

应激颗粒与mRNA处理小体的研究进展

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摘要 应激颗粒(stress granule, SG)与mRNA处理小体(processing body, PB)是真核细胞内两类高度保守的无膜核糖核蛋白(ribonucleoprotein, RNP)颗粒,二者均通过液-液相分离(liquid-liquid phase separation, LLPS)动态组装形成。SG和PB都能够参与mRNA的代谢与翻译调控,并在细胞应激应答中发挥关键作用。SG主要在应激条件下组装,用于储存翻译停滞的mRNA与核糖体相关组分,助力细胞适应应激并恢复细胞稳态;PB可组成性存在于部分细胞中,应激后数量与体积显著增加,参与mRNA降解与暂时性储存。近年来,随着超分辨显微镜成像、核糖体图谱等技术的发展,SG与PB的组装机制、动态调控网络及其与疾病的关联得到逐步解析,但二者功能的分子机制、相互作用的调控细节尚未明确。该文系统综述了SG与PB的结构组成、核心生物学功能、组装与解聚机制等,并重点探讨了两者的相互作用关系,总结了其在疾病发生发展中的作用及研究进展。

关键词 应激颗粒; mRNA处理小体; mRNA代谢; 疾病

Research Advances in Stress Granules and Processing Bodies

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Abstract SG (stress granule) and PB (processing body) are two highly conserved membrane-less RNP (ribonucleoprotein) granules in eukaryotic cells. Both are dynamically assembled via LLPS (liquid-liquid phase separation). SG and PB are both involved in mRNA metabolism and translational control, and play critical roles in cellular stress responses. SG mainly assemble under stress conditions to store translationally stalled mRNAs and ribosome-associated components, facilitating cellular adaptation to stress and the re-establishment of cellular homeostasis. PB exist constitutively in some cells and show a marked increase in number and size upon stress, participating in mRNA degradation and transient storage. In recent years, with the development of techniques such as super-resolution microscopy and Ribo-seq (ribosome profiling), the assembly mechanisms, dynamic regulatory networks of SG and PB, as well as their associations with diseases, have been gradually elucidated. However, many questions remain regarding the molecular mechanisms underlying their functions and the regulatory details of their crosstalk. This paper systematically reviews the structural composition, core biological functions, and mechanisms of assembly and disassembly of SG and PB, with a focus on their crosstalk, and summarizes the roles and research advances of these granules in the occurrence and progression of diseases.

Keywords stress granule; processing body; mRNA metabolism; diseases

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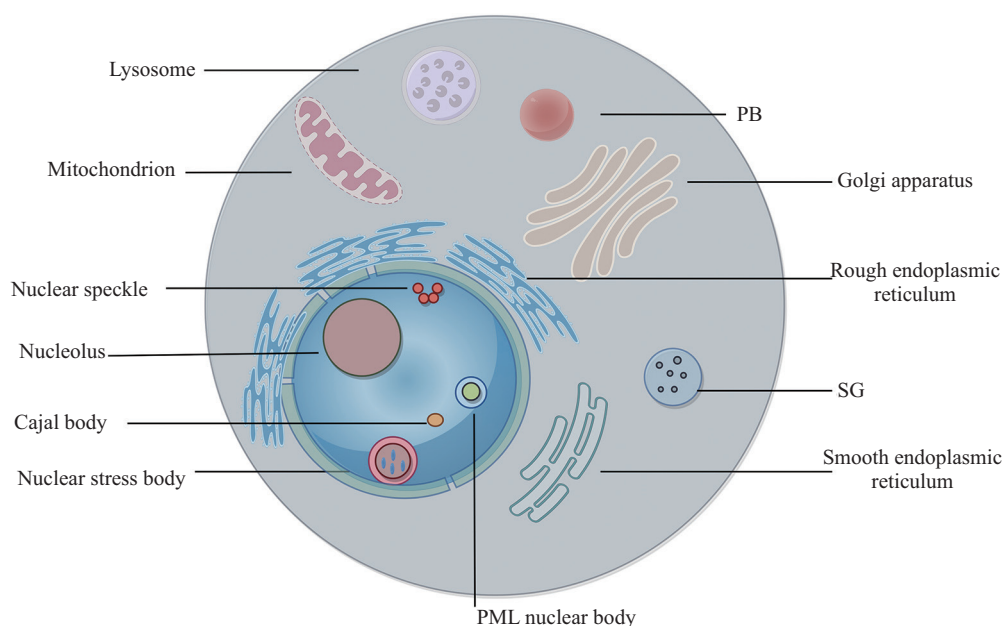
细胞是真核生物体结构和功能的最小单位。真核细胞为确保各种生化反应能够有序开展,会以区隔化的形式存在,表现为众多膜结合细胞器,如溶酶体、高尔基体、内质网等。最近的研究表明,细胞内还存在大量无膜区隔结构,如细胞核中的核仁(nucleolus)、核应激体(nuclear stress body)、卡哈尔体(Cajal body),以及细胞质中的应激颗粒(stress granule, SG)和mRNA处理小体(processing body, PB)等,它们便是典型的无膜细胞器(membraneless organelles, MLOs)(图1),这类结构同样对细胞代谢、RNA稳态、应激响应及生化反应时空调控发挥着不可或缺的关键作用。

SG与PB是细胞内两种重要的无膜RNA代谢颗粒,均由RNA结合蛋白(RNA-binding proteins, RBPs)、mRNA及部分翻译相关因子组成,通过液-液相分离(liquid-liquid phase separation, LLPS)机制实现动态组装与解聚。二者都参与mRNA的储存、转运及降解等多个过程,共同调控细胞内mRNA代谢网络与翻译组重塑^[1]。近年来,活细胞实时成像技术、核糖体分析测序技术以及蛋白质质谱鉴定技术的迭代升级,推动SG与PB相关研究不断取得突破,

其在细胞应对外界应激过程中的重要作用得到证实,二者结构异常与机体病变的关联性也成为学界研究重点。然而,SG与PB的形成机制、内部蛋白的互作网络,以及介导疾病发生发展的具体分子通路尚未明确。本文结合近期领域内研究成果,针对SG与PB展开全面的阐述。

1 SG与PB的组装与功能

SG与PB均为真核细胞内依赖LLPS形成的无膜核糖核蛋白(ribonucleoprotein, RNP)颗粒,是细胞在转录后水平调控mRNA命运的核心亚细胞结构,二者遵循高度保守的核心组装机制。两类颗粒的形成主要依赖含低复杂度结构域的RBPs与mRNA之间的多价相互作用,它们通过LLPS逐级完成成核、聚集与成熟^[2]。SG与PB均呈现典型的核壳异质分层结构:致密稳定的核心区富集骨架与调控蛋白,流动性更强的外壳区富集mRNA及穿梭型RBPs,为颗粒稳定性与动态物质交换提供了结构基础^[3-4]。此外,二者的组装与稳态维持均高度依赖核心蛋白的翻译后修饰,包括磷酸化、泛素化、SUMO化与甲基化等,通过动态修饰水平精确调控颗粒组装、生



有膜细胞器: 线粒体、糙面内质网、滑面内质网、溶酶体、高尔基体; 无膜细胞器: 应激颗粒(SG)、mRNA处理小体(PB)、核斑、核仁、卡哈尔体、核应激体、早幼粒细胞白血病(PML)核体。

Membrane-bound organelles: mitochondria, rough endoplasmic reticulum, smooth endoplasmic reticulum, lysosomes, Golgi apparatus; membraneless organelles: SGs (stress granules), PBs (processing bodies), nuclear speckles, nucleoli, Cajal bodies, nuclear stress bodies, PML (promyelocytic leukemia) nuclear bodies.

图1 细胞中有膜细胞器与无膜细胞器的定位

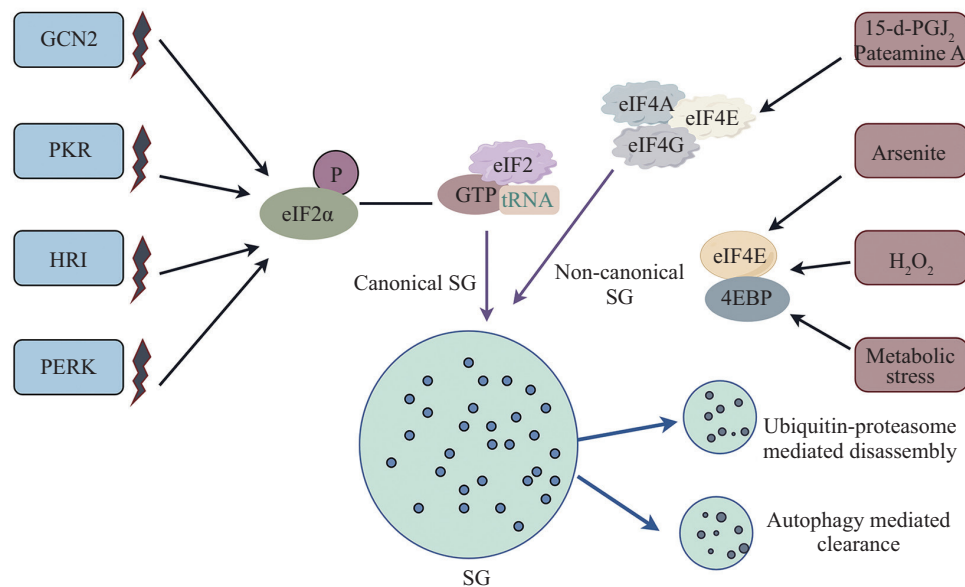
Fig.1 Localization of membranous and non-membranous organelles in cells

长与解聚,以响应胞内外应激信号^[5-6]。尽管SG与PB共享LLPS这一核心组装机制,但二者在诱导条件、核心组分、组装通路及生物学功能上存在显著分化,共同构成功能互补的mRNA调控网络。

SG是细胞特异性应激响应型无膜RNP颗粒,在正常生理条件下几乎不形成成熟结构,仅在氧化应激、热休克、营养剥夺、化疗药物等外界胁迫下快速诱导组装^[7-8]。SG直径多在100~1 000 nm,组分具有高度特异性,核心骨架蛋白为G3BP1/2与UBAP2L,是维持其结构稳定与起始成核的关键分子;颗粒内还大量富集eIF3、eIF4G、eIF4A等翻译起始因子、40S核糖体小亚基,以及大量处于翻译暂停状态的mRNA与多种RBPs^[8-9]。根据上游应激信号不同,SG组装可分为经典与非经典两条通路,共同介导翻译抑制与颗粒成熟。其中经典通路依赖eIF2 α 磷酸化:在应激状态下,GCN2、PKR、PERK、HRI四类激酶可分别感知氨基酸缺乏、病毒感染、内质网应激与热休克等刺激,催化eIF2 α 发生位点特异性磷酸化^[10-11]。磷酸化eIF2 α 丧失结合GTP的能力,导致翻译起始三元复合物生成受阻,全局翻译起始被广泛抑制;大量未完成翻译的mRNA从核糖体解离,与RBPs形成mRNP并进一步聚集,最终

驱动SG有序组装(图2)。非经典通路则不依赖eIF2 α 磷酸化,主要由特定小分子处理或细胞代谢紊乱触发,包含两种核心模式:15-d-PGJ₂可共价修饰eIF4A的Cys264位点,阻断其与eIF4G的相互作用,直接破坏eIF4F复合物的结构与功能^[12];应激导致mTORC1失活,使4EBP去磷酸化并竞争性结合eIF4E,占据eIF4G结合位点,同样抑制eIF4F组装与翻译起始^[13](图2)。

SG并非单纯封存mRNA的结构,而是具有高度动态性与生理活性的应激调控单元,可持续与胞质进行物质交换,并发生融合、分裂与迁移^[14]。传统观点认为SG内mRNA处于完全翻译沉默状态,而近年单分子活细胞成像研究证实,被招募至SG的未翻译mRNA仍保留翻译潜能,可在颗粒微环境中重新启动翻译,这一发现显著更新了学界对SG功能的认知^[15]。SG还可通过核心蛋白的翻译后修饰精细调控细胞稳态,如G3BP1磷酸化促进SG组装与稳定,泛素化则介导应激解除后SG的解聚;SUMO化、甲基化、ADP核糖基化等修饰也可调控SG动态,参与细胞应激应答^[5-6]。最近的研究发现,PABPC1的SUMO化修饰可特异性稳定SG内富含U序列的线粒体自噬相关mRNA,促进受损线粒体



应激条件下,细胞可通过典型和非典型两种途径组装SG。典型途径依赖eIF2 α 磷酸化,非典型途径则由小分子(如15-d-PGJ₂)或代谢应激诱导,无需eIF2 α 磷酸化。两类途径均通过抑制翻译起始和捕获蛋白复合物,介导SG组装。

Under stress conditions, SG assembly in cells proceeds through canonical and non-canonical pathways. The canonical pathway depends on eIF2 α phosphorylation, while the non-canonical pathway is triggered by small molecules including 15-d-PGJ₂ or metabolic stress, independent of eIF2 α phosphorylation. Both pathways mediate SG assembly by suppressing translation initiation and sequestering protein complexes.

图2 SG的组装与解聚

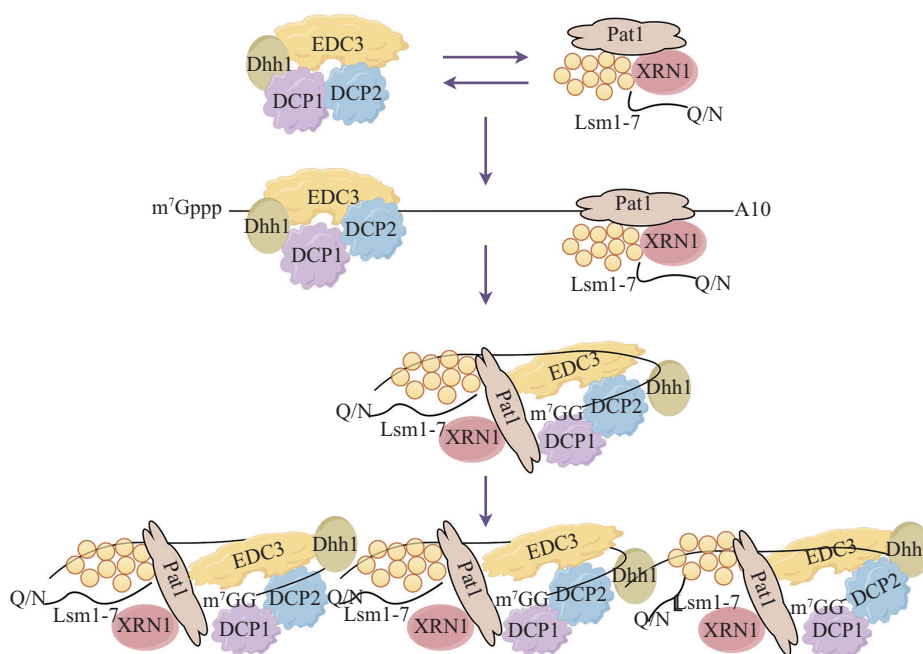
Fig.2 Assembly and disassembly of SG

清除, 增强肿瘤细胞的应激耐受能力, 揭示了SG介导细胞保护性应答的新机制^[16]。当应激消退后, 细胞可通过两条核心途径清除SG: 自噬依赖性途径依靠SQSTM1/p62与CALCOCO2/NDP52识别病理性SG组分, 介导颗粒靶向降解; 分子伴侣途径则通过HSPB8-BAG3-HSP70复合物重建胞内蛋白稳态, 恢复正常翻译进程^[17-19](图2)。

PB是真核细胞中组成型存在的一类RNP颗粒, 直径为100~300 nm, 不依赖外界应激诱导, 在生理与应激状态下均稳定位于细胞质, 是执行转录后RNA质控、mRNA降解与维持RNA稳态的关键结构^[20]。与SG的应激特异性不同, PB的主要功能是RNA代谢的精细调控, 其内部包含至少42种RNA调控因子, 可协同完成mRNA脱腺苷酸化、脱帽与完整降解过程^[20]。PB的核心组分可划分为六大功能模块: 脱帽酶DCP1/DCP2、脱帽激活因子、脱腺苷酸化相关因子、5'→3'核酸外切酶、miRNA调控因子及翻译抑制因子, 各组分有序协作以保证RNA代谢稳定进行^[20]。与SG类似, PB同样具有核心-外壳

分层结构: 致密内核富集DDX6、DCP1A等降解核心蛋白, 负责启动mRNA降解; 外层流动性较高, 分布eIF4E、YB-1等穿梭蛋白, 介导PB与胞质及SG之间的物质交换与信号交流^[4,20-21]。PB的组装严格依赖LLPS与多蛋白有序相互作用, 整体分为连续的3个阶段, 结构组装与功能成熟高度耦合^[2]。组装起始阶段, 支架蛋白EDC3特异性结合Dhh1解旋酶与DCP1/DCP2脱帽复合物, 形成功能性脱帽-解旋亚复合体; 同时Lsm1~7与Pat1、XRN1及待降解mRNA结合, 形成另一类前体复合物。在中间整合阶段, EDC3作为桥梁将两类亚复合体锚定在同一mRNA分子上, 形成具备初步脱帽与降解活性的PB核心单元。最终成熟阶段, 多个核心单元通过Lsm4的Q/N低复杂度结构域与EDC3的Yjef-N结构域发生多价弱相互作用, 经LLPS聚集堆叠, 形成结构稳定、功能完整的成熟PB^[2](图3)。

在生理功能上, PB主要作为mRNA分选平台, 富集细胞内异常、错误折叠及冗余mRNA以介导后续降解, 避免毒性转录本蓄积: 首先由脱腺苷酸



PB的组装包含3个核心阶段。初始组分互作: 支架蛋白EDC3与Dhh1、DCP1/DCP2相互作用, 形成脱帽解旋酶亚复合体; 核心复合物整合: EDC3发挥支架作用, 将该亚复合体与Lsm1~7复合物整合, 形成mRNA降解功能复合物; 聚集成熟: 多个核心单元依靠EDC3与Lsm4的特定结构域发生弱相互作用, 最终聚集形成成熟PB。

PB assembly proceeds through three core stages. Initial component interaction: the scaffold protein EDC3 interacts with Dhh1 and DCP1/DCP2 to form a decapping-helicase subcomplex. Core complex integration: EDC3 acts as a scaffold to integrate this subcomplex with the Lsm1-7 complex, generating an mRNA-degrading functional complex. Aggregation and maturation: multiple core units undergo weak interactions via specific domains of EDC3 and Lsm4, ultimately assembling into mature PB.

图3 PB的组装过程

Fig.3 PB assembly proceeds

化酶移除mRNA 3'端poly(A)尾,随后DCP1/DCP2复合物切除5'端帽子结构,最后由XRN1沿5'→3'方向将转录本完全降解,从而精确维持细胞基因表达稳态^[2,22-24]。此外,PB可根据细胞生理需求选择性保留功能性mRNA,使其脱离颗粒并重返翻译系统,实现mRNA降解与重复利用的动态平衡。

2 SG-PB动态互动: mRNA状态转换与物质交换机制

细胞内mRNA的命运调控依赖SG与PB的功能分工与协同联动,二者共同构建了mRNA“正常翻译-应激封存-异常降解”的转换网络^[4,22,25]。在正常生理条件下,细胞通过经典翻译起始通路组装80S核糖体,mRNA持续参与蛋白合成,SG几乎不形成,PB仅少量降解异常转录本,维持基础RNA稳态^[25]。当细胞遭遇应激刺激时,全局翻译起始被抑制,大量mRNA脱离翻译体系,此时细胞内形成大量SG,这些mRNA会优先被招募至SG中完成临时封存,暂停翻译进程^[26]。该机制可减少细胞在应激状态下的能量消耗,隔离毒性未翻译mRNA,发挥短期细胞保护作用。若应激信号短暂消退,SG会发生快速解聚,释放功能性mRNA重新启动翻译,此时无需PB参与;若应激持续存在,SG中冗余、损伤或异常mRNA会通过SG与PB之间的颗粒互动界面被转运至PB,由PB完成特异性降解,避免毒性转录本累积,降低细

胞代谢资源^[22,27]。此外mRNP复合物可在两类颗粒间双向穿梭,部分研究提示少量mRNA可从PB回流至SG再次封存,形成灵活的动态调控环路,精准适配细胞生理与应激需求^[20,22,27-28]。

最近的研究利用超高分辨活细胞成像已明确证实,SG与PB并非独立存在,而是通过特异性物理接触界面形成稳定结构偶联,依托共享RBPs与特异性桥接分子实现动态物质交换与信号通信,且该互动过程受精密分子调控,存在明确功能边界^[21-22]。两类颗粒存在大量共有组分,eIF4E、eIF4G1、HuR、YB-1等蛋白可共定位于SG与PB,其中TIA-1、UBAP2L等蛋白优先富集于SG界面,成为颗粒间物质穿梭的核心载体^[21-22,29](图4)。TTP、BRF1是介导SG-PB锚定结合的关键桥接分子,可在两类颗粒间动态穿梭,直接启动颗粒间的物质交换^[27,30];SG核心蛋白UBAP2L可通过相分离特性富集于颗粒接触界面,进一步提升二者互作效率^[29]。同时,细胞内存在稳态调控机制,该机制严格界定颗粒互动边界:DDX6、4E-T、DCP1A可维持PB结构稳定,抑制两类颗粒异常黏附与过度融合;CNOT1、PAT1B则正向调控生理性颗粒对接,保障互作有序进行,避免异常互动引发的RNA代谢紊乱^[21](图4和表1)。

整体而言,SG-PB互动存在明确的功能边界:在生理状态下二者实现精准分工,而在病理条件下则

SG only	SG+PB	PB only
40S subunit RACK1 eIF3 eIF4A/B eIF4G DDX3 PABP UPF1/2 Ataxin2 Caprin1 FMRP/FXR1 G3BP1/2 Pumilio Staufen TSN USP10	eIF4E CPEB Smaug Ago1/2 DDX6/RCK FASTK EDC3 HuR Roquin TIA-1/R TTP/BRF1 Rap55/Lsm14 UPF1/2 XRN1 PMR1 YB1 APOBEC3G FMRP FXR1 Lin28 Rpb4	4E-T DCP1 DCP2 Hedls/GE-1 Nesprin CAF CCR4-Not1 GW182

依据亚细胞定位,将相关RNA结合蛋白分为三类:仅定位于SG(黄色区域)、SG与PB共定位(蓝色区域)、仅定位于PB(灰色区域)。

Related RNA-binding proteins are categorized by their localization into three groups: SG-only (yellow), SG and PB colocalized (blue), and PB-only (gray).

图4 SG与PB的蛋白分类及共享蛋白示意图

Fig.4 Schematic diagram of protein classification and shared proteins of SG and PB

表1 SG与PB大小、组分、功能差异对比
Table 1 Comparison of SG and PB in size, composition and function

特征 Characteristics	SG	PB
Size of diameter	100-1 000 nm	100-300 nm
Function	Sequester stalled mRNAs, inhibit translation initiation, and participate in cellular stress protection	Mediate mRNA degradation, silencing and storage, and regulate mRNA homeostasis and translational repression
Physiological state	Stress-inducible	Constitutive presence, with changes in number and size upon stress
mRNA fate	Temporary storage of mRNAs, repression of translation, and re-entry into translation upon stress resolution	Predilection for mRNA degradation, or silenced storage, with limited re-entry into translation
Marker proteins	G3BP1/2, TIA-1/R, eIF3, eIF4G, UBP1...	DCP1A/2, EDC3/4, XRN1, Lsm1-7, CCR4-NOT...
Common proteins	Ago1/2, eIF4E, CPEB, Smaug, DDX6/RCK, HuR, YB-1, TTP/BRF1...	Ago1/2, eIF4E, CPEB, Smaug, DDX6/RCK, HuR, YB-1, TTP/BRF1...
Major pathological association	Abnormal aggregation associated with neurodegenerative diseases, tumor proliferation, and chemoradiotherapy resistance	Dysfunction associated with neurodegenerative diseases, tumorigenesis, and immune evasion
Structural dynamics	Highly dynamic, with contact and material exchange with PB	Relatively stable, serving as a core site for mRNA degradation

发生紊乱。在正常应激下二者按需完成mRNA转运与功能互补,无过度融合与功能重叠;而在病理条件下调控分子失衡则会打破该边界,导致颗粒固相化、mRNA分选紊乱,诱发细胞损伤^[9,31]。

3 SG-PB互作失衡介导疾病发生的机制

既往研究多单独罗列SG、PB与各类疾病的关联表型,缺乏机制层面的共性归纳。本文基于SG-PB的结构-功能偶联特征(图4),将二者互作紊乱介导神经退行性疾病、肿瘤等疾病的核心机制归纳为三大通用通路。

3.1 凝聚物相变异常: 液态颗粒向病理性凝胶/固态不可逆转化

在正常生理应激下,SG与PB均为可逆液态凝聚物,应激消退后可快速解聚恢复稳态。而在衰老、慢性炎症、持续氧化应激及病理蛋白突变的干预下,SG-PB动态平衡被打破,颗粒发生不可逆相变,由功能性液态逐步转化为凝胶态、固态病理性聚集物,这是各类疾病发生的始动环节^[7,31-33]。

在神经退行性疾病中,颗粒相变异常是驱动神经元进行性损伤的核心因素,不同疾病的特征性病理蛋白均可靶向干扰SG与PB的相分离稳态,打破颗粒可逆动态平衡,诱导特异性病理表型的形成^[33]。在阿尔茨海默病(Alzheimer's disease, AD)中,胞内异常剪切产生的A β 寡聚体与过度磷酸化Tau蛋白可

形成双向恶性循环,持续诱导颗粒病理性相变^[34-36]。一方面,A β 与磷酸化Tau可异常驱动SG大量组装,抑制SG生理性解聚,促使液态SG逐步固化^[35];另一方面,SG核心蛋白TIA-1可直接结合Tau蛋白,进一步促进Tau过度磷酸化与神经原纤维缠结形成,放大神经毒性损伤^[37-38]。同时,A β 斑块可激活脑内小胶质细胞,诱发持续性氧化应激,并形成促炎的组织微环境,持续刺激SG异常生成,加剧神经元突触功能障碍^[36,39]。在肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)与额颞叶痴呆(frontotemporal dementia, FTD)中,TDP-43、FUS突变蛋白及C9ORF72基因异常编码的二肽重复蛋白是核心致病因子。这类蛋白可直接结合SG组分,阻断颗粒正常周转并诱导SG发生不可逆固相化;在病理条件下还可扰动PB核心蛋白DDX6,破坏PB结构完整性,造成PB异常膨大与功能紊乱,进而异常降解神经元功能维持相关mRNA^[7,40-41]。在帕金森病中, α -突触核蛋白可通过N-端结构域特异性结合PB支架蛋白EDC4,干扰PB脱帽复合物组装,破坏RNA代谢稳态,同时诱导SG病理性聚集,激活胶质细胞炎症反应,加速神经退行进程^[42]。罕见神经遗传病BPAN由WDR45基因突变介导,传统研究认为其致病机制仅与自噬缺陷相关,新近研究证实野生型WDR45可通过WD5结构域发生相分离,竞争性解离Caprin-1-G3BP1复合物,促进SG降解清除;而致病突变型WDR45完全丧失该功能,

导致SG清除阻滞、病理性颗粒大量沉积,加重神经元损伤^[43]。上述多种神经疾病的病理机制均证实,SG-PB液态凝聚向固态病理沉淀的不可逆转化,是各类神经退行性病变的共性起始机制。而在肿瘤中,缺氧、营养匮乏、慢性炎症的肿瘤微环境及临床放化疗干预,会持续刺激肿瘤细胞内SG过度组装、PB持续重塑,两类颗粒长期处于异常凝聚状态,无法完成生理性解聚与周转,这种持续的颗粒相变异常为肿瘤细胞恶性增殖、侵袭转移、治疗耐药提供了关键结构基础^[44-47]。

3.2 RNA代谢紊乱: 翻译抑制与mRNA分选降解失衡

SG-PB的核心生理功能是协同调控mRNA翻译、储存与降解,二者互作失衡会直接引发全局RNA代谢紊乱,成为疾病进展的核心中间环节。在生理状态下,SG精准封存功能性mRNA,PB特异性降解异常mRNA,分工清晰且动态平衡。在病理状态下,颗粒互作紊乱导致mRNA分选机制完全失控^[4,27]。

在多种神经退行性疾病中,SG-PB互作紊乱引发的RNA代谢失衡具有高度神经毒性。发生不可逆固相化的SG丧失动态解聚能力,无法正常释放维持神经元存活、突触修复的功能性mRNA,导致神经元全局翻译持续抑制,蛋白合成受阻;同时结构受损、功能紊乱的PB降解保真度遭到破坏,不再精准清除异常转录本,神经保护、发育及功能维持相关mRNA被异常消耗,造成神经元功能性蛋白缺失,加剧神经损伤^[7,36,40,42,48]。此外,衰老进程中circRNA异常累积可特异性阻滞SG-PB颗粒周转,干扰mRNA正常分选与代谢,进一步加剧神经元RNA稳态崩塌,加速脑衰老与退行性病变^[49]。相较于神经疾病的神经损伤表型,肿瘤中SG-PB介导的RNA代谢紊乱呈现明显的失衡状态,全面促进肿瘤恶性进展与治疗抵抗^[32]。多种恶性肿瘤中异常激活的SG可特异性隔离抑癌转录本,维持MYC、CCND1等原癌基因mRNA的稳定,持续促进肿瘤细胞增殖、周期进展;同时封存Caspase家族等促凋亡分子,抑制肿瘤细胞程序性死亡,助力肿瘤恶性增殖^[44]。与此同时,重塑后的PB功能发生病理性偏转,不再维持细胞正常RNA稳态,而是选择性降解抑癌基因mRNA、抗肿瘤免疫趋化因子转录本,一方面解除抑癌信号抑制,另一方面阻断肿瘤微环境中T细胞浸润,介导免疫逃逸^[46,50]。临床常用的奥沙利铂、替莫唑胺、5-FU等

化疗药物及电离辐射,均可强烈诱导肿瘤细胞SG大量生成,紊乱的SG-PB网络通过暂停全局翻译、稳定促生存转录本、维持PD-L1 mRNA稳态等多重机制,帮助肿瘤细胞抵御放化疗毒性,产生治疗耐药^[32,45,51]。在乳腺癌、胃癌、结直肠癌、胶质母细胞瘤等多种肿瘤中,研究均已证实PB核心蛋白Pat1、DCP1A、DDX6的异常表达可通过调控mRNA稳定性,重塑肿瘤增殖、迁移及耐药表型,充分说明RNA分选降解失衡是肿瘤进展的核心分子基础^[46,52-53]。

3.3 细胞稳态崩溃: 蛋白质质控、自噬与细胞器互作障碍

SG-PB并非独立行使RNA调控功能,而是与自噬系统、分子伴侣、线粒体、溶酶体等构成复杂互作网络。在生理条件下该网络协同完成RNP颗粒的分选、解聚与清除;一旦互作发生紊乱,会诱发蛋白质质量控制缺陷与多细胞器功能损伤,形成级联病理损伤,是推动疾病进展的重要因素^[14,24,54]。

应激消退阶段,可逆的液态SG主要依靠分子伴侣通路完成解聚。HSPB8-BAG3-HSP70复合物能够识别SG内富集的在应激条件下产生的错误折叠蛋白,介导颗粒解聚、修复异常蛋白并重启胞内翻译;而发生不可逆相变的病理性SG,则通过核心组分泛素化修饰启动颗粒自噬实现降解清除。SUMO化修饰参与SG组装-解聚的动态调控,维持颗粒物质属性的可逆性^[5,16]。PB作为mRNA分选平台,富集脱腺苷酸化、脱帽及5'→3'降解相关机器,通过对异常、冗余转录本的分选与降解,协助维持细胞蛋白质稳态^[22]。进入病理状态后,SG-PB互作失衡会直接抑制自噬系统对病理性RNP颗粒的识别与清除,造成G3BP1等SG骨架蛋白降解受阻,异常RNP颗粒在胞内持续蓄积^[17]。同时HSPB8-BAG3-HSP70分子伴侣辅助选择性自噬(chaperone-assisted selective autophagy, CASA)通路功能受损,缺陷核糖体衍生多肽与错误折叠蛋白不断累积,最终造成细胞蛋白质质量控制体系全面崩溃^[18]。

Annexin A11能够介导SG与溶酶体膜之间的物理接触,该互作既参与神经元轴突内RNP颗粒长距离转运,也为溶酶体介导病理性SG清除提供结构基础,对维持神经元RNP颗粒稳态不可或缺^[14,55]。当SG-PB的平衡状态被打破时,Annexin A11介导的SG-溶酶体通信发生阻断,病理性SG无法被溶酶体有效降解而在神经元内大量堆积。此外SG组分的

SUMO化修饰异常可通过改变SG内部线粒体自噬相关mRNA的命运, 间接干扰线粒体自噬流程, 受损线粒体得不到及时清除, 胞内活性氧大量累积并放大氧化应激损伤。该效应存在明显的疾病背景差异: 在神经退行性疾病中促进神经元凋亡与脑功能退化; 而在肿瘤微环境中, 则帮助肿瘤细胞提升应激耐受能力, 促进细胞存活^[16]。除蛋白质与细胞器稳态紊乱外, SG-PB异常还会扰乱细胞炎症稳态。RNA解旋酶DDX3定位于SG, 可双向调控NLRP3炎症小体活性。在正常状态下SG中DDX3被颗粒隔离, 限制炎症小体过度激活; 当SG发生病理固相化后, DDX3异常释放并激活NLRP3炎症小体, 诱导持续性慢性炎症反应。由此形成“颗粒结构异常-细胞器功能损伤-慢性炎症激活-颗粒进一步病理化”的正反馈循环, 加速多种疾病发生发展^[56]。

4 总结与展望

SG与PB作为细胞质内核心无膜RNP颗粒, 以LLPS为共同组装基础, 以mRNA储存、翻译、降解为功能分工, 通过动态物理互作与物质交换构建精密的转录后调控网络^[22,28]。二者稳态失衡并非单一结构异常, 而是通过颗粒相变异常、RNA代谢紊乱、细胞稳态崩溃三大核心共性机制, 广泛参与神经退行性疾病、肿瘤等重大疾病的发生与进展^[32,57]。

目前该领域研究仍存在明显短板与转化空白: 一是SG-PB互作的精准调控分子网络尚未完全明确, 颗粒液-固相变的临界调控靶点、修饰开关及上下游信号通路仍不明确; 二是现有机制研究大多局限于细胞系、模式动物等基础模型, 缺乏大样本临床组织、患者类器官模型的验证, 研究结论的临床适用性有待考证; 三是暂无成熟的疾病特异性靶向干预策略, 现有靶向G3BP1、eIF3E、eIF2 α 、HDAC6等核心分子的干预手段缺乏特异性, 难以精准调控SG-PB动态互作, 无法区分生理性保护与病理性紊乱通路^[58-59]。未来研究应聚焦SG-PB动态互作的核心桥接分子与相变调控靶点, 系统解析颗粒相变、RNA代谢、细胞器互作三大致病机制的内在关联, 挖掘可精准逆转颗粒病理紊乱、恢复细胞RNA稳态的新型靶点。深入阐明SG-PB互作在神经退行性疾病、肿瘤中的差异化调控机制, 能够为两类难治性

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