically reversible. Under persistent or dysregulated stress, however, SGs may fail to remain fully dynamic and self-limited, instead forming more persistent assemblies with altered composition or material properties, defective disassembly or clearance, and an increased likelihood of interfering with post-stress recovery [34,35]. The pathological relevance of disrupted SG dynamics is well illustrated in neurodegenerative disease, particularly Amyotrophic lateral sclerosis (ALS) and related disorders, in which persistent or poorly resolved SGs have been widely linked to aberrant RNA-binding proteins (RBPs) behavior and proteostatic failure. Mechanistically, mutations in disease-associated RBPs such as FUS and TAR DNA-binding protein 43 (TDP-43; gene symbol TARDBP) can alter phase behavior and impair the dynamic turnover of SG-related condensates, thereby favoring the persistence of less reversible assemblies [23,36,37]. A similar conceptual framework may also be relevant to cardiovascular injury in metabolic disease, where cells are exposed to chronic and overlapping stress inputs. Because metabolic stress is frequently associated with translation inhibition and disruption of intracellular homeostasis, it may also interfere with the normal assembly–disassembly cycle of SGs and promote the persistence of maladaptive SG states [12,38].

Although emerging studies have begun to implicate SGs in cardiovascular and metabolically relevant stress settings, their role in metabolic disease-related cardiac injury remains insufficiently defined. As a result, relevant evidence remains dispersed across SG biology, metabolic stress signaling, and cardiovascular research, without being brought into a unified mechanistic perspective. This raises an important question: whether SGs contribute to metabolic cardiovascular disease and, if so, how alterations in SG dynamics shape this relationship. We propose that the pathological relevance of SGs is determined not simply by their formation, but by stress-induced changes in their assembly, maturation, reversibility, and clearance, which may shift SG responses from adaptive to maladaptive states. Therefore, this review aims to synthesize current evidence and discuss how chronic metabolic stress may intersect with SG biology to influence cardiac remodeling and dysfunction. In doing so, it may help clarify emerging mechanisms of metabolic cardiac injury.

2. Stress Granules in Cellular Stress Responses

2.1. Stress Granule Lifecycle during Stress and Recovery

A wide range of stress conditions, including heat stress, arsenite exposure, oxidative stress, viral infection, and UV irradiation, can suppress translation initiation and promote SG assembly. This is particularly relevant in metabolic disease, where oxidative stress, ER stress, mitochondrial dysfunction, and nutrient imbalance can repeatedly challenge translational homeostasis, expand the cytoplasmic pool of untranslated mRNPs, and thereby provide both the material basis and permissive conditions for SG formation.

These mRNPs are then linked through interaction networks established by RBPs. Current evidence suggests that this transition is most commonly associated with two major routes: phosphorylation of eIF2α and disruption

of the eukaryotic translation initiation factor 4F (eIF4F; gene symbol: EIF4F) cap-binding complex [29,31]. In metabolically stressed cells, one particularly relevant route involves ER stress and activation of the UPR. Among the four eIF2α kinases, PERK is of special interest in this context because it directly couples ER proteostatic stress to translational repression [39]. Upon ER stress, PERK-mediated phosphorylation of eIF2α limits ternary complex availability and suppresses translation initiation, thereby promoting polysome disassembly and increasing the cytoplasmic pool of untranslated mRNPs available for SG assembly [40]. Other stress-responsive kinases, including PKR, GCN2, and EIF2AK1/HRI, can likewise converge on eIF2α phosphorylation under distinct stress conditions. SG formation may also be promoted through disruption of cap-dependent translation, including perturbation of the mTORC1–eIF4F axis [23]. This route may likewise contribute to SG assembly under certain metabolically relevant conditions, in which altered nutrient sensing and mTORC1 inhibition impair eIF4F complex assembly and suppress cap-dependent translation, although its precise contribution to SG formation remains incompletely resolved and may be context dependent [24,41,42].

The earliest stage of SG assembly involves the formation of small seed structures that subsequently recruit additional components and grow into larger granules. This process is coordinated by a set of core SG nucleators and assembly factors. Among them, G3BP1 and G3BP2 are widely regarded as central nodes in canonical SG formation, whereas cytotoxic granule-associated RNA-binding protein TIA1 (TIA1) and TIA1-related protein (TIAR; gene symbol TIAL1 promote RNA clustering and facilitate condensation of untranslated mRNPs [43–46]. Additional factors, including UBAP2L, CAPRIN1, IGF2BP1, and FMR1, further support early granule formation by coordinating the recruitment, partitioning, and stabilization of SG-associated RNAs and RNA-binding proteins [47–50]. Thus, SG nucleation is not a passive consequence of translational arrest alone, but a regulated process in which specific RNA-binding proteins and assembly factors convert stress-induced translational stalling into condensate formation [43,44].

As granules enlarge, SG maturation depends on more than the continued recruitment of proteins and mRNAs. Current models suggest that this process is driven by multivalent protein–protein, protein–RNA, and RNA–RNA interactions, which collectively stabilize the condensate once critical interaction thresholds are reached [13]. SG formation is therefore concentration dependent, and changes in the effective saturation concentration and interaction valency of key central node proteins, especially within G3BP1-associated networks, can influence the likelihood of condensation [43,51]. During the enlargement and maturation, positive regulators may lower the threshold required for SG formation, whereas antagonistic factors may increase it and thereby restrain assembly. RNA-binding and RNA-remodeling factors such as PABPC1, DDX3X, HNRNPA1, and ATXN2 are also thought to contribute to this stage by shaping RNA–protein interaction networks and influencing condensate dynamics and stability [13,45,46,48,52–55]. The major steps involved in stress-induced SG assembly and maturation, with particular relevance to cardiovascular stress, are summarized in Figure 1.

Importantly, SG assembly is reversible rather than terminal. Once the stress signal subsides or cells adapt to the stress, SGs can disassemble, allowing previously sequestered mRNAs to re-enter the translational pool. This process contributes to the restoration of cellular homeostasis and is now recognized as an actively regulated component of stress recovery. It can involve both reversal of the conditions that promote assembly, including restoration of translation and contraction of the free untranslated mRNP pool, and additional recovery-phase mechanisms that remodel the interaction network required to maintain SG integrity [46]. At a conceptual level, SG disassembly may occur when the effective concentration of SG components falls below the saturation threshold required for condensation or when the valency of central node proteins is reduced, thereby weakening the intermolecular interactions needed for granule stability [13]. Dephosphorylation of eIF2α during recovery can promote translation re-entry and oppose SG persistence. RNA helicases such as EIF4A and DDX3X may further facilitate SG dissolution by remodeling RNA–RNA and RNA–protein interactions within the condensate, whereas ATP-dependent chaperone and ATPase systems, including HSP40/70 and valosin-containing protein (VCP)/p97, promote recovery by removing misfolded or strongly retained components and restoring condensate dynamics [47]. Under certain conditions, SQSTM1/p62-linked autophagic pathways may also contribute to the clearance of persistent or aberrant SG material through lysosomal degradation [48]. In parallel, the ubiquitin-proteasome system (UPS) can independently promote SG resolution by removing ubiquitinated protein-quality-control substrates and facilitating granule remodelling [49–51]. For example, ZFAND1 recruits VCP/p97 and the 26S proteasome to arsenite-induced SGs, thereby promoting the removal of defective ribosomal products and supporting efficient SG clearance [49]. Ubiquitin-dependent remodelling has also been observed during heat stress, where ubiquitinated G3BP1 interacts with FAF2, which recruits VCP/p97 to extract G3BP1 from SGs and weaken the interaction network required for granule stability [52]. Although autophagy and the UPS therefore act through distinct degradative mechanisms, their functions are interconnected. When proteasome-associated SG quality control is impaired, aberrant SGs can accumulate ubiquitin, SQSTM1/p62, and LC3 and become redirected toward autophagic degradation, indicating that granulophagy can

partly compensate for insufficient UPS-mediated clearance [49]. The relative contribution of these pathways appears to vary with stress type, duration, and SG state, supporting a context-dependent and partly compensatory relationship rather than strict competition between the two clearance routes. SG disassembly can thus be viewed as a regulated reconfiguration of the molecular interactions that sustain condensate organization during stress recovery. This recovery-phase control may be especially vulnerable under chronic metabolic stress, in which persistent translational repression, protein quality control burden, and impaired energy-dependent remodeling could favor delayed disassembly and the persistence of maladaptive SG states. Correspondingly, Table 1 organizes SG-related factors according to their roles in upstream stress signaling, condensate assembly, and recovery-phase remodeling, thereby reflecting the multilevel control of SG dynamics.

Table 1. Representative molecular regulators across the stress granule lifecycle.

Factor	Function	References
SG nucleation and early assembly factors		
G3BP1	Core SG nucleator and scaffold protein that promotes condensation of untranslated mRNPs and coordinates early SG assembly.	[53,54]
G3BP2	Homolog of G3BP1 that supports SG structural stability.	[55,56]
CAPRIN1	G3BP1-interacting RNA-binding protein that supports nucleation and promotes recruitment of selected mRNAs and RBPs.	[43]
UBAP2L	Key nucleation factor that promotes early SG assembly and links SG formation to ubiquitin-related pathways.	[44]
TIA-1	SG RNA-binding protein that promotes RNA clustering and granule assembly and rapidly accumulates in SGs during stress.	[57]
TIAR	TIAR homolog that cooperatively participates in SG assembly and contributes to translation repression.	[40,58]
IGF2BP1	IGF2BP1 is an early RNA scaffold that clusters mRNAs and initiates SG formation through phase separation.	[59]
RNA Binding and mRNA Remodeling Components		
FMRP	RNA-binding protein involved in translational repression and SG-associated mRNA regulation during cellular stress.	[60]
PABPC1	Poly(A)-binding protein that accumulates in SGs during translational repression and contributes to mRNA stabilization.	[61]
DDX3X	RNA helicase involved in translation regulation and RNA metabolism within SGs.	[62]
eIF3B	Component of the eIF3 translation initiation complex stalled preinitiation complexes during translation inhibition.	[63]
hnRNP A1	hnRNP A1 relocates to SGs during cellular stress to shuttle and regulate untranslated mRNAs.	[64]
hnRNP A2/B1	hnRNP A2/B1 inhibits SG disassembly, helping maintain SG integrity through regulation of G3BP1-associated protein interactions and ubiquitination dynamics.	[65]
ATXN2	RNA-binding protein that interacts with G3BP1 and contributes to SG stability, also linked to neurodegenerative disease.	[66]
SG Dynamics and Disease-Associated RNA-Binding Proteins		
TDP-43	TDP-43 regulates SG assembly and maintenance by controlling key SG components such as G3BP1 and TIA-1, thereby modulating its dynamics during stress.	[37,67]
FUS	FUS is a stress-responsive RNA-binding protein that relocates from the nucleus to SGs under specific stresses, where it contributes to SG assembly and promotes cell survival during stress.	[37,68]
Integrated Stress Response /ER Stress and Translational Control Regulators		
eIF2α	Central translational control factor whose phosphorylation suppresses translation initiation and increases the pool of untranslated mRNAs available for SG assembly.	[69]
PERK	PERK promotes SG formation by phosphorylating eIF2α during ER stress, which suppresses translation initiation and drives the accumulation of untranslated mRNAs.	[70]
eIF4F	eIF4F inhibition disrupts cap-dependent translation initiation, promotes polysome disassembly, and facilitates the accumulation of untranslated mRNPs for SG assembly.	[71]
ATF4	ATF4 is a stress-induced transcription factor selectively translated downstream of eIF2α phosphorylation and indirectly supports SG formation by promoting cellular adaptation to translational stress.	[72]
CHOP	CHOP is a downstream transcription factor of the eIF2α–ATF4 integrated stress response that regulates stress-response and apoptosis pathways activated during prolonged SG-associated translational stress.	[39,73]
GADD34	GADD34 promotes SG disassembly by recruiting protein eIF2α, thereby restoring translation initiation and terminating the stress response.	[74,75]

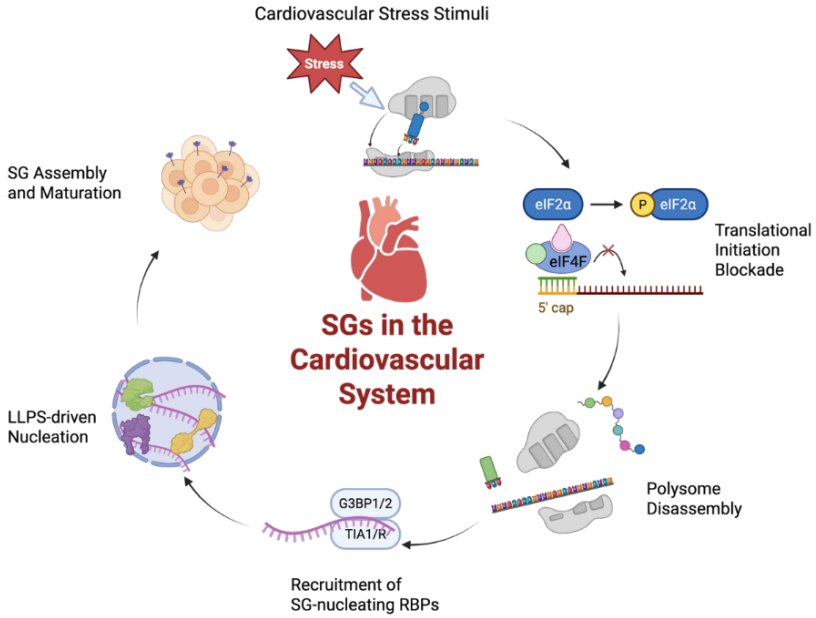


Figure 1. Stress granule dynamics in cardiovascular stress. Stress granules (SGs) assemble in response to translational inhibition under cellular stress conditions. In cardiomyocytes, diverse stress signals promote SG formation through eIF2α phosphorylation and polysome disassembly. Stress signaling induces phosphorylation of eIF2α and inhibits eIF4F, leading to suppression of translation initiation. As a result, untranslated messenger ribonucleoprotein particles accumulate and are recruited by stress granule nucleators, including G3BP1/2 and TIA1/TIAR, which promote their clustering and condensation. Through multivalent RNA–protein and protein–protein interactions, these assemblies undergo liquid–liquid phase separation (LLPS), resulting in the formation of mature and dynamic SG condensates.

2.2. Molecular Organization of Stress Granules

Stress granules are now generally understood as internally heterogeneous condensates with hierarchical organization. Current models propose that SGs contain a relatively less dynamic and more densely packed core surrounded by a more exchangeable shell, thereby generating marked spatial and kinetic asymmetry within the granule [13,76]. Evidence from electron microscopy, super-resolution fluorescence imaging, and biochemical purification further supports this model, in which dense and relatively stable substructures are embedded within a more diffuse phase with faster molecular exchange [34,77]. Recognition of this internal organization has expanded current research on SG organization, prompting closer examination of subdomains that differ in molecular packing, stability, and exchange behavior.

In general, the core is considered a more stable compartment enriched in tightly associated untranslated mRNPs and key scaffold proteins [13]. Available evidence supports the view that G3BP1/2 may occupy a central organizing position, with G3BP1 acting as an RNA-responsive switch that promotes LLPS driven by intrinsically disordered protein regions (IDR) of RBPs once collective interactions exceed a threshold, while proteins such as UBAP2L and CAPRIN1 further promote nucleation and core growth [53,78]. This activity depends on N-terminal dimerization mediated by its NTF2-like domain together with multivalent RNA binding, which collectively promote local crosslinking and condensation of untranslated mRNPs. The relative stability of the core likely reflects the emergence of a more densely connected interaction hub, in which untranslated mRNPs and scaffold proteins are retained through stronger or more multivalent associations than those operating in the surrounding shell [53,77].

The shell is generally regarded as a more dynamic peripheral phase in which associated RNAs and proteins are retained through weaker and more transient interactions, thereby permitting faster exchange with the surrounding cytoplasm [13]. Electron microscopy further suggests that the shell does not exist as an isolated layer separate from the core but corresponds to the outer region of the same condensate, where intermolecular connectivity is lower and component residence is shorter. It comprises untranslated RNAs, abundant cytoplasmic RNA-binding proteins, and certain translation initiation-related factors. Mammalian SG proteomic studies have identified highly represented SG-associated proteins such as G3BP1/2, CAPRIN1, UBAP2L, and DDX3, together with small ribosomal subunits [20]. In parallel, several RNA-binding proteins that are mainly nuclear under basal conditions, including TIA1/TIAR, FUS, and TDP43, can relocate to the cytoplasm and enter SGs during stress.

Together, these features suggest that the shell serves as a continuously remodeled reservoir of SG-associated components, enabling ongoing compositional tuning of the granule during stress [78].

2.3. Stress Granule Remodeling under Chronic Metabolic Stress

Under chronic metabolic stress, SG behavior may no longer follow a fully reversible cycle of assembly and recovery. This issue may be particularly relevant in metabolic disease, where hyperglycemia, lipotoxicity, oxidative stress, ER stress, impairment of proteolytic pathways, and mitochondrial dysfunction together create a persistent intracellular stress environment. Under these conditions, SGs may undergo repeated cycles of assembly with incomplete resolution, thereby increasing the likelihood of progressive remodeling over time [23].

Such remodeling may involve changes in SG composition, assembly behavior, and molecular exchange. Because SG internal organization is closely linked to molecular partitioning, exchange kinetics, and reversibility, chronic stress-induced alterations in RNA–protein interaction networks may shift SGs toward less dynamic and less readily reversible states [79]. This view is further supported by studies showing that SGs can be remodeled according to stress context, with comparisons across different stressors revealing stress-specific differences in SG composition, assembly, and dynamics [80].

Recovery from stress also depends on efficient SG disassembly and clearance. These processes require ATP-dependent remodeling factors, chaperones, VCP-associated extraction pathways, the UPS, and autophagic mechanisms. Experimental evidence supports the functional importance of these pathways: inhibition of autophagy, lysosomal function, or VCP disrupts normal SG handling and causes abnormal retention of defective ribosomal products and 60S ribosomal subunits within SGs, indicating that protein quality-control pathways influence SG integrity and composition [81]. Consistent with this, another study demonstrated that ULK1/2 localize to SGs and promote their disassembly through phosphorylation and activation of VCP/p97, directly linking recovery-phase SG resolution to defined regulatory machinery [82].

In chronic metabolic disease, where multiple stress inputs coexist and persist, these same regulatory systems may become overloaded or dysregulated. Sustained translational repression, repeated accumulation of untranslated mRNPs, proteostatic burden, and impaired energy-dependent remodeling could therefore favor progressive SG remodeling and delayed resolution, creating conditions that permit more persistent maladaptive SG states to emerge. These considerations provide a mechanistic basis for examining how SG dysregulation may contribute to tissue injury in metabolic disease in later sections.

3. Maladaptive Stress Granules in Metabolic Cardiac Injury

3.1. Metabolic Contexts That Create an SG-Permissive Environment

HFpEF is increasingly recognized as a major clinical manifestation of cardiometabolic disease, with obesity, diabetes, insulin resistance, and hypertension contributing substantially to its development [1]. These conditions do not appear to converge on HFpEF through a single metabolic pathway [83]. In obesity-associated HFpEF, visceral adiposity and insulin resistance promote systemic inflammation and immune dysregulation, accompanied by altered myocardial energetics, fibrosis, increased cardiomyocyte stiffness, and impaired diastolic relaxation [84]. In diabetic HFpEF, metabolic rewiring, altered substrate utilization, endothelial dysfunction, and inter-organ crosstalk involving adipose tissue, liver, kidney, and immune compartments add further layers of metabolic stress [85]. Consistent with this heterogeneity, human HFpEF myocardium exhibits cell-type-specific disturbances in metabolism, immune activation, transcription and translation, and protein-quality-control pathways [86].

The association between HFpEF and SG biology remains incompletely defined, but several levels of evidence suggest a potential connection. First, inflammation, oxidative and nitrosative stress, metabolic dysfunction, and impaired proteostasis are well-established features of HFpEF and represent cellular conditions capable of influencing SG assembly and resolution. Second, stress-response pathways immediately upstream of SG regulation are themselves altered in HFpEF. In both human myocardium and experimental HFpEF, disruption of the IRE1α–XBP1 arm of the unfolded protein response has been demonstrated, and restoration of XBP1s in cardiomyocytes ameliorates the HFpEF phenotype [87,88]. More recent studies further implicate adaptive translational stress-response pathways, including PERK–ATF4 signaling, in HFpEF-associated proteostatic adaptation and dysfunction [89]. Third, although SGs have not yet been directly characterized in HFpEF myocardium, studies in other cardiac stress settings show that SG dynamics can modify cardiomyocyte responses to stress. For example, LPS induces eIF2α phosphorylation and G3BP1/TIA1-positive SG formation in cardiomyocytes, whereas enhancement of G3BP1-dependent SG assembly reduces inflammatory signaling, preserves mitochondrial membrane potential, and improves cardiomyocyte functional responses [90].

These observations suggest that HFpEF provides a biologically plausible context for altered SG regulation, while the specific effects may differ across cardiometabolic conditions. This supports considering individual metabolic disease contexts separately when evaluating how metabolic stress reshapes SG dynamics in the heart. The major metabolic disturbances and shared stress pathways that may contribute to SG remodeling are summarized in Figure 2.

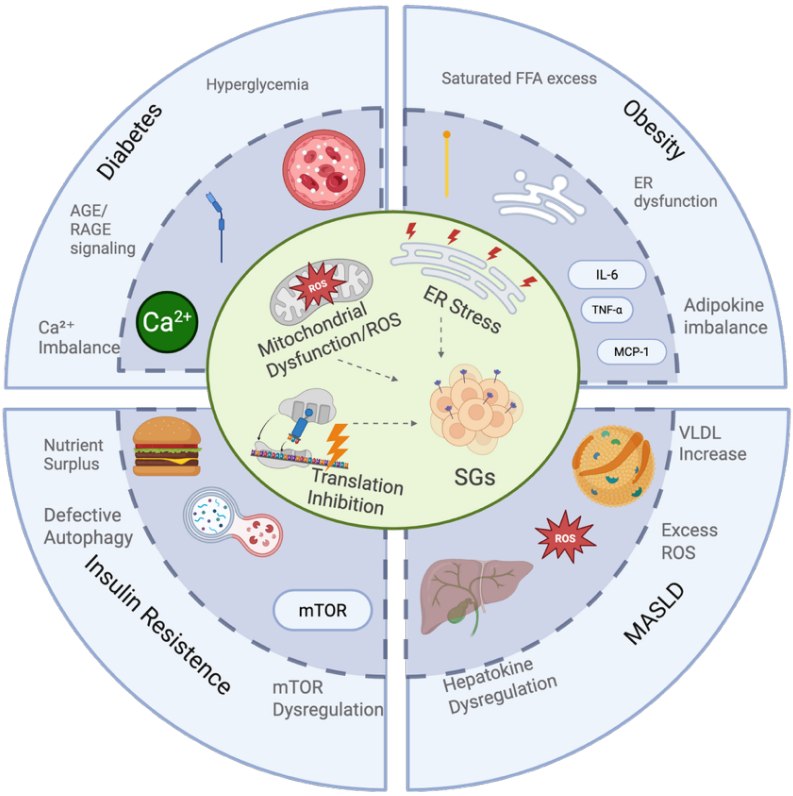


Figure 2. Metabolic drivers of stress granule remodeling. Diabetes, obesity, insulin resistance, and metabolic dysfunction-associated steatotic liver disease (MASLD) impose distinct metabolic disturbances, including hyperglycemia, saturated free fatty acid excess, nutrient surplus, and altered lipid handling, together with Ca^{2+} imbalance, adipokine dysregulation, mTOR signaling alteration, and increased reactive oxygen species (ROS). These perturbations converge on mitochondrial dysfunction with elevated ROS production and endoplasmic reticulum (ER) stress at the cellular level, which promote translational inhibition. The resulting accumulation of untranslated messenger ribonucleoprotein particles supports stress granule (SG) formation.

3.1.1. Diabetes

Diabetes is a major metabolic condition that exposes the heart to persistent metabolic stress and promotes progressive injury. In both type 1 and type 2 diabetes, persistent hyperglycemia, insulin deficiency or insulin resistance, and dysregulated lipid metabolism progressively reshape myocardial structure and function, while profoundly altering cardiac substrate availability and utilization [91–93]. Clinically, diabetic cardiomyopathy is one of the most characteristic and mechanistically relevant phenotypes, among the cardiovascular manifestations of diabetes, typically presenting with ventricular remodeling, fibrosis, increased myocardial stiffness, and early diastolic dysfunction, with progression to overt heart failure in more advanced disease [94]. Although type 1 and type 2 diabetes can show somewhat different cardiac phenotypes, both ultimately converge on chronic myocardial stress and structural deterioration [95].

The diabetic heart is characterized in part by a progressive loss of metabolic flexibility [95]. In both type 1 and type 2 diabetes, reduced insulin-mediated glucose utilization shifts cardiomyocytes toward greater reliance on fatty acid uptake and oxidation [96]. With insulin resistance, increased CD36-mediated fatty acid uptake further enhances this shift and promotes accumulation of toxic lipid intermediates [97]. Although this metabolic adaptation initially helps maintain ATP production, it becomes maladaptive over time because fatty acid oxidation no longer adequately matches substrate influx. The result is intracellular lipid accumulation, mitochondrial

dysfunction, and lipotoxic stress, together with impaired glucose handling and disturbed cardiac energy metabolism [98].

These metabolic disturbances establish a persistent intracellular stress environment within cardiomyocytes. Mitochondrial dysfunction and excessive fatty acid load promote increased generation of reactive oxygen and nitrogen species, which in turn drive oxidative stress, ER stress, and impaired autophagy [99]. Meanwhile, AGE accumulation, inflammatory activation, and disturbed calcium handling further aggravate myocardial injury and functional decline [91,94,98]. Reduced SERCA2-associated calcium reuptake contributes to impaired relaxation and contractile dysfunction, while oxidative and inflammatory signaling promote fibrosis, hypertrophy, and adverse remodeling [100]. Taken together, diabetes exposes the heart to a chronic stress state marked by bioenergetic imbalance, oxidative and ER stress, mitochondrial dysfunction, impaired protein quality control, and defective stress recovery, thereby creating a myocardial environment that is highly permissive for downstream stress-pathway dysregulation.

3.1.2. Obesity

Obesity is another major metabolic disease context in which cardiac involvement is highly relevant. Obesity has been widely associated with a pattern of cardiac remodeling marked by increased ventricular mass, myocardial hypertrophy, interstitial fibrosis, impaired diastolic relaxation, and a strong predisposition to heart failure, particularly HFpEF [101,102]. In addition to hemodynamic burden, obesity-related cardiac injury is increasingly understood because of metabolic and inflammatory remodeling within the myocardium itself. Visceral adiposity, particularly expansion and dysfunction of epicardial adipose tissue, may be especially important in this setting because its close anatomic and microvascular relationship with the myocardium enables local paracrine effects that promote cardiomyocyte inflammation, metabolic disturbance, fibrotic remodeling, and lipotoxic stress [103,104].

A central metabolic feature of obesity-related cardiac injury is chronic lipid oversupply. In the obese heart, increased fatty acid availability and uptake can exceed the oxidative capacity of cardiomyocytes, leading to intracellular accumulation of toxic lipid intermediates and the development of cardiac lipotoxicity, in which excess lipids and their bioactive derivatives impair mitochondrial energetics, disturb intracellular signaling and membrane homeostasis, and trigger oxidative stress, ER stress, and inflammatory injury [105]. Although enhanced fatty acid utilization may initially serve as an adaptive response to excess substrate availability, prolonged lipid overload disrupts metabolic flexibility and promotes inefficient energy metabolism. This state is further shaped by systemic insulin resistance, altered nutrient sensing, and adipose tissue dysfunction, all of which reinforce abnormal myocardial substrate handling and increase susceptibility to structural and functional deterioration [106–108].

Within cardiomyocytes, lipotoxicity does not simply reflect passive lipid accumulation. When fatty acid uptake chronically exceeds oxidative capacity, bioactive lipid intermediates such as ceramides and diacylglycerols can accumulate and perturb membrane composition, organelle homeostasis, and intracellular signaling [103,109]. Under such circumstances, ER homeostasis becomes particularly vulnerable, because altered lipid composition, redox imbalance, and disturbed calcium handling increase the burden of protein misfolding and activate the unfolded protein response [109]. Excessive lipid load and oxidative stress also challenge intracellular protein quality-control systems, including chaperone function, proteasomal degradation, and autophagy-dependent clearance, thereby promoting proteostatic burden [110]. These changes are especially relevant because sustained ER and proteostatic stress can engage signaling pathways that suppress translation initiation, while impaired quality control may reduce the efficiency with which cardiomyocytes recover translational homeostasis after injury [111]. This creates a cellular context in which stress-responsive RNA–protein regulatory mechanisms are likely to be repeatedly engaged under chronic metabolic overload.

3.1.3. Insulin Resistance

Insulin resistance represents a central metabolic abnormality that extends across multiple cardiometabolic disease contexts, including obesity, prediabetes, type 2 diabetes, and metabolic syndrome [112]. It is defined as a reduced responsiveness of certain tissues to normal circulating insulin levels, such that higher insulin concentrations are required to maintain normal insulin action [113]. This decreasing response to insulin stimulation causes a reduction in glycogen synthesis and the ability to suppress lipid oxidation. Such metabolic change leads to hyperglycemia, elevated free fatty acids, and increased VLDL production, which disrupts the metabolic flexibility of cardiomyocytes, so that the myocardium becomes more dependent on fatty acid oxidation and less able to shift toward glucose use under stress [114]. As fatty acid uptake exceeds oxidative capacity, excess lipids are diverted into non-oxidative pathways, resulting in the accumulation of lipotoxic intermediates that disrupt mitochondrial function, increase reactive oxygen species production, and further impair insulin signaling [115].

Also, chronic hyperglycemia and lipid overload disturb redox balance, calcium homeostasis, and protein quality control, thereby increasing the folding burden on the ER and predisposing cardiomyocytes to ER stress. Under these conditions, adaptive suppression of protein synthesis may be engaged to limit further proteostatic overload [114]. Thus, insulin resistance should be viewed not only as a metabolic defect, but also as a persistent intracellular stress state that creates a permissive background for downstream stress-response dysregulation in the heart.

3.1.4. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), describes a spectrum of liver disease characterized by hepatic steatosis accompanied by cardiometabolic risk factors [116].

Patients with MASLD often exhibit metabolic dysfunction, insulin resistance, and a tendency toward ectopic fat accumulation in the liver and adjacent tissues, features that are associated with an increased risk of endothelial dysfunction, systemic inflammation, and epicardial fat deposition [4]. These pathological changes further promote myocardial remodeling and impair cardiac performance. Therefore, patients with MASLD more frequently develop coronary atherosclerosis, subclinical myocardial dysfunction, and structural cardiac changes, including left ventricular hypertrophy and diastolic dysfunction, even in the absence of overt heart failure [4]. Collectively, these findings suggest that MASLD exerts a broad macro-level impact on the cardiovascular system, linking hepatic steatosis to vascular injury, altered cardiac structure, and increased susceptibility to cardiometabolic heart disease.

The cardiac consequences of MASLD are shaped by a liver–heart axis that alters both substrate delivery and the inflammatory milieu surrounding the myocardium. Hepatic steatosis and hepatic insulin resistance increase very-low-density lipoprotein (VLDL) secretion and circulating lipid flux, while expanded visceral adipose tissue releases chemotactic and pro-inflammatory mediators such as MCP-1 and TNF-α, promoting macrophage accumulation and further enhancing lipolysis. This combination increases myocardial lipid exposure and is often accompanied by expansion of epicardial adipose tissue, further aggravating local cardiac stress [117]. Under these conditions, cardiomyocytes are exposed to a cardiometabolic milieu that substantially overlaps with obesity, while also being shaped by the broader systemic consequences of hepatic steatosis [118].

Although direct characterization of SG dynamics remains limited, alterations in SG-related proteins have been reported across several experimental models of metabolic disease. Notably, even within HFD-based models, the direction of G3BP1 expression changes is not consistent across studies, suggesting that SG-related responses may depend on experimental conditions, tissue context, or disease stage. These findings are summarised in Table 2.

Table 2. SG alterations across metabolic disease models.

Metabolic Model	Tissue/Cell Type	SG-Related Protein(s) and Observation	References
HFD-induced obesity	Primary macrophages; liver	TIA1-positive SGs increased after HFD feeding; Pdcd4 deficiency markedly reduced SG formation	[119]
HFD-induced MASLD	Liver	G3BP1 and TIA1 expression increased, accompanied by increased G3BP1–TIA1 colocalisation	[120]
HFD-induced MASLD	Liver	G3BP1 protein expression decreased; SG assembly was not directly assessed	[121]
HFD-induced obesity	Pancreatic β cells/islets	HFD/SFA exposure increased SG formation; PDX1 was recruited to SGs, while TIA1 deletion suppressed SG assembly	[122]
db/db type 2 diabetes and STZ-induced type 1 diabetes	Kidney	Renal G3BP2 expression was increased in diabetic nephropathy models; SG formation or distribution was not directly assessed.	[123]

Abbreviations: db/db, leptin receptor-deficient diabetic mice; HFD, high-fat diet; PDX1, pancreatic and duodenal homeobox 1; SFA, saturated fatty acid; STZ, streptozotocin.

3.2. Stress Pathways Linking Metabolic Disturbance to SG Remodeling

These metabolic disturbances ultimately converge on persistent and interconnected stress pathways, thereby reshaping the intracellular environment. As outlined above, chronic nutrient excess, hyperglycemia, lipotoxicity, and associated inflammatory cues can drive persistent ER stress, oxidative stress, mitochondrial dysfunction, and proteostatic burden. These signals can drive stress granule assembly while also influencing multiple aspects of stress granule behavior, including molecular composition, material dynamics, reversibility, and clearance chronically.

3.2.1. ER Stress

In cardiovascular disease, ER stress emerges when persistent cardiometabolic and hemodynamic stressors overwhelm the protein-folding and quality-control capacity of the endoplasmic/sarcoplasmic reticulum, leading to disruption of luminal proteostasis and activation of the UPR [124]. Once BiP/GRP78, a major ER luminal chaperone that normally restrains UPR sensor activation, dissociates from the luminal domains of the three canonical ER stress sensors, IRE1α and ATF6 initiate compensatory programs aimed at restoring ER homeostasis [125,126]. Activated IRE1α undergoes oligomerization and autophosphorylation, enabling XBP1 mRNA splicing and downstream transcriptional programs that support chaperone production, ER-associated degradation, and membrane homeostasis [127], whereas ATF6 is transported to the Golgi for regulated proteolysis and subsequently induces genes involved in protein folding and quality control [128]. PERK is particularly relevant in the cardiovascular stress response because its activation directly engages translational control: oligomerized PERK phosphorylates eIF2α, attenuates bulk translation initiation, and permits selective translation of ATF4, which coordinates adaptive gene expression and, under sustained stress, can progress toward CHOP-associated maladaptive signaling [129,130]. Thus, in the diseased cardiovascular system, ER stress is coupled not only to proteostatic overload but also to a pronounced shift in translational regulation, providing a mechanistic basis for downstream changes in cytoplasmic RNA–protein organization.

Among the three UPR branches, the PERK arm provides the most direct mechanistic link between ER stress and SG remodeling. Upon activation, PERK phosphorylates eIF2α, which limits the availability of the ternary complex eIF2–GTP–$tRNA_i^{Met}$ and thereby suppresses translation initiation [131]. Under these conditions, untranslated mRNAs together with ternary complex-deficient preinitiation complexes accumulate in the cytoplasm, creating the molecular substrate for SG assembly. Consistent with this model, mammalian SGs have been shown to contain stalled preinitiation complexes that are deficient in ternary complex components, indicating that SG formation is closely coupled to defects in translation initiation and the consequent accumulation of untranslated mRNPs [131]. In addition, the RNA-binding proteins TIA-1 and TIAR link eIF2α phosphorylation to SG assembly by promoting the condensation of untranslated mRNPs into microscopically detectable SGs [40]. Beyond this canonical translational route, emerging evidence further suggests that the ER may participate more directly in SG biogenesis by influencing mRNA trafficking, localization, and local translation, raising the possibility that ER stress reshapes not only the amount of untranslated mRNPs available for SG assembly but also the spatial organization in which SG assembly occurs [132]. Together, these findings support the view that sustained ER stress is well positioned to influence SG remodeling at the level of both translational control and ER-associated RNA organization.

Although direct evidence linking ER stress to pathological SG states in metabolic cardiovascular disease remains limited, findings from broader SG research suggest that persistent stress signaling and defective SG resolution can shift SGs away from their normally dynamic and reversible state. Studies in neurodegeneration have shown that aberrant SG dynamics are associated with disease-related persistent assemblies, and chronic or repetitive SG induction can even drive the evolution of SGs into cytoplasmic inclusions with pathological features or aberrant protein aggregates [27,133]. Also, age- or stress-related decline in protein quality control and clearance systems has been proposed to favor the formation and persistence of aberrant SGs [134]. On this basis, it is possible that, in the diseased heart, sustained ER stress may do more than reshape SG assembly and organization; by imposing prolonged translational repression, protein quality control burden, and impaired stress resolution, it may also increase the likelihood that remodeled SGs progress toward less reversible and potentially pathological states. This possibility remains to be directly tested in metabolic cardiovascular disease, but it provides a plausible framework for linking chronic ER stress to maladaptive SG behavior in cardiometabolic pathology.

3.2.2. Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction are tightly coupled in metabolic cardiovascular disease. In cardiomyocytes, mitochondria are the major site of ATP production and a major intracellular source of reactive oxygen species (ROS), so disturbances in electron transport rapidly affect both redox balance and cellular energetics [99]. Under chronic cardiometabolic stress, impairment of the electron transport chain, particularly at complexes I and III, can increase electron leakage to oxygen and enhance mitochondrial ROS generation, while excessive ROS in turn damages mitochondrial lipids, proteins, and DNA, further compromising respiratory efficiency [135,136]. This creates a self-amplifying cycle in which mitochondrial injury promotes oxidative stress, and oxidative stress further aggravates mitochondrial dysfunction. In the diseased heart, these alterations are frequently accompanied by reduced ATP production, impaired substrate utilization, abnormal mitochondrial dynamics, and defective mitophagy, all of which contribute to bioenergetic insufficiency and progressive

myocardial injury [137]. Thus, it might be viewed as a chronic stress background that may influence how cardiomyocytes handle further proteotoxic or translational challenges.

Chronic oxidative-mitochondrial stress can perturb translation and RNA–protein homeostasis, thereby favoring repeated SG engagement. At the same time, the relationship appears to be bidirectional. In atrial fibrillation models, G3BP1-driven SG formation was associated with reduced oxidative stress, attenuation of calcium overload, and suppression of profibrotic responses, supporting the idea that SGs can modulate how cardiomyocytes cope with redox injury [138]. Consistent with this, SG activation in cardiomyocytes has also been reported to preserve mitochondrial membrane potential and improve cellular function under inflammatory stress [90]. Beyond these protective observations, SGs have been shown to directly regulate mitochondrial metabolism by limiting fatty acid import into mitochondria through modulation of VDAC-dependent permeability, thereby suppressing fatty acid oxidation [139]. Although direct evidence in metabolic cardiovascular disease remains limited, these findings raise the possibility that under chronic oxidative-mitochondrial stress, repeated SG engagement may gradually shift from an adaptive response toward remodeled states with reduced reversibility. Such a possibility is mechanistically plausible because persistent redox imbalance, energetic insufficiency, and impaired stress resolution would be expected to increase the burden on SG turnover and recovery, even though this transition has not yet been directly established in the diseased heart.

3.2.3. Inflammation

Persistent inflammatory signaling is also a central feature of tissue injury and remodeling in metabolic cardiovascular disease. This inflammatory state is sustained by the convergence of several innate immune pathways, among which NF-κB, NLRP3 inflammasome signaling, and cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase-stimulator of interferon genes (cGAS-STING) are particularly prominent in the cardiovascular system [140,141].

NF-κB functions as a major transcriptional hub that amplifies the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules, whereas NLRP3 inflammasome activation promotes caspase-1-dependent maturation of IL-1β and IL-18 and can drive pyroptotic injury [142]. Besides, cGAS–STING signaling links cytosolic DNA stress to inflammatory activation through downstream IRF3- and NF-κB-associated programs, and has been increasingly implicated in diabetic and ischemic cardiovascular injury [143]. These pathways are highly relevant in cardiometabolic disease because they are repeatedly engaged by sterile stress signals derived from metabolic dysfunction, thereby establishing a chronic inflammatory environment in the diseased heart and vasculature. In this setting, inflammatory signaling is positioned to influence cellular injury responses and to shape how subsequent stress-adaptive pathways are organized and maintained.

Inflammatory signaling is closely connected to SG remodeling at multiple levels. In atherosclerotic lesions, SG accumulation has been observed in vascular smooth muscle cells and macrophages, indicating that SG responses are engaged within chronically inflamed vascular microenvironments rather than being restricted to isolated *in vitro* stress models. Moreover, inflammatory signaling can directly modulate SG behavior: in vascular cells, SG formation is associated with inflammatory activation and translational silencing, and can be attenuated by anti-inflammatory signaling [144]. The interaction is also bidirectional. In diabetic myocardial ischemia-reperfusion injury, SGs have been reported to suppress cGAS–STING-associated inflammation, supporting a functional role for SGs in restraining innate immune signaling under cardiac stress [145]. Conversely, NLRP3 inflammasome formation can inhibit SG assembly through multiple mechanisms, suggesting that inflammasome-mediated pyroptotic signaling and SG-associated stress adaptation may compete with one another [146,147]. Many inflammatory cytokines act to activate the JAK-STAT pathway, where phosphorylated STATs form dimers or oligomers and translocate canonically into the nucleus for transactivation of a host of genes, including ones for negative feedback (e.g., SOCSs) and others to regulate inflammation and immunity. Aberrant protein aggregation, which could result from impaired SG dynamics, has been shown recently to hijack the phosphorylated STATs into aberrant protein aggregates, thereby decoying the JAK-STAT pathway while exacerbating proteotoxicity [148]. Together, these findings indicate that inflammatory signaling is positioned to both influence SG assembly and shape the functional consequences of SG remodeling in cardiovascular disease.

3.2.4. Impaired Proteostasis and SG Clearance

Disruption of proteostasis in metabolic stress is closely linked to impairment of the autophagic-lysosomal pathway and the UPS. Chronic metabolic stress can increase the burden of misfolded proteins, damaged organelles, and oxidized macromolecules, while simultaneously weakening the quality-control systems responsible for their removal. In the heart, both autophagy and the UPS are indispensable catabolic pathways for the clearance and

recycling of damaged proteins and organelles, and their dysfunction has been widely implicated in cardiovascular aging, metabolic stress, and heart disease [149–151]. These alterations are particularly relevant because effective stress adaptation depends not only on the capacity to mount a transient response, but also on the ability to resolve stress-induced macromolecular assemblies once the insult subsides [152]. Thus, proteostatic overload and defective autophagic or proteasomal clearance establish conditions under which stress-induced assemblies may be more difficult to efficiently remove.

These considerations become particularly important in the context of SG clearance. SG disassembly is an active process that requires dedicated recovery machinery and does not rely solely on spontaneous dissolution [76]. In mammalian cells, ULK1 and ULK2 have been shown to localize to SGs and promote their disassembly through phosphorylation and activation of VCP/p97, an AAA+ ATPase required for extracting and remodeling SG-associated components [82]. In parallel, persistent SGs can also be targeted for selective autophagic removal through granulophagy, and inhibition of autophagy or depletion of VCP markedly reduces SG clearance [152]. More recent work has further emphasized that defects in autophagy-related pathways favor SG persistence, supporting the view that efficient SG resolution relies on intact proteostatic and degradative capacity [35,152]. Like inhibition of ubiquitination or VCP/p97, suppressing proteasomes also impairs the clearance of heat shock- or arsenite-induced SGs [50]. These studies indicate that impaired autophagy or UPS-mediated proteolysis can compromise SG recovery and clearance, thereby increasing the likelihood that SGs remain persistent under chronic metabolic stress.

Metabolic regulation and SG dynamics appear to be bidirectionally coupled. AMP-activated protein kinase (AMPK), a major sensor of cellular energy status, can directly influence SG biogenesis; AMPKα2 is recruited to SGs under stress, interacts with the SG nucleator G3BP1, and modulates SG assembly. SGs can, in turn, regulate metabolic signalling through mechanistic target of rapamycin complex 1 (mTORC1). Under stress, Astrin promotes the recruitment of the mTORC1 component Raptor to SGs, thereby restraining mTORC1 activity, while DYRK3-dependent SG dissolution releases sequestered mTORC1 and facilitates signalling recovery [153–155]. This regulatory relationship extends to lipid metabolism. SG formation is reciprocally coupled to lipid droplet biogenesis and promotes fatty acid accumulation within lipid droplets. During prolonged starvation, SGs also suppress fatty acid oxidation by modulating voltage-dependent anion channels and limiting mitochondrial fatty acid import, thereby redirecting fatty acids toward lipid storage [139]. Collectively, these findings position SGs at the interface between cellular energy sensing, metabolic signalling, and substrate utilization. Whether similar mechanisms contribute to metabolic adaptation or maladaptation in cardiomyocytes and the metabolically stressed heart remains to be established.

3.3. SG Functions Across Cardiac Cell Types

The composition, dynamics, and functional consequences of SGs vary across cell types and stress contexts. During metabolic stress, cardiac cell populations differ in their metabolic programs and stress responses, potentially exposing them to distinct intracellular signals that shape SG formation and behavior [156].

In cardiomyocytes, SG formation appears to support adaptation to acute cellular stress. In an *in vitro* model of atrial fibrillation, rapid electrical pacing induced G3BP1/PABP1-positive SGs, while G3BP1 overexpression enhanced SG formation and reduced ROS accumulation and calcium overload, suggesting a protective response to electrophysiological stress [138]. However, this interpretation requires caution because G3BP1 overexpression may influence ROS handling, calcium homeostasis, and stress-response pathways independently of its role as an SG nucleator. Thus, the observed protection cannot be attributed exclusively to SG formation unless it is also reproduced by more specific manipulation of SG assembly or disrupted by selectively preventing SG formation without altering other G3BP1 functions.

In diabetic myocardial ischaemia-reperfusion injury, the normal SG response becomes disrupted. High glucose combined with ischaemia-reperfusion reduces ALKBH5 together with the SG-associated proteins G3BP1 and TIA1, resulting in impaired SG formation and limiting the ability of cardiomyocytes to re-establish this protective stress response. Restoration of ALKBH5 or SG formation suppresses cGAS-STING activation, inflammation, and apoptosis, indicating that preservation of SG dynamics contributes to cardiomyocyte protection during diabetic ischaemic stress [145]. Nevertheless, direct evidence defining SG function during persistent metabolic stress alone remains limited. Future studies could examine how chronic hyperglycaemia, lipotoxicity, and other metabolically relevant stressors affect SG dynamics in cardiomyocytes, and whether prolonged metabolic stress increases SG persistence or alters SG composition and material properties in ways that impair proteostasis and cardiomyocyte function.

Macrophage SG responses appear to be closely linked to metabolic and inflammatory stress. During atherosclerosis, SGs accumulate in plaque macrophages with disease progression, while oxidized LDL, cholesterol

loading, and oxidative stress directly induce G3BP1-positive SG formation in bone marrow-derived macrophages, suggesting that SG assembly is part of the macrophage response to the lipid-rich and oxidative plaque environment [144]. In contrast, hyperglycaemia is associated with reduced G3BP1 expression alongside increased PKM2-mediated NLRP3 inflammasome activation and IL-1β/IL-18 production, indicating disruption of SG-associated signaling during enhanced inflammatory activation [157]. Together, these findings suggest that macrophage SG regulation is sensitive to the nature of metabolic stress and may interact with inflammatory pathways that contribute to cardiometabolic disease. However, whether these changes in SG formation actively restrain or promote macrophage inflammation remains unresolved, particularly because some studies rely on G3BP1 expression as a surrogate for SGs rather than directly assessing SG assembly and dynamics.

Fibroblasts are another important cardiac cell type in which SG-associated pathways may influence fibrotic remodelling. In one study using an *in vitro* model of atrial fibrillation-associated fibrosis, G3BP1 overexpression suppressed AngII-induced cardiac fibroblast proliferation and reduced collagen I and fibronectin-1 expression, although SG formation was not directly demonstrated in these cells [138]. Supporting evidence from human fibroblasts provides a mechanistic rationale for this potentially protective role: under repeated oxidative stress, G3BP1-dependent SG formation sequesters PAI-1, thereby limiting its secretion and suppressing the development of senescence, whereas G3BP1 depletion disrupts SG formation and increases fibroblast susceptibility to senescence [158]. Overall, these findings suggest that SG-associated responses may help preserve fibroblast homeostasis under stress, although their specific role in cardiac fibroblasts and metabolic fibrosis remains poorly defined.

SG-associated responses may also influence other vascular cell populations that contribute to vascular injury and remodelling. In VSMCs, atherogenic stimuli, including oxidized LDL and oxidative or mitochondrial stress, induce G3BP1/PABP-positive SGs through eIF2α phosphorylation, while the anti-inflammatory cytokine IL-19 suppresses this response. Disruption of G3BP1 reduces SG formation and alters inflammatory and proliferative gene expression, suggesting that SGs participate in VSMC adaptation and remodelling during vascular injury [144]. In endothelial cells, G3BP2 has been linked to NF-κB-dependent inflammatory activation and atherosclerosis, although the contribution of bona fide SG assembly remains less clearly established [159]. Further studies are therefore needed to explore how metabolic stress regulates SG formation, composition, and resolution in endothelial and other vascular cells, and whether these responses contribute to microvascular inflammation and dysfunction in metabolic heart disease.

4. Therapeutic Modulation of SG Remodeling

Current evidence suggests that SGs in the heart cannot be viewed as uniformly pathogenic structures. In cardiomyocytes, G3BP1-associated SG formation has been linked to protective responses under acute stress [138], including attenuation of lipopolysaccharide-induced dysfunction and reduction of reactive oxygen species and calcium overload in atrial fibrillation-related models [90]. Protective effects of G3BP1 have also been reported in metabolic disease outside the heart, including MASLD [120]. By contrast, under the post-infarct condition, G3BP1-dependent SG signaling in inflammatory macrophages appears to promote inflammatory cascades and adverse remodeling [160]. Taken together, these findings suggest that, in metabolic heart disease, the key therapeutic issue is unlikely to be SG formation per se, but the transition of adaptive granules into persistent, maladaptive assemblies with impaired reversibility and defective clearance under chronic metabolic stress. Based on this, therapeutic targeting of SG biology should emphasize context, cell type, stress duration, and disease stage rather than indiscriminate suppression of SG formation. Potential therapeutic targets for modulating SG dynamics are summarized in Table 3 and discussed in the following sections.

4.1. Targeting Excessive SG Initiation

One potential therapeutic entry point in metabolic heart disease is the initiation phase of SG assembly. Chronic metabolic stress can sustain translational arrest and increase the availability of non-translating mRNAs, thereby lowering the threshold for persistent or excessive SG assembly. Therefore, modulating the early steps of SG initiation may help limit pathological granule accumulation. Consistent with this rationale, potential targets span the PERK/GCN2–eIF2α–eIF2B signalling axis, mechanisms governing polysome disassembly, and the G3BP1/2-dependent nucleation threshold. Representative evidence includes ISRIB, which counteracts the translational consequences of eIF2α phosphorylation and blocks SG assembly while promoting disassembly of pre-formed granules [161], cardiac-myocyte work linking O-GlcNAcylation loss to the integrated stress response [162], and classical observations that polysome-stabilizing agents such as cycloheximide and emetine suppress SG assembly [76]. However, most currently available agents act on global translational control rather than SG-specific mechanisms, raising concerns about cardiomyocyte toxicity, impaired adaptive stress responses, and broad

interference with protein synthesis. Thus, therapeutic modulation of SG initiation would likely require partial, time-limited, or cell-selective strategies rather than complete blockade of stress-induced translational arrest.

4.2. Targeting Maladaptive SG Maturation

Another potential therapeutic perspective is the maturation phase of SGs. This strategy focuses on SGs that have already formed but, under chronic metabolic stress, may undergo fusion, compositional remodeling, and loss of dynamic exchange, thereby becoming less reversible and more pathologically persistent. Hence, potential targets include G3BP1/2-centred interaction surfaces and regulators of SG material properties and fusion dynamics, including metabolite- and PAR-dependent pathways. These findings provide proof of principle that SG behavior can be biochemically regulated. AdoMet influences SG assembly through a conserved metabolite-dependent mechanism, while PARP13-dependent regulation of SG maturation demonstrates that SG material properties remain tunable after assembly [163]. Future development may therefore focus on compounds that selectively restrain pathological SG maturation or preserve granule reversibility, although an important concern is that broad disruption of SG scaffold interactions could also interfere with adaptive stress responses [163,164].

4.3. Targeting Impaired SG Resolution and Clearance

Whereas the previous category concerns how already formed SGs evolve into a maladaptive state, the present category concerns whether such persistent SGs can be efficiently dismantled or cleared once they have become pathological.

Candidate targets therefore include the ULK1/2–VCP/p97 axis, which promotes SG disassembly, the HSPB8–BAG3–HSP70 chaperone system, which helps maintain SG dynamism and proteostasis surveillance, and granulophagy-related pathways involving autophagy receptors such as SQSTM1/p62 and CALCOCO2/NDP52 [48,82,165]. At present, direct SG-clearance drugs remain limited, but pharmacological enhancement of autophagy provides proof of principle: stress granules are cleared by granulophagy, and rapamycin has been shown to accelerate SG removal in recent disease models [166]. This category is especially attractive in metabolic heart disease because chronic metabolic stress is likely to compromise proteostasis and favor persistent SGs; notably, BAG3 is already recognized as a central proteostasis factor in the heart, supporting the translational relevance of this axis [167]. Given the necessity of protein degradation by proteasomes in the clearance of SGs induced by at least some stressors and the frequently impaired UPS performance in cardiac metabolic disease, such as heart failure with preserved ejection fraction (HFpEF) and myocardial ischemic/reperfusion injury [149,168], proteasome enhancement through for example augmentation of cAMP and cGMP signaling [169,170], which has shown great promise in attenuating proteotoxicity in experimental settings [151,169,171], is another conceivable direction to explore for the intervention of aberrant SG dynamics. Looking forward, potential strategies may include more selective enhancement of SG-directed autophagy, pharmacological support of VCP-dependent disassembly, or approaches that reinforce BAG3/HSP70-mediated granulostasis or proteasomal degradation, although an important concern is that broad activation of autophagy or proteolytic pathways may have substantial pleiotropic effects beyond SGs themselves.

Table 3. Potential therapeutic targets for modulating stress granule dynamics in metabolic heart disease.

Potential Therapeutic Target	Proposed Therapeutic Effect	References
SG initiation		
PERK/GCN2–eIF2α–eIF2B signalling axis	Modulates stress-induced translational arrest to limit excessive or persistent SG assembly	[161,162]
Polysome stabilization	Reduces the availability of non-translating mRNAs for SG assembly	[76]
G3BP1/2-dependent nucleation	Modulates the nucleation threshold for SG assembly	[55]
SG maturation		
G3BP1/2-centred interaction surfaces	Modulates SG interaction networks and material properties to restrain maladaptive maturation	[163]
PARP13-dependent regulation	Modulates SG maturation and post-assembly material properties	[164]
SG resolution and clearance		
ULK1/2–VCP/p97 axis	Promotes SG disassembly	[82]
HSPB8–BAG3–HSP70 chaperone system	Maintains SG dynamism and supports proteostasis surveillance	[165]
SQSTM1/p62 and CALCOCO2/NDP52	Mediate granulophagy-dependent clearance of persistent SGs	[48,82,165]
Ubiquitin–proteasome system	Supports proteasomal degradation involved in SG clearance	[149,168]

5. Conclusions

Stress granules are emerging as dynamic regulators of cellular stress adaptation at the intersection of translational control, proteostasis, and organelle homeostasis in cardiometabolic disease. Though transient SG formation may support adaptation to acute stress, prolonged metabolic stress may interfere with the timely resolution of SGs. Persistent disruption of SG dynamics may then promote maladaptive remodeling, including altered composition, reduced reversibility, and impaired clearance. These changes may ultimately contribute to proteostatic dysfunction and cardiac injury. Direct evidence in metabolic heart disease remains limited. Nevertheless, emerging findings support the concept that SG dysregulation may represent an important component of cardiometabolic stress pathology. Further studies using disease-relevant cardiac models will be essential to determine whether selectively restoring SG homeostasis, while preserving adaptive stress responses, can provide therapeutic benefit in metabolic cardiovascular disease. However, studying SG dynamics directly in cardiac tissue poses substantial technical challenges, particularly because approaches for real-time *in vivo* visualization at subcellular resolution are limited. This limitation complicates direct assessment of SG assembly, persistence, and resolution in the intact heart. Overcoming these limitations will therefore be important for defining the temporal dynamics and pathological relevance of SG remodelling in the intact heart.

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References

1. Eroglu, T.; Capone, F.; Schiattarella, G.G. The evolving landscape of cardiometabolic diseases. *eBioMedicine* **2024**, *109*, 105447. https://doi.org/10.1016/j.ebiom.2024.105447.
2. Phelps, N.H.; Singleton, R.K.; Zhou, B.; et al. Worldwide trends in underweight and obesity from 1990 to 2022: A pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet* **2024**, *403*, 1027–1050. https://doi.org/10.1016/S0140-6736(23)02750-2.
3. Duncan, B.B.; Magliano, D.J.; Boyko, E.J. IDF Diabetes Atlas 11th edition 2025: Global prevalence and projections for 2050. *Nephrol. Dial. Transplant.* **2026**, *41*, 7–9. https://doi.org/10.1093/ndt/gfaf177.
4. Targher, G.; Byrne, C.D.; Tilg, H. MASLD: A systemic metabolic disorder with cardiovascular and malignant complications. *Gut* **2024**, *73*, 691–702. https://doi.org/10.1136/gutjnl-2023-330595.
5. Malik, S.; Wong, N.D.; Franklin, S.S.; et al. Impact of the Metabolic Syndrome on Mortality from Coronary Heart Disease, Cardiovascular Disease, and All Causes in United States Adults. *Circulation* **2004**, *110*, 1245–1250. https://doi.org/10.1161/01.CIR.0000140677.20606.0E.
6. Vaduganathan, M.; Mensah, G.A.; Turco, J.V.; et al. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. *J. Am. Coll. Cardiol.* **2022**, *80*, 2361–2371. https://doi.org/10.1016/j.jacc.2022.11.005.
7. Schiattarella, G.G.; Alcaide, P.; Condorelli, G.; et al. Immunometabolic Mechanisms of Heart Failure with Preserved Ejection Fraction. *Nat. Cardiovasc. Res.* **2022**, *1*, 211–222. https://doi.org/10.1038/s44161-022-00032-w.
8. Jia, G.; Hill, M.A.; Sowers, J.R.; et al. Diabetic Cardiomyopathy. *Circ. Res.* **2018**, *122*, 624–638. https://doi.org/10.1161/CIRCRESAHA.117.311586.
9. Lopaschuk, G.D.; Karwi, Q.G.; Tian, R.; et al. Cardiac Energy Metabolism in Heart Failure. *Circ. Res.* **2021**, *128*, 1487–1513. https://doi.org/10.1161/CIRCRESAHA.121.318241.
10. Liu, Y.; Huo, J.-L.; Ren, K.; et al. Mitochondria-associated endoplasmic reticulum membrane (MAM): A dark horse for diabetic cardiomyopathy treatment. *Cell Death Discov.* **2024**, *10*, 148. https://doi.org/10.1038/s41420-024-01918-3.
11. Baliga, U.K.; Yang, L.; Ivanov, A.; et al. Translational Control in Cardiac Pathophysiology and Therapeutic Development: When mRNA Meets the Heart. *Int. J. Mol. Sci.* **2025**, *26*, 7863. https://doi.org/10.3390/ijms26167863.
12. Yang, G.; Wang, Y.; Guo, J.; et al. Connecting the Dots: Stress Granule and Cardiovascular Diseases. *J. Cardiovasc. Transl. Res.* **2025**, *18*, 738–748. https://doi.org/10.1007/s12265-025-10619-w.

13. Protter, D.S.W.; Parker, R. Principles and Properties of Stress Granules. *Trends Cell Biol.* **2016**, *26*, 668–679. https://doi.org/10.1016/j.tcb.2016.05.004.
14. Mateju, D.; Eichenberger, B.; Voigt, F.; et al. Single-Molecule Imaging Reveals Translation of mRNAs Localized to Stress Granules. *Cell* **2020**, *183*, 1801–1812.e13. https://doi.org/10.1016/j.cell.2020.11.010.
15. Glauninger, H.; Wong Hickernell, C.J.; Bard, J.A.M.; et al. Stressful steps: Progress and challenges in understanding stress-induced mRNA condensation and accumulation in stress granules. *Mol. Cell* **2022**, *82*, 2544–2556. https://doi.org/10.1016/j.molcel.2022.05.014.
16. Pakos-Zebrucka, K.; Koryga, I.; Mnich, K.; et al. The integrated stress response. *EMBO Rep*. **2016**, *17*, 1374–1395. https://doi.org/10.15252/embr.201642195
17. Kroschwald, S.; Maharana, S.; Mateju, D.; et al. Promiscuous interactions and protein disaggregases determine the material state of stress-inducible RNP granules. *eLife* **2015**, *4*, e06807. https://doi.org/10.7554/eLife.06807.
18. Molliex, A.; Temirov, J.; Lee, J.; et al. Phase Separation by Low Complexity Domains Promotes Stress Granule Assembly and Drives Pathological Fibrillization. *Cell* **2015**, *163*, 123–133. https://doi.org/10.1016/j.cell.2015.09.015.
19. Sanders, D.W.; Kedersha, N.; Lee, D.S.W.; et al. Competing protein-RNA interaction networks control multiphase intracellular organization. *Cell* **2020**, *181*, 306–324.e28. https://doi.org/10.1016/j.cell.2020.03.050.
20. Millar, S.R.; Huang, J.Q.; Schreiber, K.J.; et al. A New Phase of Networking: The Molecular Composition and Regulatory Dynamics of Mammalian Stress Granules. *Chem. Rev.* **2023**, *123*, 9036–9064. https://doi.org/10.1021/acs.chemrev.2c00608.
21. Wadsworth, G.M.; Srinivasan, S.; Lai, L.B.; et al. RNA-driven phase transitions in biomolecular condensates. *Mol. Cell* **2024**, *84*, 3692–3705. https://doi.org/10.1016/j.molcel.2024.09.005.
22. Wang, T.; Tian, X.; Kim, H.B.; et al. Intracellular energy controls dynamics of stress-induced ribonucleoprotein granules. *Nat. Commun.* **2022**, *13*, 5584. https://doi.org/10.1038/s41467-022-33079-1.
23. Wolozin, B.; Ivanov, P. Stress granules and neurodegeneration. *Nat. Rev. Neurosci.* **2019**, *20*, 649–666. https://doi.org/10.1038/s41583-019-0222-5.
24. Zhu, J.; Su, H. Assembly and disassembly of stress granules in kidney diseases. *iScience* **2025**, *28*, 112578. https://doi.org/10.1016/j.isci.2025.112578.
25. Jain, S.; Wheeler, J.R.; Walters, R.W.; et al. ATPase modulated stress granules contain a diverse proteome and substructure. *Cell* **2016**, *164*, 487–498. https://doi.org/10.1016/j.cell.2015.12.038.
26. Mackenzie, I.R.; Nicholson, A.M.; Sarkar, M.; et al. TIA1 mutations in amyotrophic lateral sclerosis and frontotemporal dementia promote phase separation and alter stress granule dynamics. *Neuron* **2017**, *95*, 808–816.e9. https://doi.org/10.1016/j.neuron.2017.07.025.
27. Zhang, P.; Fan, B.; Yang, P.; et al. Chronic optogenetic induction of stress granules is cytotoxic and reveals the evolution of ALS-FTD pathology. *eLife* **2019**, *8*, e39578. https://doi.org/10.7554/eLife.39578.
28. Liu, Y.; Li, Y.; Zhang, P. Stress granules and organelles: Coordinating cellular responses in health and disease. *Protein Cell* **2024**, *16*, 418–438. https://doi.org/10.1093/procel/pwae057.
29. Hamanaka, R.B.; Bennett, B.S.; Cullinan, S.B.; et al. PERK and GCN2 Contribute to eIF2α Phosphorylation and Cell Cycle Arrest after Activation of the Unfolded Protein Response Pathway. *Mol. Biol. Cell* **2005**, *16*, 5493–5501. https://doi.org/10.1091/mbc.e05-03-0268.
30. Farny, N.G.; Kedersha, N.L.; Silver, P.A. Metazoan stress granule assembly is mediated by P-eIF2α-dependent and -independent mechanisms. *RNA* **2009**, *15*, 1814–1821. https://doi.org/10.1261/rna.1684009.
31. Wek, R.C. Role of eIF2α Kinases in Translational Control and Adaptation to Cellular Stress. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*, a032870. https://doi.org/10.1101/cshperspect.a032870.
32. Khong, A.; Matheny, T.; Jain, S.; et al. The stress granule transcriptome reveals principles of mRNA accumulation in stress granules. *Mol. Cell* **2017**, *68*, 808–820.e5. https://doi.org/10.1016/j.molcel.2017.10.015.
33. Hu, S.; Zhang, Y.; Yi, Q.; et al. Time-resolved proteomic profiling reveals compositional and functional transitions across the stress granule life cycle. *Nat. Commun.* **2023**, *14*, 7782. https://doi.org/10.1038/s41467-023-43470-1.
34. Baymiller, M.; Moon, S.L. Stress Granules as Causes and Consequences of Translation Suppression. *Antioxid. Redox Signal* **2023**, *39*, 390–409. https://doi.org/10.1089/ars.2022.0164.
35. Ryan, L.; Rubinsztein, D.C. The autophagy of stress granules. *FEBS Lett.* **2024**, *598*, 59–72. https://doi.org/10.1002/1873-3468.14787.
36. Taylor, J.P.; Brown, R.H.; Cleveland, D.W. Decoding ALS: From genes to mechanism. *Nature* **2016**, *539*, 197–206. https://doi.org/10.1038/nature20413.
37. Song, J. Molecular Mechanisms of Phase Separation and Amyloidosis of ALS/FTD-linked FUS and TDP-43. Aging Dis **2024**, *15*, 2084–2112. https://doi.org/10.14336/AD.2023.1118.
38. Zhang, Q.; Liu, Y.; Tang, J.; et al. Emerging roles of stress granules in liver diseases: A comprehensive review. *Front. Cell Dev. Biol.* **2025**, *13*, 1731227. https://doi.org/10.3389/fcell.2025.1731227.

39. Costa-Mattioli, M.; Walter, P. The integrated stress response: From mechanism to disease. *Science* **2020**, *368*, eaat5314. https://doi.org/10.1126/science.aat5314.
40. Kedersha, N.L.; Gupta, M.; Li, W.; et al. RNA-Binding Proteins Tia-1 and Tiar Link the Phosphorylation of Eif-2α to the Assembly of Mammalian Stress Granules. *J. Cell Biol.* **1999**, *147*, 1431–1442. https://doi.org/10.1083/jcb.147.7.1431.
41. Su, K.-H.; Dai, C. mTORC1 senses stresses: Coupling stress to proteostasis. *BioEssays* **2017**, *39*, 1600268. https://doi.org/10.1002/bies.201600268.
42. Janapala, Y.; Preiss, T.; Shirokikh, N.E. Control of Translation at the Initiation Phase During Glucose Starvation in Yeast. *Int. J. Mol. Sci.* **2019**, *20*, 4043. https://doi.org/10.3390/ijms20164043.
43. Solomon, S.; Xu, Y.; Wang, B.; et al. Distinct Structural Features of Caprin-1 Mediate Its Interaction with G3BP-1 and Its Induction of Phosphorylation of Eukaryotic Translation Initiation Factor 2α, Entry to Cytoplasmic Stress Granules, and Selective Interaction with a Subset of mRNAs. *Mol. Cell Biol.* **2007**, *27*, 2324–2342. https://doi.org/10.1128/MCB.02300-06.
44. Asano-Inami, E.; Yokoi, A.; Sugiyama, M.; et al. The association of UBAP2L and G3BP1 mediated by small nucleolar RNA is essential for stress granule formation. *Commun. Biol.* **2023**, *6*, 415. https://doi.org/10.1038/s42003-023-04754-w.
45. Garg, M.; Lamba, S.; Rajyaguru, P.I. Emerging trends in the disassembly of stress granules and P-bodies. *Cell Rep.* **2025**, *44*, 116340. https://doi.org/10.1016/j.celrep.2025.116340.
46. Buchan, J.R. Stress granule and P-body clearance: Seeking coherence in acts of disappearance. *Semin. Cell Dev. Biol.* 2024, 159–160, 10–26. https://doi.org/10.1016/j.semcdb.2024.01.002.
47. Shih, J.-W.; Wang, W.-T.; Tsai, T.-Y.; et al. Critical roles of RNA helicase DDX3 and its interactions with eIF4E/PABP1 in stress granule assembly and stress response. *Biochem. J.* **2012**, *441*, 119–129. https://doi.org/10.1042/BJ20110739.
48. Yang, C.; Wang, Z.; Kang, Y.; et al. Stress granule homeostasis is modulated by TRIM21-mediated ubiquitination of G3BP1 and autophagy-dependent elimination of stress granules. *Autophagy* **2023**, *19*, 1934–1951. https://doi.org/10.1080/15548627.2022.2164427.
49. Turakhiya, A.; Meyer, S.R.; Marincola, G.; et al. ZFAND1 Recruits p97 and the 26S Proteasome to Promote the Clearance of Arsenite-Induced Stress Granules. *Mol. Cell* **2018**, *70*, 906–919.e7. https://doi.org/10.1016/j.molcel.2018.04.021.
50. Shi, W.; Ding, R.; Chen, Y.; et al. The HRD1-SEL1L ubiquitin ligase regulates stress granule homeostasis in couple with distinctive signaling branches of ER stress. *iScience* **2024**, *27*, 110196. https://doi.org/10.1016/j.isci.2024.110196.
51. Steinberger, S.; Adler, J.; Myers, N.; et al. Proteasome caspase-like activity regulates stress granules and proteasome condensates. *Front. Cell Dev. Biol.* **2025**, *13*, 1570499. https://doi.org/10.3389/fcell.2025.1570499.
52. Gwon, Y.; Maxwell, B.A.; Kolaitis, R.-M.; et al. Ubiquitination of G3BP1 mediates stress granule disassembly in a context-specific manner. *Science* **2021**, *372*, eabf6548. https://doi.org/10.1126/science.abf6548.
53. Yang, P.; Mathieu, C.; Kolaitis, R.M.; et al. G3BP1 is a tunable switch that triggers phase separation to assemble stress granules. *Cell* **2020**, *181*, 325–345.e28. https://doi.org/10.1016/j.cell.2020.03.046.
54. Glineburg, M.R.; Yildirim, E.; Gomez, N.; et al. Stress granule formation helps to mitigate neurodegeneration. *Nucleic Acids Res.* **2024**, *52*, 9745–9759. https://doi.org/10.1093/nar/gkae655.
55. Matsuki, H.; Takahashi, M.; Higuchi, M.; et al. Both G3BP1 and G3BP2 contribute to stress granule formation. *Genes. Cells* **2013**, *18*, 135–146. https://doi.org/10.1111/gtc.12023.
56. Jin, G.; Zhang, Z.; Wan, J.; et al. G3BP2: Structure and function. *Pharmacol. Res.* **2022**, *186*, 106548. https://doi.org/10.1016/j.phrs.2022.106548.
57. Gilks, N.; Kedersha, N.; Ayodele, M.; et al. Stress Granule Assembly Is Mediated by Prion-like Aggregation of TIA-1. *Mol. Biol. Cell* **2004**, *15*, 5383–5398. https://doi.org/10.1091/mbc.E04-08-0715.
58. Meyer, C.; Garzia, A.; Mazzola, M.; et al. The TIA1 RNA-binding-protein family regulates EIF2AK2-mediated stress response and cell cycle progression. *Mol. Cell* **2018**, *69*, 622–635.e6. https://doi.org/10.1016/j.molcel.2018.01.011.
59. Zeng, W.; Lu, C.; Shi, Y.; et al. Initiation of stress granule assembly by rapid clustering of IGF2BP proteins upon osmotic shock. *Biochim. Biophys. Acta Mol. Cell Res.* **2020**, *1867*, 118795. https://doi.org/10.1016/j.bbamcr.2020.118795.
60. Lai, A.; Valdez-Sinon, A.N.; Bassell, G.J. Regulation of RNA granules by FMRP and implications for neurological diseases. *Traffic* **2020**, *21*, 454–462. https://doi.org/10.1111/tra.12733.
61. Yamagishi, R.; Inagaki, H.; Suzuki, J.; et al. Concerted action of ataxin-2 and PABPC1-bound mRNA poly(A) tail in the formation of stress granules. *Nucleic Acids Res.* **2024**, *52*, 9193–9209. https://doi.org/10.1093/nar/gkae497.
62. Samir, P.; Kesavardhana, S.; Patmore, D.M.; et al. DDX3X acts as a live-or-die checkpoint in stressed cells by regulating NLRP3 inflammasome. *Nature* **2019**, *573*, 590–594. https://doi.org/10.1038/s41586-019-1551-2.
63. Buchan, J.R.; Parker, R. Eukaryotic Stress Granules: The Ins and Outs of Translation. *Mol. Cell* **2009**, *36*, 932–941. https://doi.org/10.1016/j.molcel.2009.11.020.
64. Guil, S.; Long, J.C.; Cáceres, J.F. hnRNP A1 Relocalization to the Stress Granules Reflects a Role in the Stress Response. *Mol. Cell Biol.* **2006**, *26*, 5744–5758. https://doi.org/10.1128/MCB.00224-06.
65. Wang, X.; Fan, X.; Zhang, J.; et al. hnRNPA2B1 represses the disassembly of arsenite-induced stress granules and is essential for male fertility. *Cell Rep.* **2024**, *43*, 113769. https://doi.org/10.1016/j.celrep.2024.113769.

66. Nonhoff, U.; Ralser, M.; Welzel, F.; et al. Ataxin-2 Interacts with the DEAD/H-Box RNA Helicase DDX6 and Interferes with P-Bodies and Stress Granules. *Mol. Biol. Cell* **2007**, *18*, 1385–1396. https://doi.org/10.1091/mbc.E06-12-1120.
67. McDonald, K.K.; Aulas, A.; Destroismaisons, L.; et al. TAR DNA-binding protein 43 (TDP-43) regulates stress granule dynamics via differential regulation of G3BP and TIA-1. *Hum. Mol. Genet.* **2011**, *20*, 1400–1410. https://doi.org/10.1093/hmg/ddr021.
68. Sama, R.R.K.; Ward, C.L.; Kaushansky, L.J.; et al. FUS/TLS assembles into stress granules and is a prosurvival factor during hyperosmolar stress. *J. Cell Physiol.* **2013**, *228*, 2222–2231. https://doi.org/10.1002/jcp.24395.
69. Dang, Y.; Kedersha, N.; Low, W.-K.; et al. Eukaryotic Initiation Factor 2α-independent Pathway of Stress Granule Induction by the Natural Product Pateamine A. *J. Biol. Chem.* **2006**, *281*, 32870–32878. https://doi.org/10.1074/jbc.M606149200.
70. Kedersha, N.; Anderson, P. Chapter 4 Regulation of Translation by Stress Granules and Processing Bodies. In *Translational Control in Health and Disease*; Academic Press: Cambridge, MA, USA, 2009; Volume 90, pp. 155–185. https://doi.org/10.1016/S1877-1173(09)90004-7.
71. Tauber, D.; Tauber, G.; Khong, A.; et al. Modulation of RNA Condensation by the DEAD-Box Protein eIF4A. *Cell* **2020**, *180*, 411–426.e16. https://doi.org/10.1016/j.cell.2019.12.031.
72. Helton, N.S.; Dodd, B.; Moon, S.L. Ribosome association inhibits stress-induced gene mRNA localization to stress granules. *Genes. Dev.* **2025**, *39*, 826–848. https://doi.org/10.1101/gad.352899.125.
73. Kaspar, S.; Oertlin, C.; Szczepanowska, K.; et al. Adaptation to mitochondrial stress requires CHOP-directed tuning of ISR. *Sci. Adv.* **2021**, *7*, eabf0971. https://doi.org/10.1126/sciadv.abf0971.
74. Yan, Y.; Shetty, M.; Harding, H.P.; et al. Substrate recruitment via eIF2γ enhances catalytic efficiency of a holophosphatase that terminates the integrated stress response. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2320013121. https://doi.org/10.1073/pnas.2320013121.
75. Klein, P.; Kallenberger, S.M.; Roth, H.; et al. Temporal control of the integrated stress response by a stochastic molecular switch. *Sci. Adv.* **2022**, *8*, eabk2022. https://doi.org/10.1126/sciadv.abk2022.
76. Hofmann, S.; Kedersha, N.; Anderson, P.; et al. Molecular mechanisms of stress granule assembly and disassembly. *Biochim. Biophys. Acta Mol. Cell Res.* **2021**, *1868*, 118876. https://doi.org/10.1016/j.bbamcr.2020.118876.
77. Demeshkina, N.A.; Ferré-D'Amaré, A.R. Large-scale purifications reveal yeast and human stress granule cores are heterogeneous particles with complex transcriptomes and proteomes. *Cell Rep.* **2025**, *44*, 115738. https://doi.org/10.1016/j.celrep.2025.115738.
78. Wheeler, J.R.; Matheny, T.; Jain, S.; et al. Distinct stages in stress granule assembly and disassembly. *eLife* **2016**, *5*, e18413. https://doi.org/10.7554/eLife.18413.
79. Wang, J.; Gan, Y.; Cao, J.; et al. Pathophysiology of stress granules: An emerging link to diseases (Review). *Int. J. Mol. Med.* **2022**, *49*, 44. https://doi.org/10.3892/ijmm.2022.5099.
80. Aulas, A.; Fay, M.M.; Lyons, S.M.; et al. Stress-specific differences in assembly and composition of stress granules and related foci. *J. Cell Sci.* **2017**, *130*, 927–937. https://doi.org/10.1242/jcs.199240.
81. Seguin, S.J.; Morelli, F.F.; Vinet, J.; et al. Inhibition of autophagy, lysosome and VCP function impairs stress granule assembly. *Cell Death Differ.* **2014**, *21*, 1838–1851. https://doi.org/10.1038/cdd.2014.103.
82. Wang, B.; Maxwell, B.A.; Joo, J.H.; et al. ULK1/2 Regulates Stress Granule Disassembly Through Phosphorylation and Activation of VCP/p97. *Mol. Cell* **2019**, *74*, 742–757.e8. https://doi.org/10.1016/j.molcel.2019.03.027.
83. Peterseim, C.M.; Jabbour, K.; Kamath Mulki, A. Metabolic Syndrome: An Updated Review on Diagnosis and Treatment for Primary Care Clinicians. *J. Prim. Care Community Health* **2024**, *15*, 21501319241309168. https://doi.org/10.1177/21501319241309168.
84. Verma, R.; Dhingra, N.K.; Connelly, K.A. Obesity/cardiometabolic phenotype of heart failure with preserved ejection fraction: Mechanisms to recent trials. *Curr. Opin. Cardiol.* **2024**, *39*, 92–97. https://doi.org/10.1097/HCO.0000000000001113.
85. Luo, L.; Zuo, Y.; Dai, L. Metabolic rewiring and inter-organ crosstalk in diabetic HFpEF. *Cardiovasc. Diabetol.* **2025**, *24*, 155. https://doi.org/10.1186/s12933-025-02707-7.
86. Hahn, V.S.; Chaffin, M.; Simonson, B.; et al. Single-Cell Analysis of Human Heart Failure with Preserved Ejection Fraction. *Circ. Res.* **2026**, *139*, e327433. https://doi.org/10.1161/CIRCRESAHA.125.327433.
87. Schiattarella, G.G.; Altamirano, F.; Tong, D.; et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature* **2019**, *568*, 351–356. https://doi.org/10.1038/s41586-019-1100-z.
88. Fu, F.; Doroudgar, S. IRE1/XBP1 and endoplasmic reticulum signaling—from basic to translational research for cardiovascular disease. *Curr. Opin. Physiol.* **2022**, *28*, 100552. https://doi.org/10.1016/j.cophys.2022.100552.
89. Xu, H.; Zhang, H.; Azam, T.; et al. A Novel Pak1 Activator Ameliorates ER Stress for HFpEF Therapy. *Adv. Sci.* **2026**, e76964. https://doi.org/10.1002/advs.76964.

90. Wang, Y.; Liu, R.; Wu, K.; et al. Stress granule activation attenuates lipopolysaccharide-induced cardiomyocyte dysfunction. *BMC Cardiovasc. Disord.* **2023**, *23*, 277. https://doi.org/10.1186/s12872-023-03281-0.
91. Wu, L.; Parhofer, K.G. Diabetic dyslipidemia. *Metabolism* **2014**, *63*, 1469–1479. https://doi.org/10.1016/j.metabol.2014.08.010.
92. Iaccarino, G.; Franco, D.; Sorriento, D.; et al. Modulation of Insulin Sensitivity by Exercise Training: Implications for Cardiovascular Prevention. *J. Cardiovasc. Transl. Res.* **2021**, *14*, 256–270. https://doi.org/10.1007/s12265-020-10057-w.
93. Sorriento, D.; Rusciano, M.R.; Visco, V.; et al. The Metabolic Role of GRK2 in Insulin Resistance and Associated Conditions. *Cells* **2021**, *10*, 167. https://doi.org/10.3390/cells10010167.
94. Jankauskas, S.S.; Kansakar, U.; Varzideh, F.; et al. Heart failure in diabetes. *Metabolism* **2021**, *125*, 154910. https://doi.org/10.1016/j.metabol.2021.154910.
95. Balakrishnan, B.; Somashekara, D.M.; Nayak, V.; et al. Diabetic cardiomyopathy: A comprehensive review of diagnosis, management, and future directions. *Diabetol. Metab. Syndr.* **2025**, *17*, 422. https://doi.org/10.1186/s13098-025-01986-0.
96. Sears, B.; Perry, M. The role of fatty acids in insulin resistance. *Lipids Health Dis.* **2015**, *14*, 121. https://doi.org/10.1186/s12944-015-0123-1.
97. Shu, H.; Peng, Y.; Hang, W.; et al. The role of CD36 in cardiovascular disease. *Cardiovasc. Res.* **2022**, *118*, 115–129. https://doi.org/10.1093/cvr/cvaa319.
98. Boudina, S.; Abel, E.D. Diabetic cardiomyopathy, causes and effects. *Rev. Endocr. Metab. Disord.* **2010**, *11*, 31–39. https://doi.org/10.1007/s11154-010-9131-7.
99. Bhatti, J.S.; Bhatti, G.K.; Reddy, P.H. Mitochondrial dysfunction and oxidative stress in metabolic disorders—A Step towards mitochondria based therapeutic strategies. *Biochim. Biophys. Acta* **2017**, *1863*, 1066–1077. https://doi.org/10.1016/j.bbadis.2016.11.010.
100. Torre, E.; Arici, M.; Lodrini, A.M.; et al. SERCA2a stimulation by istaroxime improves intracellular Ca^{2+} handling and diastolic dysfunction in a model of diabetic cardiomyopathy. *Cardiovasc. Res.* **2021**, *118*, 1020–1032. https://doi.org/10.1093/cvr/cvab123.
101. Alpert, M.A.; Karthikeyan, K.; Abdullah, O.; et al. Obesity and Cardiac Remodeling in Adults: Mechanisms and Clinical Implications. *Prog. Cardiovasc. Dis.* **2018**, *61*, 114–123. https://doi.org/10.1016/j.pcad.2018.07.012.
102. Borlaug, B.A.; Jensen, M.D.; Kitzman, D.W.; et al. Obesity and heart failure with preserved ejection fraction: New insights and pathophysiological targets. *Cardiovasc. Res.* **2022**, *118*, 3434–3450. https://doi.org/10.1093/cvr/cvac120.
103. Sletten, A.C.; Peterson, L.R.; Schaffer, J.E. Manifestations and mechanisms of myocardial lipotoxicity in obesity. *J. Intern. Med.* **2018**, *284*, 478–491. https://doi.org/10.1111/joim.12728.
104. Antonopoulos, A.S.; Papastamos, C.; Cokkinos, D.V.; et al. Epicardial Adipose Tissue in Myocardial Disease: From Physiology to Heart Failure Phenotypes. *Curr. Probl. Cardiol.* **2023**, *48*, 101841. https://doi.org/10.1016/j.cpcardiol.2023.101841.
105. Goldberg, I.J.; Trent, C.M.; Schulze, P.C. Lipid Metabolism and Toxicity in the Heart. *Cell Metab.* **2012**, *15*, 805–812. https://doi.org/10.1016/j.cmet.2012.04.006.
106. Griffin, T.M.; Humphries, K.M.; Kinter, M.; et al. Nutrient Sensing and Utilization: Getting to the Heart of Metabolic Flexibility. *Biochimie* **2016**, *124*, 74–83. https://doi.org/10.1016/j.biochi.2015.10.013.
107. Schulze, P.C.; Drosatos, K.; Goldberg, I.J. Lipid Use and Misuse by the Heart. *Circ. Res.* **2016**, *118*, 1736–1751. https://doi.org/10.1161/CIRCRESAHA.116.306842.
108. Chait, A.; den Hartigh, L.J. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. *Front. Cardiovasc. Med.* **2020**, *7*, 22. https://doi.org/10.3389/fcvm.2020.00022.
109. Han, J.; Kaufman, R.J. The role of ER stress in lipid metabolism and lipotoxicity. *J. Lipid Res.* **2016**, *57*, 1329–1338. https://doi.org/10.1194/jlr.R067595.
110. Guerra, J.; Matta, L.; Bartelt, A. Cardiac proteostasis in obesity and cardiovascular disease. *Herz* **2024**, *49*, 118–123. https://doi.org/10.1007/s00059-024-05233-6.
111. Da Dalt, L.; Cabodevilla, A.G.; Goldberg, I.J.; et al. Cardiac lipid metabolism, mitochondrial function, and heart failure. *Cardiovasc. Res.* **2023**, *119*, 1905–1914. https://doi.org/10.1093/cvr/cvad100.
112. Lee, S.-H.; Park, S.-Y.; Choi, C.S. Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes Metab. J.* **2022**, *46*, 15–37. https://doi.org/10.4093/dmj.2021.0280.
113. Krentz, A.J. Fortnightly Review: Insulin resistance. *BMJ* **1996**, *313*, 1385–1389. https://doi.org/10.1136/bmj.313.7069.1385.
114. Ormazabal, V.; Nair, S.; Elfeky, O.; et al. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc. Diabetol.* **2018**, *17*, 122. https://doi.org/10.1186/s12933-018-0762-4.
115. Tong, Y.; Xu, S.; Huang, L.; et al. Obesity and insulin resistance: Pathophysiology and treatment. *Drug Discov. Today* **2022**, *27*, 822–830. https://doi.org/10.1016/j.drudis.2021.11.001.
116. Zheng, H.; Sechi, L.A.; Navarese, E.P.; et al. Metabolic dysfunction-associated steatotic liver disease and cardiovascular risk: A comprehensive review. *Cardiovasc. Diabetol.* **2024**, *23*, 346. https://doi.org/10.1186/s12933-024-02434-5.

117. Targher, G.; Byrne, C.D.; Tilg, H. NAFLD and increased risk of cardiovascular disease: Clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut* **2020**, *69*, 1691–1705. https://doi.org/10.1136/gutjnl-2020-320622.
118. Sandireddy, R.; Sakthivel, S.; Gupta, P.; et al. Systemic impacts of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) on heart, muscle, and kidney related diseases. *Front. Cell Dev. Biol.* **2024**, *12*, 1433857. https://doi.org/10.3389/fcell.2024.1433857.
119. Bai, Y.; Dong, Z.; Shang, Q.; et al. Pdcd4 Is Involved in the Formation of Stress Granule in Response to Oxidized Low-Density Lipoprotein or High-Fat Diet. *PLoS ONE* **2016**, *11*, e0159568. https://doi.org/10.1371/journal.pone.0159568.
120. Liu, X.; Yu, H.; Hu, T.; et al. G3BP1, a stress granule core protein, ameliorates metabolic dysfunction-associated fatty liver disease by attenuating hepatocyte lipid deposition. *Diabetes Obes. Metab.* **2025**, *27*, 2985–2995. https://doi.org/10.1111/dom.16302.
121. Ouyang, Q.; Su, J.; Li, Y.; et al. Dysregulation of GTPase-activating protein-binding protein1 in the pathogenesis of metabolic dysfunction-associated steatotic liver disease. *Nat. Commun.* **2025**, *16*, 7570. https://doi.org/10.1038/s41467-025-63022-z.
122. Zhang, M.; Yang, C.; Zhu, M.; et al. Saturated fatty acids entrap PDX1 in stress granules and impede islet beta cell function. *Diabetologia* **2021**, *64*, 1144–1157. https://doi.org/10.1007/s00125-021-05389-4.
123. Zhao, B.; Li, H.; Liu, J.; et al. MicroRNA-23b Targets Ras GTPase-Activating Protein SH3 Domain-Binding Protein 2 to Alleviate Fibrosis and Albuminuria in Diabetic Nephropathy. *J. Am. Soc. Nephrol.* **2016**, *27*, 2597–2608. https://doi.org/10.1681/ASN.2015030300.
124. Chen, X.; Shi, C.; He, M.; et al. Endoplasmic reticulum stress: Molecular mechanism and therapeutic targets. *Signal Transduct. Target. Ther.* **2023**, *8*, 352. https://doi.org/10.1038/s41392-023-01570-w.
125. Wang, M.; Wey, S.; Zhang, Y.; et al. Role of the Unfolded Protein Response Regulator GRP78/BiP in Development, Cancer, and Neurological Disorders. *Antioxid. Redox Signal* **2009**, *11*, 2307–2316. https://doi.org/10.1089/ars.2009.2485.
126. Wang, S.; Binder, P.; Fang, Q.; et al. Endoplasmic reticulum stress in the heart: Insights into mechanisms and drug targets. *Br. J. Pharmacol.* **2018**, *175*, 1293–1304. https://doi.org/10.1111/bph.13888.
127. Yoshida, H.; Matsui, T.; Yamamoto, A.; et al. XBP1 mRNA Is Induced by ATF6 and Spliced by IRE1 in Response to ER Stress to Produce a Highly Active Transcription Factor. *Cell* **2001**, *107*, 881–891. https://doi.org/10.1016/S0092-8674(01)00611-0.
128. Yoshida, H.; Okada, T.; Haze, K.; et al. ATF6 Activated by Proteolysis Binds in the Presence of NF-Y (CBF) Directly to the cis-Acting Element Responsible for the Mammalian Unfolded Protein Response. *Mol. Cell Biol.* **2000**, *20*, 6755–6767. https://doi.org/10.1128/MCB.20.18.6755-6767.2000.
129. Harding, H.P.; Zhang, Y.; Ron, D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* **1999**, *397*, 271–274. https://doi.org/10.1038/16729.
130. Harding, H.P.; Novoa, I.; Zhang, Y.; et al. Regulated Translation Initiation Controls Stress-Induced Gene Expression in Mammalian Cells. *Mol. Cell* **2000**, *6*, 1099–1108. https://doi.org/10.1016/S1097-2765(00)00108-8.
131. Kedersha, N.; Chen, S.; Gilks, N.; et al. Evidence That Ternary Complex (eIF2-GTP-tRNAiMet)–Deficient Preinitiation Complexes Are Core Constituents of Mammalian Stress Granules. *Mol. Biol. Cell* **2002**, *13*, 195–210. https://doi.org/10.1091/mbc.01-05-0221.
132. Nicchitta, C.V. An emerging role for the endoplasmic reticulum in stress granule biogenesis. *Semin. Cell Dev. Biol.* **2024**, *156*, 160–166. https://doi.org/10.1016/j.semcdb.2022.09.013.
133. Advani, V.M.; Ivanov, P. Stress granule subtypes: An emerging link to neurodegeneration. *Cell Mol. Life Sci.* **2020**, *77*, 4827–4845. https://doi.org/10.1007/s00018-020-03565-0.
134. Cao, X.; Jin, X.; Liu, B. The involvement of stress granules in aging and aging-associated diseases. *Aging Cell* **2020**, *19*, e13136. https://doi.org/10.1111/acel.13136.
135. Hoffman, D.L.; Brookes, P.S. Oxygen Sensitivity of Mitochondrial Reactive Oxygen Species Generation Depends on Metabolic Conditions. *J. Biol. Chem.* **2009**, *284*, 16236–16245. https://doi.org/10.1074/jbc.M809512200.
136. Zhao, R.-Z.; Jiang, S.; Zhang, L.; et al. Mitochondrial electron transport chain, ROS generation and uncoupling (Review). Int J Mol Med **2019**, *44*, 3–15. https://doi.org/10.3892/ijmm.2019.4188.
137. Vásquez-Trincado, C.; García-Carvajal, I.; Pennanen, C.; et al. Mitochondrial dynamics, mitophagy and cardiovascular disease. *J. Physiol.* **2016**, *594*, 509–525. https://doi.org/10.1113/JP271301.
138. Dong, G.; Liang, F.; Sun, B.; et al. Presence and function of stress granules in atrial fibrillation. *PLoS ONE* **2019**, *14*, e0213769. https://doi.org/10.1371/journal.pone.0213769.
139. Amen, T.; Kaganovich, D. Stress granules inhibit fatty acid oxidation by modulating mitochondrial permeability. *Cell Rep.* **2021**, *35*, 109237. https://doi.org/10.1016/j.celrep.2021.109237.
140. An, C.; Li, Z.; Chen, Y.; et al. The cGAS-STING pathway in cardiovascular diseases: From basic research to clinical perspectives. *Cell Biosci.* **2024**, *14*, 58. https://doi.org/10.1186/s13578-024-01242-4.

141. Qian, X.; Sun, J.; Li, F.; et al. Inflammasomes as the molecular hub of cardiovascular-metabolic-immune comorbidity networks. *Front. Immunol.* **2025**, *16*, 1690443. https://doi.org/10.3389/fimmu.2025.1690443.
142. Zhang, Q.; Shen, L.; Ruan, H.; et al. cGAS-STING signaling in cardiovascular diseases. *Front. Immunol.* **2024**, *15*, 1402817. https://doi.org/10.3389/fimmu.2024.1402817.
143. Zhang, X.; Gu, A.; Zhou, L.; et al. Multi-omics analysis reveals STING activation mediates NLRP3-related pyroptosis and exacerbates myocardial ischemia-reperfusion injury. *PLoS ONE* **2026**, *21*, e0341839. https://doi.org/10.1371/journal.pone.0341839.
144. Herman, A.B.; Afonso, M.S.; Kelemen, S.E.; et al. Regulation of Stress Granule Formation by Inflammation, Vascular Injury, and Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 2014–2027. https://doi.org/10.1161/ATVBAHA.119.313034.
145. Li, W.; Qin, R.; Tang, Z.; et al. Inhibition of inflammation and apoptosis through the cyclic GMP-AMP synthase-stimulator of interferon genes pathway by stress granules after ALKBH5 demethylase activation during diabetic myocardial ischaemia-reperfusion injury. *Diabetes Obes. Metab.* **2024**, *26*, 3940–3957. https://doi.org/10.1111/dom.15743.
146. Paik, S.; Kim, J.K.; Silwal, P.; et al. An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cell Mol. Immunol.* **2021**, *18*, 1141–1160. https://doi.org/10.1038/s41423-021-00670-3.
147. Yoshioka, D.; Nakamura, T.; Kubota, Y.; et al. Formation of the NLRP3 inflammasome inhibits stress granule assembly by multiple mechanisms. *J. Biochem.* **2024**, *175*, 629–641. https://doi.org/10.1093/jb/mvae009.
148. Cai, M.; Pan, B.; Xiao, P.; et al. Sustained but Decoyed Activation of the JAK1-STAT Pathway by Aberrant Protein Aggregation Exacerbates Proteotoxicity. *Circulation* **2024**, *150*, 1302–1305. https://doi.org/10.1161/CIRCULATIONAHA.124.070067.
149. Lira, J.R.; Guymon, A.L.; Yang, L.; et al. The double-hit protocol induces HFpEF and impairs myocardial ubiquitin-proteasome system performance in FVB/N mice. *Front. Physiol.* **2023**, *14*, 1208153. https://doi.org/10.3389/fphys.2023.1208153.
150. Ma, C.; Liu, Y.; Fu, Z. Implications of endoplasmic reticulum stress and autophagy in aging and cardiovascular diseases. *Front. Pharmacol.* **2024**, *15*, 1413853. https://doi.org/10.3389/fphar.2024.1413853.
151. Ahammed, M.S.; Wang, X. Promoting Proteostasis by cAMP/PKA and cGMP/PKG. *Trends Mol. Med.* **2025**, *31*, 224–239. https://doi.org/10.1016/j.molmed.2024.10.006.
152. Buchan, J.R.; Kolaitis, R.-M.; Taylor, J.P.; et al. Eukaryotic stress granules are cleared by granulophagy and Cdc48/VCP function. *Cell* **2013**, *153*, 1461–1474. https://doi.org/10.1016/j.cell.2013.05.037.
153. Thedieck, K.; Holzwarth, B.; Prentzell, M.T.; et al. Inhibition of mTORC1 by Astrin and Stress Granules Prevents Apoptosis in Cancer Cells. *Cell* **2013**, *154*, 859–874. https://doi.org/10.1016/j.cell.2013.07.031.
154. Wippich, F.; Bodenmiller, B.; Trajkovska, M.G.; et al. Dual Specificity Kinase DYRK3 Couples Stress Granule Condensation/Dissolution to mTORC1 Signaling. *Cell* **2013**, *152*, 791–805. https://doi.org/10.1016/j.cell.2013.01.033.
155. Mahboubi, H.; Barisé, R.; Stochaj, U. 5′-AMP-activated protein kinase alpha regulates stress granule biogenesis. *Biochim. Biophys. Acta Mol. Cell Res.* **2015**, *1853*, 1725–1737. https://doi.org/10.1016/j.bbamcr.2015.03.015.
156. Van Treeck, B.; Parker, R. Principles of Stress Granules Revealed by Imaging Approaches. *Cold Spring Harb. Perspect. Biol.* **2019**, *11*, a033068. https://doi.org/10.1101/cshperspect.a033068.
157. Li, Q.; Leng, K.; Liu, Y.; et al. The impact of hyperglycaemia on PKM2-mediated NLRP3 inflammasome/stress granule signalling in macrophages and its correlation with plaque vulnerability: An *in vivo* and *in vitro* study. *Metabolism* **2020**, *107*, 154231. https://doi.org/10.1016/j.metabol.2020.154231.
158. Omer, A.; Patel, D.; Lian, X.J.; et al. Stress granules counteract senescence by sequestration of PAI-1. *EMBO Rep.* **2018**, *19*, e44722. https://doi.org/10.15252/embr.201744722.
159. Li, T.; Safitri, M.; Zhang, K.; et al. Downregulation of G3BP2 reduces atherosclerotic lesions in ApoE–/– mice. *Atherosclerosis* **2020**, *310*, 64–74. https://doi.org/10.1016/j.atherosclerosis.2020.08.003.
160. Jung, M.; Schmidt, A.; Sansonetti, M.; et al. Macrophage-specific circular RNA circHIPK2, inflammation, and fibrosis after myocardial infarction. *Eur. Heart J.* **2026**, *47*, 2831–2847. https://doi.org/10.1093/eurheartj/ehaf1116.
161. Sidrauski, C.; McGeachy, A.M.; Ingolia, N.T.; et al. The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly. *eLife* **2015**, *4*, e05033. https://doi.org/10.7554/eLife.05033.
162. Papanicolaou, K.N.; Zhang, W.; Dunphy, A.J.; et al. Loss of O-GlcNAcylation in cardiac myocytes triggers the integrated stress response, contributing to heart failure. *J. Biol. Chem.* **2025**, *301*, 110818. https://doi.org/10.1016/j.jbc.2025.110818.
163. Begovich, K.; Vu, A.Q.; Yeo, G.; et al. Conserved metabolite regulation of stress granule assembly via AdoMet. *J. Cell Biol.* **2020**, *219*, e201904141. https://doi.org/10.1083/jcb.201904141.
164. Cheng, S.-J.; Gafaar, T.; Kuttiyatveetil, J.R.A.; et al. Regulation of stress granule maturation and dynamics by poly(ADP-ribose) interaction with PARP13. *Nat. Commun.* **2025**, *16*, 621. https://doi.org/10.1038/s41467-024-55666-0.
165. Ganassi, M.; Mateju, D.; Bigi, I.; et al. A Surveillance Function of the HSPB8-BAG3-HSP70 Chaperone Complex Ensures Stress Granule Integrity and Dynamism. *Mol. Cell* **2016**, *63*, 796–810. https://doi.org/10.1016/j.molcel.2016.07.021.

166. Dong, T.; Li, N.; Wang, H.; et al. Stress granule clearance mediated by V-ATPase-interacting protein NCOA7 mitigates ovarian aging. *Nat. Aging* **2025**, *5*, 1548–1567. https://doi.org/10.1038/s43587-025-00927-w.
167. Mizushima, W.; Sadoshima, J. BAG3 plays a central role in proteostasis in the heart. *J. Clin. Invest.* **2017**, *127*, 2900–2903. https://doi.org/10.1172/JCI95839.
168. Tian, Z.; Zheng, H.; Li, J.; et al. Genetically Induced Moderate Inhibition of the Proteasome in Cardiomyocytes Exacerbates Myocardial Ischemia-Reperfusion Injury in Mice. *Circ. Res.* **2012**, *111*, 532–542. https://doi.org/10.1161/CIRCRESAHA.112.270983.
169. Ranek, M.J.; Terpstra, E.J.M.; Li, J.; et al. Protein Kinase G Positively Regulates Proteasome-Mediated Degradation of Misfolded Proteins. *Circulation* **2013**, *128*, 365–376. https://doi.org/10.1161/CIRCULATIONAHA.113.001971.
170. Yang, L.; Parajuli, N.; Wu, P.; et al. S14-Phosphorylated RPN6 Mediates Proteasome Activation by PKA and Alleviates Proteinopathy. *Circ. Res.* **2023**, *133*, 572–587. https://doi.org/10.1161/CIRCRESAHA.123.322887.
171. Zhang, H.; Pan, B.; Wu, P.; et al. PDE1 inhibition facilitates proteasomal degradation of misfolded proteins and protects against cardiac proteinopathy. *Sci. Adv.* **2019**, *5*, eaaw5870. https://doi.org/10.1126/sciadv.aaw5870.