



Stress granules: Emerging regulators of reproductive aging

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Abstract

Reproductive aging progressively impairs fertility and contributes to broader systemic decline. Stress granules (SGs), transient membraneless ribonucleoprotein assemblies formed during cellular stress, have recently emerged as important regulators of gonadal homeostasis. Their function is highly context dependent: properly resolved SGs promote cellular adaptation and survival, whereas persistent SGs disrupt proteostasis and trigger cell death pathways. In the testis, transient SGs protect germ cells under stress; however, persistent SG accumulation activates necroptosis through the ZBP1-RIPK3 axis, a pathway implicated in human non-obstructive azoospermia and testicular aging. In the ovary, defective autophagic clearance leads to pathological SG persistence in granulosa cells, while several SG-associated proteins are indispensable for normal oogenesis. Together, these findings indicate that dysregulated SG dynamics, particularly impaired clearance, represent a convergent mechanism linking cellular stress responses to reproductive decline. Despite these advances, critical gaps remain. The cell-type-specific regulation of SG assembly and disassembly within the gonad is not fully defined, and the molecular mechanisms by which persistent SGs drive tissue-level aging require clarification. Addressing these questions will refine our understanding of reproductive aging and its mechanistic connection to proteostatic imbalance.

Keywords: Stress granules, reproductive system, testicular aging, ovarian aging, reproduction disorders

1. Introduction

The reproductive system is essential for producing gametes and secreting sex hormones, which maintain organismal fecundity and physiological homeostasis^[1]. The pace and extent of reproductive aging largely determine an individual's reproductive lifespan. In males, age-associated testicular alterations are typically gradual, yet advanced paternal age is associated with impaired spermatogenesis and reduced sperm quality and quantity. In females, ovarian aging drives age-related infertility and culminates in menopause, with reproductive function generally ending around age 50 years^[2]. Beyond subfertility and infertility, reproductive aging increases the risk of cardiovascular diseases, cognitive decline, and metabolic syndrome, underscoring its broad impact on long-term health and quality of life^[2,3].

At the cellular level, reproductive aging is increasingly linked to impaired stress adaptation. Genetic, environmental, and immunological stressors disrupt cellular homeostasis, and mounting evidence implicates dysregulated stress responses as a central mechanism^[4,5]. Stress granules (SGs) are dynamic, membraneless cytoplasmic condensates that assemble via liquid-liquid phase



separation (LLPS) in response to stress^[6]. By transiently sequestering translationally stalled mRNAs and RNA-binding proteins (RBPs), SGs preserve RNA homeostasis, modulate signaling pathways, and promote cellular survival. Although SG dysfunction is well established in neurodegeneration and cancer^[7,8], emerging studies now implicate aberrant SG dynamics in reproductive homeostasis and age-related gonadal decline^[4,5].

Here, we examine the mechanisms governing SG assembly and clearance, with particular emphasis on their roles in ovarian and testicular aging. We summarize current mechanistic insights and highlight key conceptual and experimental challenges in the field.

2. Formation, Regulation, and Functions of SGs

SGs are dynamic cytoplasmic condensates that assemble within minutes to hours of stress exposure and disassemble once homeostasis is restored^[9]. They arise through condensation of untranslated messenger ribonucleoprotein (mRNP) complexes, composed of mRNA, the 40S ribosomal subunit, and associated initiation factors, including eIF3 and the eIF4F complex^[10]. Accumulation of stalled mRNPs nucleates SG formation by recruiting key RBPs, such as G3BP1/2 and TIA1, through multivalent interactions mediated by domains including the RGG and prion-like regions^[4,11,12]. Subsequent fusion and maturation events, facilitated by intrinsically disordered regions (IDRs), stabilize these assemblies through LLPS-driven interactions^[13].

SG assembly proceeds through canonical and non-canonical pathways, distinguished by their dependence on eIF2 α phosphorylation^[14]. In the canonical pathway, phosphorylation of eIF2 α at serine 51 serves as the principal trigger. In mammalian cells, four kinases mediate this modification in response to distinct stressors: PKR (viral double-stranded RNA), PERK (endoplasmic reticulum stress), GCN2 (amino acid deprivation and UV irradiation), and HRI (oxidative stress and heat shock)^[15–17]. Phosphorylated eIF2 α sequesters its guanine nucleotide exchange factor, reducing formation of the eIF2-GTP-tRNAi ternary complex. This blocks 48S pre-initiation complex assembly, halts translation initiation, and promotes SG formation^[18–20].

Non-canonical SG assembly occurs independently of eIF2 α phosphorylation and instead involves inhibition of the eIF4F complex, which is required for 5' cap-dependent mRNA unwinding^[14]. The RNA helicase eIF4A can be directly inhibited by metabolites such as 15-deoxy- Δ (12,14)-prostaglandin J2 (15-d-PGJ2), generated during sodium arsenite stress, or by pharmacological agents^[21–23]. Alternatively, under stresses including sodium selenite or hydrogen peroxide exposure, eIF4E-binding protein (4E-BP) becomes dephosphorylated and competitively binds to eIF4E^[24], displacing eIF4G, disrupting eIF4F integrity, and suppressing translation initiation^[24–26].

Upon stress resolution, SGs disassemble through coordinated reversal of assembly processes^[27]. Restoration of translation decreases recruitment of mRNAs into granules, multivalent RNA-protein interactions are destabilized, and ATP-dependent chaperones and segregases fragment SGs, returning stored mRNAs to the translational pool^[28,29]. It has been alternatively proposed that mRNA molecules localized into granules during stress have translational rates similar to their cytosolic counterparts when stress is relieved, suggesting granule localization in stress does not affect translation or decay during recovery^[30]. Persistent SGs, however, are cleared by selective autophagy, with receptors SQSTM1/p62 and CALCOCO2/NDP52 directly interacting with G3BP1 to mediate degradation^[31–33]. Proteasomal pathways also contribute; for example, ZFAND1 facilitates SG turnover during recovery^[34]. Disruption of the SUMO-targeted ubiquitin ligase (StUbl) pathway further delays SG clearance following arsenite- or heat-induced stress^[35].

By dynamically assembling and disassembling, SGs act as multifunctional hubs vital for maintaining cellular homeostasis. First, SGs maintain RNA homeostasis through spatial compartmentalization^[36,37]. By safeguarding mRNAs from degradation by RNases and other pathways, such as the proteasome and autophagy, SGs ensure the stability of these molecules during stress, enabling a timely restart of translation and cellular activities once the stress subsides^[38,39]. Second, SGs act as transient signaling platforms by sequestering adaptor proteins, kinases, and GTPases^[40,41]. For instance, sequestration of TRAF2 attenuates TNF α -induced NF κ B signaling, while retention of RACK1 suppresses activation of the pro-apoptotic p38/JNK cascade^[41,42]. More recently, SGs have been shown to stabilize damaged endolysosomal membranes, further illustrating their role in safeguarding cellular homeostasis^[43].

3. SGs Participate in the Regulation of Reproductive Disorders

3.1 The role of SGs in male reproductive aging and disease

The age-related decline in male reproductive function, characterized by diminished sperm quality and germ cell loss, is closely linked to the cumulative effects of various stressors. The dynamic equilibrium of SGs emerges as a critical but double-edged regulator: their precise assembly and disassembly are essential for germ cell homeostasis, while disruption of this balance represents a novel mechanism driving testicular aging and age-related male infertility.

Testicular germ cells, particularly spermatogonia and early and late spermatocytes at stages I–VIII of the seminiferous epithelium, are highly sensitive to stresses such as heat stress^[44]. Heat stress induces the phosphorylation of eIF2 α , which triggers the formation of SGs in these vulnerable cells^[45]. These SGs act as a protective mechanism by sequestering untranslated mRNAs and recruiting proteins like DAZL and BOULE, thereby mitigating stress-induced apoptosis^[44,46]. This protective response is further modulated by specific regulators. The testis-specific protein MAGE-B2 enhances thermotolerance by modulating translation of the SG nucleator

G3BP1^[47], while hnRNP2B1 stabilizes SGs during stress; its deletion results in Sertoli cell-only syndrome and complete male sterility^[48].

To ensure the protective function of SGs, their timely disassembly is as crucial as their formation. Proteins such as NEDD4 and SERBP1 are critical for this timely disassembly process, preventing the pathological persistence of SGs^[49,50]. When clearance fails, SGs transition from adaptive to cytotoxic structures. A key discovery reveals that persistent SGs nucleated by G3BP1 can directly activate a necroptotic cell death pathway via the ZBP1–RIPK3–MLKL axis^[5]. Within these SGs, G3BP1 scaffolds the activation of ZBP1, leading to RIPK3-mediated phosphorylation of MLKL and subsequent necroptosis of key cells, like spermatogonia and Sertoli cells^[5]. This pathway is highly activated in human non-obstructive azoospermia (NOA) and exhibits molecular signatures highly similar to those observed in testicular aging, establishing a direct mechanistic link between SG dysregulation and reproductive decline^[5]. Thus, male reproductive health depends on precise SG turnover: transient SGs are protective, whereas persistent SGs, arising from aging or impaired clearance drive germ cell loss and progressive testicular dysfunction.

3.2 The role of SGs in ovarian function and female reproductive aging

Female reproductive aging is characterized by a diminished ovarian reserve and declining oocyte quality, processes that accelerate later in life and reflect diminished stress resilience^[2,54]. Although direct visualization of canonical SGs in mammalian oocytes remains limited, accumulating evidence implicates SG-associated proteins in maintaining oocyte homeostasis, regulating oogenesis, and responding to age-associated cumulative stress^[47,52,53]. Therefore, their dysfunction likely represents a key mechanism underlying ovarian aging, operating through two interconnected aspects: the essential roles of SG-associated proteins in normal oogenesis, and the pathological consequences of impaired SG clearance with age.

The integrity of the female germline depends on SG-associated proteins, even when classical SG morphology is not readily observed. In mammalian oocytes, proteins such as FMRP, PABP, and TIA-1 are shared with constitutive ribonucleoprotein granules (e.g., P-granules), complicating morphological distinction^[54,55]. Functionally, however, these assemblies differ: constitutive granules regulate developmental RNA metabolism, whereas SGs are transient, stress-induced condensates that support acute adaptation. Despite this overlap, multiple SG-associated proteins are indispensable for oogenesis, and their deficiency directly causes sterility or ovarian abnormalities. FMRP is highly enriched in human fetal germ cells^[56]. A GGC repeat expansion in the *FMR1* gene reduces FMRP protein levels and causes Fragile X-associated primary ovarian insufficiency (POI), directly linking an SG protein to ovarian aging^[57,58]. In *C. elegans*, *TIAR-1* mutants exhibit meiotic defects and infertility^[53]. In *Drosophila*, *dFMRP* and *Caprin* are required for germline stem cell maintenance and follicle cell maturation, and loss of *Caprin* disrupts early egg chamber development^[59–64]. The SG nucleator Rasputin (Rin/G3BP) is essential for female fertility in flies, with mutants displaying defective egg chambers^[62]. In mice, loss of PABPN1L results in sterility^[63]. These phenotypes underscore that RNA metabolism regulated by SG-associated proteins is fundamental for producing high-quality oocytes.

With advancing age, a failure to resolve stress responses becomes a dominant pathological mechanism. The clearance of aberrant, persistent SGs is progressively compromised with age, largely due to declining efficiency of the ubiquitin-proteasome system and autophagy^[33,34]. Inefficient clearance of SGs in oocytes or surrounding granulosa cells could lead to their abnormal accumulation^[4]. These persistent granules might sequester crucial maternal mRNAs and regulatory proteins, disrupting translational programs and cellular homeostasis, and ultimately contributing to the acceleration of ovarian aging^[64,65]. A recent study demonstrated that loss of NCOA7 impairs selective autophagic degradation of SGs, resulting in their accumulation in granulosa cells and promoting cellular senescence, thereby accelerating ovarian aging in mice^[4]. Notably, enhancing the NCOA7–SG–autophagy axis reduces SG burden and ameliorates associated cellular defects, highlighting the therapeutic potential of restoring SG clearance to mitigate ovarian aging^[4].

In summary, ovarian aging involves both the loss of essential SG-related RNA metabolism and the gain of toxic SG persistence, together compromising female reproductive function. This dual mechanism contrasts with the predominantly necroptosis-driven pathology observed in the testis, emphasizing the tissue-specific roles of SGs in male and female reproductive aging (Table 1).

Table 1. A comparative overview of SG dysregulation in testicular and ovarian aging.

	Testicular Aging	Ovarian Aging	Ref.
Stressor	Acute, often exogenous (e.g., heat, toxins) stress	Chronic, cumulative metabolic and oxidative stress	[4,44]
Dysregulation Mechanism	Aberrant SG assembly, and failed clearance leading to germ cell necroptosis	Loss of essential SG-related RNA metabolism; impaired autophagic clearance leading to SG accumulation	[5,45,48,57,58]
Cellular Targets	Spermatogonia, Sertoli cells	Granulosa cells, oocytes	[4,5,46,48,53,62]
Functional Consequence	Germ cell loss, disrupted spermatogenesis	Granulosa cell senescence, follicular atresia, reduced oocyte quality	[4,5,44–47,59–61, 64]

Therapeutic Strategies	Inhibition of necroptosis; enhancement of pathological SG clearance	Augmentation of selective autophagy; restoration of proteostasis	[4,5,33,34,49,50]
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SG: stress granules.

4. Conclusion

Accumulating evidence indicates that SGs act as a double-edged regulator of reproductive aging. Specifically, while transient and well-regulated SGs are essential for cellular adaptation and survival under stress, persistent or clearance-defective SGs become pathological and contribute to aging and disease. In both testis and ovary, the precise dynamics of SG assembly and disassembly are critical for cellular protection, whereas age-related decline in proteostasis leads to persistent SGs that drive germ cell loss and progressive functional decline^[4,5].

Although the functions of specific SG-associated proteins, such as G3BP1 and SERBP1, are beginning to be elucidated^[6,50], SG biology in reproductive tissues remains incompletely defined. Several areas warrant further clarification, including: (1) mapping the complete SG proteome and transcriptome in specific reproductive cell types, particularly within the broader gonadal microenvironment, encompassing immune and stromal compartments; (2) elucidating how persistent SGs directly trigger cell death or cellular senescence pathways; and (3) defining the potential impact of SG modulation on reproductive function, such as through small molecules that enhance SG clearance or via conditional knockout models targeting proteins like G3BP1/2. In addition, it remains unclear whether SG-mediated stress responses in gametes contribute to transgenerational epigenetic inheritance.

Declarations

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AI-based software (DeepSeek V3.2) was used to assist with language editing during the preparation of this manuscript. The authors take full responsibility for the content of the manuscript.

Authors contribution

Li N, Zhu H: Conceptualization, writing-original draft.
Qin Y, Jiao X: Supervision, writing-review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

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