



液-液相分离在肿瘤中作用的研究新进展*

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【摘要】 液-液相分离(liquid-liquid phase separation, LLPS)是指细胞蛋白质和核酸等生物大分子在弱多价相互作用的驱动下,凝聚成液态无膜细胞器的可逆过程。目前检测生物大分子相分离的方法主要包括光漂白后荧光恢复法等。异常LLPS与人类多种癌症发生发展相关,肿瘤相关生物大分子(mRNA、lncRNA、肿瘤相关蛋白等)可通过发生相分离或异常相分离,影响转录翻译和DNA损伤修复、调控细胞自噬和铁死亡功能,进而调控多种肿瘤的发生发展。本文总结了LLPS在肿瘤发生发展中作用机制的最新研究进展,阐述了包括mRNA、lncRNA、蛋白质等生物分子发生异常相分离后促进/抑制自噬、肿瘤免疫、DNA损伤修复、细胞铁死亡等,进而影响肿瘤发生发展。目前研究表明,多种生物大分子能够发生相分离调控转录翻译、表达、转录后修饰、细胞信号转导等生物学过程。基于此,拓展相分离研究领域,深入研究其分子机制和调控过程具有深远的科学前景。

【关键词】 液-液相分离 生物分子凝聚体 肿瘤 综述

Research Progress in the Role of Liquid-Liquid Phase Separation in Human Cancer TAO Ruolin^{1,2}, ZHANG Shuijun^{1,2}, GUO Wenzhi^{1,2}, YAN Zhiping^{1,2△}. 1. Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450000, China; 2. Henan Key Laboratory for Digestive Organ Transplantation, Zhengzhou 450000, China

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【Abstract】 Liquid-liquid phase separation (LLPS) is a reversible process, during which biological macromolecules, including proteins and nucleic acids, condense into liquid membraneless organelles under the influence of weak multivalent interactions. Currently, fluorescence recovery after photobleaching is the primary method used to detect the phase separation of biological macromolecules. Recent studies have revealed the link between abnormal LLPS and the pathogenesis and development of various human cancers. Through phase separation or abnormal phase separation, tumor-related biological macromolecules, such as mRNA, long noncoding RNAs (lncRNAs), and tumor-related proteins, can affect transcriptional translation and DNA damage repair, regulate the autophagy and ferroptosis functions of cells, and thus regulate the development of various tumors. In this review, we summarized the latest research findings on the mechanism of LLPS in the pathogenesis and progression of tumors and elaborated on the promotion or inhibition of autophagy, tumor immunity, DNA damage repair, and cell ferroptosis after abnormal phase separation of biomolecules, including mRNA, lncRNA, and proteins, which subsequently affects the pathogenesis and progression of tumors. According to published findings, many biological macromolecules can regulate transcriptional translation, expression, post-transcriptional modification, cell signal transduction, and other biological processes through phase separation. Therefore, further expansion of the research field of phase separation and in-depth investigation of its molecular mechanisms and regulatory processes hold extensive research potential.

【Key words】 Liquid-liquid phase separation Biomolecular condensates Cancer Review

真核细胞中会发生大量的蛋白质相互作用和生化反应,细胞内具有磷脂双分子层膜的细胞器能保持相对独立的空间,以保障各种信号通路和生物相互作用有效而特异性地进行^[1]。同时,细胞内也存在许多无膜区域,这些区域的生物分子凝聚体(biomolecular condensates, BC)在没有物理屏障的情况下会浓缩生物分子,将内部成分与周围物质分离,保证生化反应的正常进行。BC通常由

模块化的结构域或可溶性生物分子的液-液相分离(liquid-liquid phase separation, LLPS)诱导形成。LLPS是指细胞里不同成分间相互碰撞、融合形成液滴,使一些成分包裹在液滴内,一些成分阻隔在液滴外的现象。相分离通过多价蛋白质构建相互作用网络,发生相分离的凝聚体可以特异性地浓缩或排斥特定分子,使这些分子与周围或凝聚体内部分离,从而促进或抑制各种关键的生物反应^[2]。

LLPS受多价弱相互作用驱动^[3],这类作用力来自于蛋白内在无序区(intrinsically disordered region, IDR)/类朊病毒病序列(PrLD)、支架DNA或RNA分子等^[4-5]。LLPS在核仁、P小体、Cajal小体、核斑点和应激颗粒(stress

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granules, SGs) 等无膜细胞器的形成中起到重要作用^[6] (图1)。LLPS 的发生高度依赖溶液中生物大分子的浓度、物理化学性质以及溶液所处的环境, 如: 温度、pH、

盐离子浓度以及溶液中其他生物大分子。当这些因素改变或被破坏时, 生物大分子发生异常相分离, 如编码相分离蛋白的基因突变会导致蛋白质凝聚异常等^[7]。

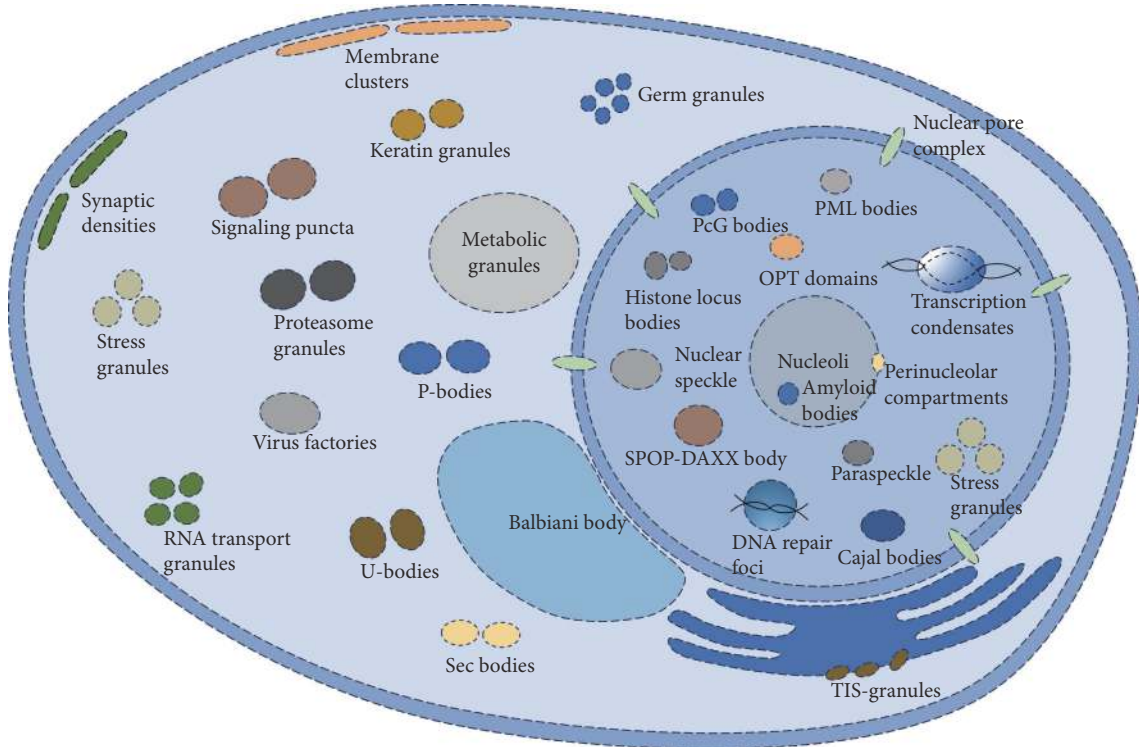


图 1 真核细胞中生物大分子凝聚体

Fig 1 Biomolecular condensates in eukaryotic cells

PML bodies: promyelocytic leukemia bodies; PcG bodies: polycomb bodies; OPT: Oct-1, PTF, transcription; TIS granules: TIS11B forms a membraneless organelle.

近年来研究表明, 生物大分子异常相分离与多种人类疾病(神经退行性疾病、癌症等)密切相关^[8-10]。因此, 本文总结人类肿瘤中相分离作用的最新研究进展, 重点论述LLPS影响人类肿瘤发生发展的作用途径和分子机制, 以期发展为肿瘤药物作用靶点和创新治疗策略提供新的理论参考。

1 LLPS的检测技术

发生相分离的特点是溶液会从澄清变得浑浊, 体外的相分离现象可以采用普通光学显微镜观察, 在镜检时会看到溶液中存在一些像水中油滴状态的液滴。此外, 也可使用检测溶液浑浊度或离心沉淀法来检测相分离^[11]。

而体内生物大分子相分离基于相分离液滴的融合性、可逆性和高动态性, 主要检测方法包括光漂白后荧光恢复法、密度梯度离心法、力光谱技术、核磁共振、荧光相关光谱、偏振荧光显微镜等^[4, 12]。

依据研究目的, 适用不同检测方法, 如光漂白后荧光恢复法通常用于分析液滴内外不同位置的分子扩散率以

验证LLPS的存在^[13]; 密度梯度离心法可用来测定液滴的密度, 反映凝集相的致密性; 力光谱技术, 包括原子力显微镜^[14]、生物膜力探针光谱学和光镊, 能够确定LLPS液滴的刚度和弹性模量等力学性能; 核磁共振用于检测分散相和凝集相样品中瞬态分子内/间相互作用的原子分辨率信息; 荧光相关光谱可准确检测相分离液滴内部某一分子的扩散能力; 而偏振荧光显微镜可检测相分离液滴内部纤维性或固态样结构的各向异性成分。

2 生物大分子LLPS调控肿瘤进展

肿瘤相关生物大分子可通过发生相分离或错误相分离, 影响转录翻译、调控细胞自噬和铁死亡功能、阻碍DNA损伤修复等, 调控多种肿瘤的发生发展(图2)。

2.1 相分离与肿瘤相关mRNA

RNA分子参与多种生物大分子凝聚体的形成, 包括核仁、转录凝聚体、共转录剪接凝聚体、核斑点和SGs等^[15]。其中mRNA通过相分离过程, 广泛参与了富含RNA/蛋白质的无膜细胞器的形成^[9]。

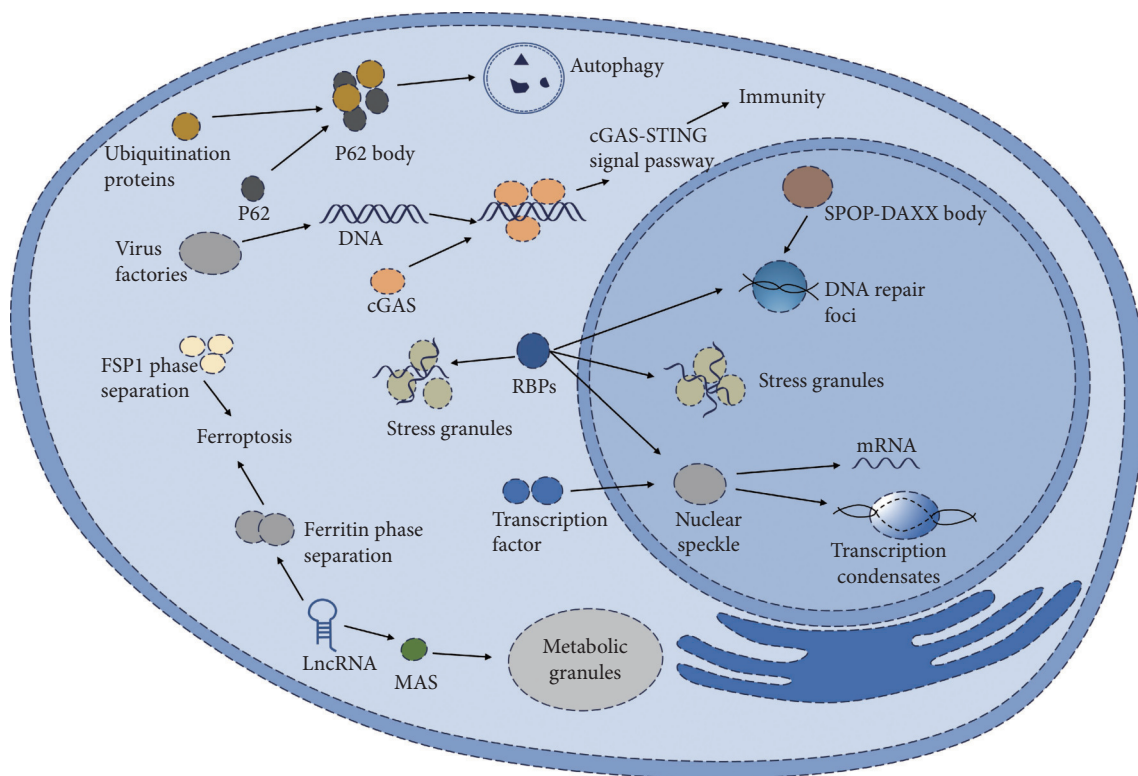


图 2 生物分子凝聚体通过调控自噬等影响肿瘤进展

Fig 2 Biomolecular condensates affect tumor progression by regulating autophagy, etc.

The abnormal phase separation of biomolecules can promote or inhibit autophagy, tumor immunity, DNA damage repair, metabolism, and ferroptosis and then affect the development of tumors. RBPs: RNA binding proteins; MAS: malate-aspartate shuttle.

RNA结合蛋白(RNA binding proteins, RBPs)可调控 mRNA在细胞质中的定位、翻译和稳定性等功能,其包含的低复杂性区域能够促进RNA分子相分离形成生物分子凝聚体^[16]。研究发现,Whi3蛋白可诱导mRNA发生构象变化,决定了mRNA凝聚体的特异性^[17]。去泛素化酶 USP42可形成核点状结构,引导剪接体成分PLPGA整合到核斑点中,使核斑点发生LLPS。而下调USP42可消除多个mRNA的剪接,抑制肿瘤细胞的生长^[18]。

应激颗粒是应激反应过程中由翻译停滞的mRNA和RBPs发生LLPS形成的非膜类组装体,可影响mRNA功能、定位和下游信号通路^[19-20]。如细胞周期相关蛋白1-CAPRIN1可与G3BP1、mRNA和非编码RNA通过LLPS相互作用共同形成SGs^[21]。肿瘤细胞可以通过激活应激反应,利用SGs适应肿瘤微环境中的应激条件,以保护肿瘤细胞,削弱抗癌杀伤^[22]。

2.2 相分离与肿瘤相关lncRNA

长链非编码RNA(long noncoding RNAs, lncRNA)作为一类重要的信号转导调控因子,可结合和调节RBPs的活性,通过相分离在DNA断裂修复、组织稳态和肿瘤的发展中发挥着重要作用^[23-24]。

lncRNA通过相分离调控肿瘤基因组稳定性。在结

肠癌^[25]和乳腺癌^[26]中,由DNA损伤激活的lncRNA-NORAD,可促使转录后抑制因子Pumilio蛋白发生相分离并抑制其活性,阻止异常有丝分裂的发生,维持基因组稳定性^[27],抑制肿瘤的发生发展。

lncRNA通过相分离调控肿瘤代谢。谷氨酰胺可被谷氨酰胺酶-1(glutaminase-1, GLS1)催化生成谷氨酸,维持机体所需。当机体缺乏谷氨酰胺时,lncRNA-GIRGL水平升高,可促使胞质磷酸蛋白二聚体与GLS1的mRNA形成复合物,发生相分离并诱导SGs形成,抑制GLS1 mRNA的翻译,使癌细胞在缺乏谷氨酰胺的应激反应下存活^[28]。研究发现,苹果酸-天冬氨酸穿梭(malate-aspartate shuttle, MAS)对于维持肿瘤中的糖酵解和能量代谢至关重要。GATA2-AS1可通过调节SUZ12的活性抑制FUBP3相分离,上调GATA2和其他肿瘤抑制基因的转录水平,抑制MAS和神经母细胞瘤的进展^[29]。此外,与脂质代谢相关的lncRNA-SNHG9可促进LATS1相分离,下调LATS1激酶活性和酪氨酸蛋白激酶相关蛋白(Yes-associated protein, YAP)磷酸化水平,促进YAP靶基因的转录和乳腺癌细胞增殖^[30]。

2.3 相分离与肿瘤相关蛋白

真核细胞转录过程中涉及到转录聚合酶、剪切体、

转录因子等分子,这些大分子蛋白的内部无序区(internal disordered regions, IDRs)为发生相分离奠定了结构基础。如转录调节因子BRD4的亚型之一BRD4S可形成核斑点,通过相分离调控染色质和转录因子活性,维持基因转录,促进癌细胞增殖^[31]。同样可以促进肿瘤生长的还有KMT2D,可形成稳定的LLPS微环境,通过表观遗传调控多种肿瘤发生及转移相关信号分子的基因表达^[32]。

3 肿瘤进展关键过程中的相分离

3.1 DNA损伤修复中的相分离

DNA损伤修复贯穿肿瘤的发生发展过程,可能会使原癌基因激活和抑癌基因失活,是细胞恶变的重要机制。生物大分子聚集到DNA断裂位点是DNA损伤修复反应的一个重要前提,而异常相分离会干扰DNA损伤修复。

DNA损伤修复相关因子或蛋白,可通过相分离调控DNA损伤修复,影响肿瘤的发生发展,如肿瘤抑制因子SPOP与死亡结构域相关蛋白DAXX的异常相分离和共定位会诱导肿瘤发生^[33-34];而p53结合蛋白1过度累积会增强其相分离,进一步调控DNA损伤和p53信号通路,降低肿瘤细胞的生存能力^[35]。

3.2 自噬中的相分离

自噬指自噬体识别、隔离和降解特定靶标,如可溶性蛋白、生物分子凝聚体、异常或多余的细胞器以及侵入性细菌等,维持细胞内环境的稳定^[36]。当应激和病理因素使蛋白质发生异常相分离,逃避自噬的监视,可导致相关疾病的产生^[37]。自噬与肿瘤发生发展密切相关,在不同阶段起着不同作用。研究表明,在正常细胞中存在着低水平的自噬,抑制肿瘤的发生;而在肿瘤转移和应对应激反应时,肿瘤细胞可通过自噬清除受损细胞器和其他生物大分子,实现重新利用以达到抵抗细胞凋亡、维持细胞能量和物质平衡的作用^[38-39]。

p62/SQSTM1蛋白是一种自噬底物连接蛋白,参与细胞内氧化应激、感染、免疫和炎症等多种生物学过程。p62可形成有LLPS特性的丝状结构^[40],与泛素化蛋白相互作用形成多聚泛素结构^[41],发生相分离形成p62小体,并作为形成自噬小体的场所,调控氧化应激反应^[42-43]和选择性自噬^[44],共同诱导器官损伤^[45]和肿瘤的发生发展。核受体Nur77通过与p62相互作用发生相分离,可以隔离受损的线粒体,连接自噬靶向的线粒体,介导自噬的发生^[46]。

肝脏Mallory-Denk小体(MDBs)常见于酒精性/非酒精性脂肪性肝炎、非酒精性肝硬化、肝细胞肝癌(hepatocellular carcinoma, HCC)等疾病^[47],而p62是

MDBs成熟所必需的^[48],HCC中的MDBs包含Ser349磷酸化的p62,通过敲除p62可抑制肿瘤的生长^[49]。KURUSU等^[50-51]发现由蛋白质和非编码RNA组成的非膜细胞器-vault,可通过依赖于p62相分离的选择性自噬降解,其损伤与非酒精性脂肪性肝炎导致的HCC有关。

综上,自噬底物蛋白p62通过液-液相分离过程调控自噬的发生发展,降解受损细胞器或非膜细胞器,调控HCC的进展。

3.3 铁死亡中的相分离

铁死亡是一种以铁依赖性脂质过氧化为特征、非凋亡性细胞死亡的代谢形式,与人类疾病高度相关,如癌症、神经退行性疾病、缺血再灌注损伤等。铁死亡能增加癌症对放疗的易感性,与癌症免疫疗法具有协同作用,甚至可以杀死耐药和转移性肿瘤,如可通过抑制URB1-AS1表达来抑制铁蛋白相分离,进而促进索拉非尼诱导的铁死亡,增强HCC细胞对索拉非尼的敏感性^[52];LncFASA可通过促进PRDX1形成液滴,导致脂质过氧化积累,进而调节铁死亡来抑制乳腺癌进展^[53];此外,结直肠癌中膜蛋白EphA2可通过相分离发挥促肿瘤作用,且其表达与嗜铁相关基因的表达和免疫细胞浸润正相关^[54]。最近有研究证明,与经典铁死亡抑制剂的作用机制不同,hFSP1特异性抑制剂icFSP1可通过触发铁死亡抑制蛋白1-FSP1的相分离,诱导肿瘤细胞的铁死亡^[55]。因此,未来有望通过作用于相关蛋白或因子触发铁死亡,作为一种新的抗癌方式抑制肿瘤生长并根除肿瘤。

3.4 肿瘤免疫中的相分离

免疫因素在调控肿瘤发生发展的作用日益得到重视,相分离在肿瘤免疫相关信号转导中发挥重要作用。在多种癌症中,cGAS-STING信号通路介导天然抗肿瘤免疫作用。致病性DNA与cGAS结合产生cGAMP,cGAMP结合并激活STING,触发机体先天免疫反应^[56]。

研究表明,cGAS相分离可诱导免疫反应的发生,而STING相分离会抑制抗肿瘤免疫作用^[57-58]。DU等^[59]发现,DNA与cGAS结合并诱导其二聚体发生相分离,激活cGAS以激活免疫反应。虽然DNA和RNA均可结合cGAS形成凝聚体,但RNA不能激活cGAS产生cGAMP,这说明需在DNA诱导正确构象变化的情况下,LLPS才可以激活cGAS。YAO等^[60]发现完全激活cGAS的分子基础包含DNA结合位点上DNA与cGAS的相互作用以及cGAS二聚体的形成,而DNA介导的相分离是增加局部浓度并促进cGAS与DNA结合的重要辅助因素。此外,某些蛋白可通过自身或分子间相互作用发生LLPS,抑制或激活cGAS-STING信号通路,影响抗肿瘤免疫反应,如疱疹病

毒家族编码的病毒蛋白^[61]、NF2突变体^[62],以及组蛋白去甲基化酶KDM4A^[63]等。

综上,靶向调控cGAS-STING信号通路的关键分子通过相分离过程调节机体抗肿瘤免疫,抑制肿瘤的发生发展,这为肿瘤免疫治疗提供新的治疗策略。

4 总结与展望

本文总结了LLPS在肿瘤发生发展中作用机制的最新研究进展,阐述了包括mRNA、lncRNA、蛋白质等生物分子发生异常相分离后促进/抑制自噬、肿瘤免疫、DNA损伤修复、细胞铁死亡等,进而影响肿瘤发生发展。目前研究表明,多种生物大分子能够发生相分离调控转录翻译、表达、转录后修饰、细胞信号转导等生物学过程。基于此,拓展相分离研究领域,深入研究其分子机制和调控过程具有深远的科学前景。

生物大分子LLPS作为一种生物物理学现象,目前已成为生命科学的前沿领域之一。LLPS可以使更好地理解生物大分子的组织模式,更深刻地认识生物大分子直接调控的真核细胞生理和病理过程。关于生物大分子发生LLPS在疾病发生发展中的作用的相关研究越来越多,但是截至目前,对相分离的研究仍然还停留在描述基本现象上,因此迫切需要更多的定量、实时检测和观察相分离发生的精细过程和调控机制的原创研究。在未来,研究LLPS调控的生物分子、疾病发生过程和生物学意义将有助于开发新的药物作用靶点和全新模式的诊疗策略。

* * *

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Author Contribution TAO Ruolin is responsible for the conceptualization, funding acquisition, writing--original draft, and writing--review and editing. ZHANG Shuijun and GUO Wenzhi are responsible for the resources and supervision. YAN Zhiping is responsible for the conceptualization, funding acquisition, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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