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# 神经退行性疾病相关淀粉样蛋白的液-液相分离

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**摘要** 神经退行性疾病是一类由于大脑和周围神经系统中的细胞与神经元死亡或功能丧失而引发的疾病, 包括阿尔茨海默病(AD)、帕金森病(PD)、肌萎缩侧索硬化症(ALS)和额颞叶痴呆(FTD)等. 由于神经退行性疾病的病理机制尚未被完全探明, 因此缺乏有效的治疗方法. 大多数神经退行性疾病具有一个共同的病理表现, 即淀粉样蛋白质聚集体和包涵体的形成. 在过去很长一段时间内, 成核聚集被认为是蛋白质聚集体形成的主要方式. 然而, 近几年的研究显示, 越来越多的神经退行性疾病相关淀粉样蛋白可能经历液-液相分离介导的聚集, 暗示淀粉样蛋白的相行为与病理之间可能存在重要关联. 本文综述几种重要的神经退行性疾病相关淀粉样蛋白的性质和相分离行为研究的最新进展, 包括Aβ、Tau、α-突触核蛋白、TDP-43和SOD1等. 希望有助于加深人们对于神经退行性疾病相关蛋白病理机制的理解, 为疾病治疗带来新的思路.

**关键词** 神经退行性疾病, 淀粉样蛋白, 聚集, 相分离

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神经退行性疾病是一类由于大脑和周围神经系统中的细胞和神经元死亡或功能丧失而引发的疾病, 包括阿尔茨海默病(Alzheimer's Disease, AD)、帕金森病(Parkinson's Disease, PD)、肌萎缩侧索硬化症(Amyotrophic Lateral Sclerosis, ALS)和额颞叶痴呆(Frontotemporal Dementia, FTD)等[1~3]. 由于神经退行性疾病的病理机制尚未被完全探明, 因此目前可用的治疗手段仅能缓解一些相关症状, 有效治疗的方法仍然缺乏.

大多数神经退行性疾病具有一个共同的病理表现, 即蛋白质聚集体和包涵体的形成[4~6]. 在这些疾病中,

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某些肽或蛋白质从其可溶性状态转化为高度组装的纤维聚集体[7]. 不同疾病中的特征性聚集蛋白不同, 例如AD中的淀粉样蛋白-β(Aβ)和Tau, PD中的α-突触核蛋白(α-synuclein), ALS和FTD中的FUS、TDP-43和SOD1, 以及亨廷顿病中的亨廷顿蛋白(Huntingtin, HTT)等[8,9]. 这些蛋白都属于淀粉样蛋白. 淀粉样蛋白是一个通用术语, 指的是易交叉β结构形成聚集体的蛋白质, 这些聚集体具有特定的着色特性(与刚果红和硫黄素S结合), 不易被蛋白质水解酶所降解, 在电子显微镜下呈纤维状外观(直的、无分支的纤维)[10,11]. 蛋白质聚集体在神经退行性疾病中的普遍存在暗示了它们在疾病发生、进展中的特殊作用, 对于它们产生、发展的机理研究将有助于进一步理解神经退行性疾病的致病机制.

在过去很长一段时间内, 成核聚集都被认为是蛋白质聚集体形成的唯一方式. 成核聚集是指完全或部分无序的蛋白质单体转化为聚集核; 随后更多的蛋白单体被吸引到聚集核上, 并逐渐形成原纤维; 接着, 更多的蛋白以此为模板继续生长, 并逐渐成熟为纤维状聚集体. Aβ[12,13]、朊病毒蛋白[14,15]、α-突触核蛋白[16,17]、Tau[18,19]等淀粉样蛋白都存在经历成核聚集的聚集过程. 然而, 最近一系列研究表明, 这些蛋白质可能经历另一种聚集过程——液-液相分离介导的聚集[20~22]. 在这种情况中, 蛋白质自发凝聚为一个局部富集的小液滴. 因为液滴内部的蛋白质浓度可能超过蛋白质聚集的阈值浓度, 所以一旦原本维持体系稳定的因素, 如分子伴侣蛋白、RNA等失去作用, 像淀粉样蛋白这样具有聚集倾向的蛋白质将很容易发生聚集并最终形成聚集体. 这个现象在Aβ[23]、TDP-43[24]和Tau[25]等蛋白质上都有发现.

## 1 相分离的驱动力与固有无序蛋白

神经退行性疾病相关淀粉样蛋白通常具有部分或全部无序结构. 这些固有无序区域或蛋白质(Intrinsically Disordered Regions/Proteins, IDRs/IDPs)是不具有稳定三维折叠结构的蛋白质片段或蛋白质[26~28], 它们是动态的, 具有不均匀的构象. 一些IDRs的氨基酸组成可能具有明显的偏向性, 导致特定氨基酸在这个序列中重复出现, 它们也称为低复杂度域[29]. 由于缺乏明确的三维结构, IDRs相比于折叠域具有更高的动态性和灵活性, 因此有更多的机会发生分子间接触和相互作用[30,31]. IDRs分子内或与其他生物大分子分子间的多价相互作用是相分离的重要驱动力, 具体包括静电、π相关、氢键、疏水相互作用等[30](图1).

(1) 静电相互作用. IDRs中常含有大量带电氨基酸, 包括带负电的天冬氨酸(D)、谷氨酸(E)和带正电的赖氨酸(K)、组氨酸(H)和精氨酸(R)等. 这些带电氨基酸产生的静电力可能在相分离中起重要作用[32,33]. 同时包含正电和负电氨基酸的分子可能发生由分子内电荷相互作用驱动的相分离[34], 两种带相反电荷的分子间也可能发生由分子间电荷相互作用驱动的相分离[35].
(2) π相关相互作用. π电子体系之间的平面相互作用称为π-π相互作用, 这种作用通常发生在芳香环之间, 因此在苯丙氨酸(F)、酪氨酸(Y)和色氨酸(W)这些芳香族氨基酸中最为常见[36,37]. 除了两个芳香环基团之间的相互作用外, 芳香环和带电氨基酸之间也存在相互作用, 特别是与阳离子残基. 芳香环和阳离子残基之间的阳

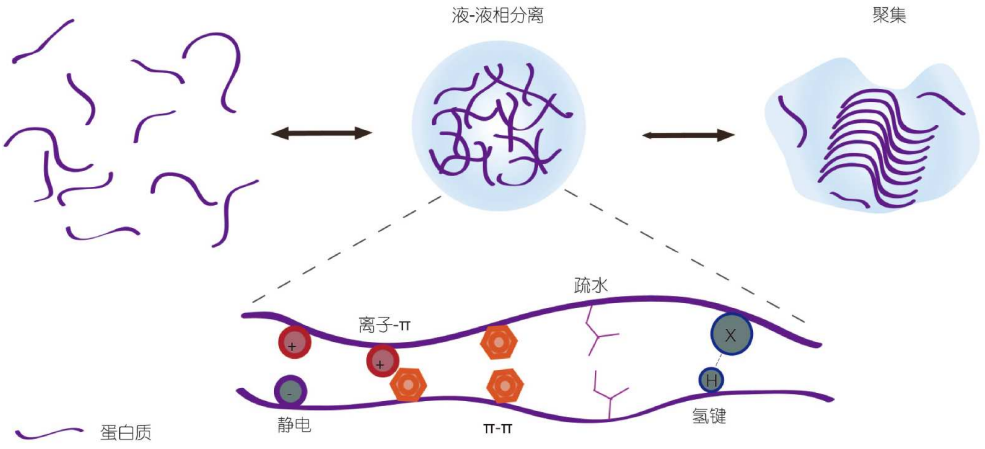


**图 1** 蛋白质相分离的过程以及其中的多价相互作用力
**Figure 1** The process of protein phase separation and the multivalent interactions involved

离子-π相互作用对FUS等蛋白质的相分离非常重要, 常见发生于精氨酸和酪氨酸残基之间的相互作用[38,39]. (3) 疏水相互作用. 疏水相互作用是蛋白质折叠的重要驱动力, 促进各种折叠结构域和低聚物的形成和稳定性, 这可能在一定程度上促进相分离[40]. IDRs体系内的疏水相互作用通常不像在折叠蛋白质中那样多, 但如果IDRs序列中含有较多的疏水氨基酸, 它可能也对体系的相分离有较大贡献[41,42]. (4) 氢键. 虽然氢键在很大程度上被认为是极性氨基酸溶剂化的原因, 但它们对生物分子的自缔合也有很大贡献, 也是生物分子相分离的驱动力之一[43,44]. 各类氨基酸都可以参与形成氢键. 然而, 最易受影响的通常是那些具有极性或带电侧链的氨基酸. 大多数氨基酸都含有氢键供体和受体, 这表明氢键在高度富集的蛋白质相分离体系中可能非常常见[45].

一些氨基酸可以通过几种不同的作用模式相互作用, 这些模式可以协同工作以提供更强的结合. 由于相分离体系的组分是高度动态的, 通常是无序的, 因此直接确定一个相分离体系内部各种相互作用的强弱具有难度. 针对蛋白质内部相互作用的研究可能有助于确定哪些相互作用贡献较大, 可以帮助我们进一步理解序列上的微小变化是如何改变宏观相分离行为, 以及自然发生的突变如何产生重大的生理和生物物理影响.

## 2 淀粉样蛋白的相分离

近年来, 关于生物大分子凝聚物的发现将相分离与神经退行性疾病中的蛋白质聚集联系起来, 提高了人们对相分离在生理和病理中作用的理解. 许多神经退行性疾病相关淀粉样蛋白都能发生相分离, 暗示淀粉样蛋白的相行为与病理之间可能存在潜在关联. 本节内容中将讨论几种常见神经退行性疾病相关淀粉样蛋白(图2)发生相分离的研究进展, 这将有助于加深对于相关疾病的理解.

### 2.1 Aβ

淀粉样蛋白-β(amyloid-β, Aβ)由淀粉样前体蛋白的内蛋白水解产生的, 这是通过一组被称为α-、β-和γ-分泌酶的酶或酶复合物对APP的顺序切割来实现的. 这种切割主要产生Aβ40(序列为1~40)以及Aβ42(序列为1~42). 1984年, Glenner等人[46]首次从AD患者的脑膜血管中鉴定出Aβ组分. 一年后, Aβ被认定为AD患者脑组织老年斑块或神经炎斑块的主要成分[47,48]. Aβ通常被认为本质上无固定结构, 研究表明Aβ40和Aβ42存在多种可能的构象, 包括α-螺旋或β-折叠, 并且它的结构在几种状态之间迅速转换[49]. Aβ单体可以聚集成各种类型的组装体, 包括低聚物、原纤维和淀粉样纤维等[50,51]. 淀粉样纤维较大且不溶, 它们可以进一步组装成淀粉样斑块, 而淀粉样寡聚物是可溶的.

Gui等人[23]在十二烷基硫酸钠环境中制备了Aβ低聚物, 观察到了它的相分离, 并且发现这个过程主要由疏水相互作用介导. 他们通过高通量蛋白质相分离分析方法观察Aβ低聚物的相分离体系, 发现Aβ低聚物相

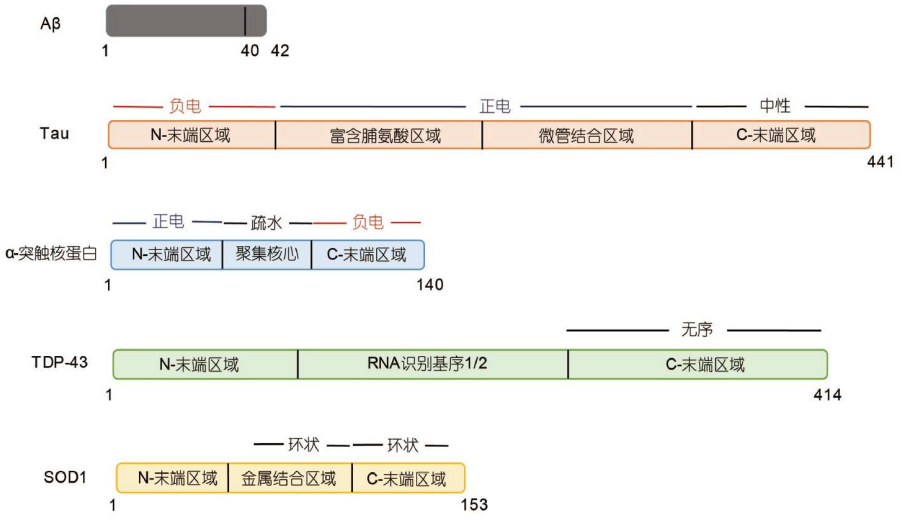


图 2 五种神经退行性疾病相关淀粉样蛋白的主要结构
Figure 2 The main structures of five neurodegenerative diseases-related amyloid-like proteins

分离调节了液固相转变, 并改变了Aβ聚集途径, 形成淀粉样纤维. Sudhakar等人[52]报道了无机生物聚合物聚磷酸盐(polyP)在不同pH条件下对Aβ的相分离和聚集表现出不同的调控效果. 在pH 7(中性)时, polyP以类似于带负电荷的纳米颗粒的状态存在, 并且以剂量依赖性的方式抑制淀粉样蛋白相分离和聚集. 相反, 在pH 3(酸性)时, polyP通过促进Aβ相分离的形式, 加速淀粉样蛋白聚集动力学, 表现为富含蛋白质的相分离液滴中出现成熟的聚集体. 类似的, Morris等人[53]通过使用微流体方法, 观察到Aβ40在氨基甾醇类小分子claramine存在的情况下可以发生相分离, 并且液滴内富集的Aβ40能够进一步自组装并聚集成淀粉样纤维.

### 2.2 Tau

Tau是1975年首次发现的一种微管相关蛋白, 在微管组装和稳定中起着重要作用[54]. 过度磷酸化的微管相关Tau蛋白是AD 患者神经原纤维缠结中的主要成分, 同时在肌萎缩侧索硬化症、皮质基底变性等其他大多数神经退行性疾病和衰老的神经原纤维缠结中也观察到Tau蛋白存在[55,56]. Tau存在于许多动物物种中, 如秀丽隐杆线虫、果蝇和人类[57]. 在人类中, Tau主要在神经元中表达, 其他非神经元细胞可能也有微量表达[58]. Tau可分为四个区域: N端结构域、富含脯氨酸的结构域、微管结合结构域和C端区域. 在成人大脑中N-末端区域和微管结合结构域周围的选择性剪接可产生六种主要亚型, 其中最短的亚型有352个氨基酸, 最长的亚型由441个氨基酸组成. Tau总体上是一个正电的蛋白质, 然而, 位于N-末端的约120个残基片段整体呈现偏负电的, 位于C末端的约40个残基片段基本呈现中性. 这种电荷的不均匀分布对于Tau相关的相互作用、内部折叠和聚集都很重要.

昆虫细胞中表达的磷酸化Tau(p-Tau441)最先被发现可以发生相分离, 这个过程需要在拥挤剂的存在下发生[25,59]. 对于p-Tau441, 磷酸化是Tau相分离的重要驱动因素, 静电和疏水相互作用共同组合, 驱动相分离发生[25]. 近期一系列研究证明, 在生理条件下, 非磷酸化全长Tau也会发生显著的相分离, 并且发现Tau蛋白带负电荷的N末端和带正电荷的中间/C末端结构域之间的静电相互作用是相分离的主要驱动力[60,61]. 除了Tau自身的相分离之外, RNA[62]、肝素[63]、某些金属离子[64~66]和分子伴侣等蛋白[67,68]也可能参与或调节Tau的相分离. 微管蛋白也能与Tau发生相分离[68]. 在拥挤剂的存在下, 微管蛋白与Tau形成相分离液滴, 并促进微管蛋白在几分钟内快速聚集成稳定成熟的微管网络[59], 这说明Tau参与的相分离过程可能对其行使生理功能起到重要贡献.

相分离的Tau也可能转化为聚集状态. Kanaan等人[61]发现随着时间的变化, 未修饰的全长Tau的相分离液滴中会出现小的Tau寡聚体和聚集体, 但不会聚集为成熟淀粉样原纤维. 而磷酸化Tau形成的相分离液滴可迅速失去其最初的液体动态特性, 在经过孵育后, 液滴内的Tau转变为具有成熟淀粉样原纤维特征的聚集体, 说明磷酸化促进了Tau从相分离到聚集状态的转变[25]. 除了翻译后修饰, 病理相关突变也能大大加快Tau的相分离液滴向流动性差的聚集体的转变速度[69]. 这些调节现象说明, Tau的致病相关因素与Tau的相分离行为直接相关. 不仅如此, 研究人员发现促进或抑制Tau聚集和相分离的因素经常表现出一致的作用结果. 例如, 拥挤环境、RNA[70]、金属离子[71,72]既促进Tau的相分离又促进Tau的聚集. 而乙酰化修饰[73]、有机物紫草素[74]等则同时抑制Tau的相分离和聚集. 这些证据进一步说明Tau的相分离和聚集之间的关联.

### 2.3 α-突触核蛋白

突触核蛋白(synuclein)是在大脑中大量表达的蛋白质. 突触核蛋白家族由三个成员组成——α-突触核蛋白、β-突触核蛋白和γ-突触核蛋白, 它们的长度在127到140个氨基酸之间[75,76]. α-突触核蛋白集中分布在神经末梢, 靠近突触小泡. 正常生理情况下, α-突触核蛋白在调节神经递质释放、突触功能和可塑性方面发挥作用[77]. 而α-突触核蛋白的异常沉积是路易体疾病的主要病理特征[78,79]. 路易体疾病是一组异质性疾病, 包括帕金森病、帕金森病伴痴呆症和路易体痴呆症[17,80,81]. α-突触核蛋白是一种14 kDa的蛋白质, 具有一个富含赖氨酸的氨基末端, 它在调节其与膜的相互作用中起着至关重要的作用; 以及一个无序的酸性羧基末端, 它与α-突触核蛋白的核定位及其与金属、小分子和蛋白质的相互作用有关[82]. 位于α-突触核蛋白中间的氨基酸残基65~90区域含有一个高度疏水的基序, 被称为非淀粉样β成分, 它是介导α-突触核蛋白聚集的核心区域. 天然α-突触核蛋白整体呈现未折叠状态, 只有少量二级结构[83]. 然而, 在与脂质膜或洗涤剂胶束结合时, α-突触核蛋白会发生结构转变, 形成α-螺旋构象.

2020年, Ray等人[84]报道了α-突触核蛋白的相分离. 他们发现在拥挤剂的存在下, α-突触核蛋白会经历由N末端和疏水性聚集核心主要驱动的相分离. 与疾病相关的金属离子、与脂膜的相互作用、磷酸化和病理突变会进一步促进相分离. α-突触核蛋白的液滴还可以经历从液态到固态的转变, 这导致了原纤维聚集体和低聚物的形成. Sawner等人[85]也报道了抑制α-突触核蛋白聚集的条件, 如盐、pH、N-末端乙酰化等, 也阻碍了α-突触核蛋白的相分离, 这意味着相分离是其成核和聚集的关键步骤. 与疾病相关的突变, 如A30P、E46K、H50Q和A53T, 表现出加速α-突触核蛋白相分离体系中淀粉样蛋白聚集的形成[86]. 通过溶液核磁共振技术检测到α-突触核蛋白的构象在相分离液滴内从初始的发夹状结构转化为松散的富含β折叠的组装结构, 并逐渐成熟为淀粉样纤维的过程[87,88]. 除了自身相分离, α-突触核蛋白也可以与其他蛋白发生共相分离[89,90].

### 2.4 TDP-43

TDP-43蛋白全称TAR DNA结合蛋白-43 kDa, 由位于1号染色体上的TARDBP基因编码, 是一种高度保守、广泛表达的RNA/DNA结合蛋白, 属于异质核糖核蛋白(hnRNP)家族[91]. 人源全长TDP-43蛋白由414个氨基酸组成, 分子量约为43 kDa, 包括一个N末端区(N-terminal Domain, NTD)、两个RNA识别基序(RNA Recognition Motif, RRM): RRM1和RRM2, 和一个富含甘氨酸的C末端区域(C-terminal Domain, CTD)[92]. TDP-43的不同区域具有不同的结构和功能. 其中NTD表现出泛素样折叠, 并介导了TDP-43的二聚化[93]. 两个RRM结构域由β-折叠和α-螺旋组成, 赋予了TDP-43较高的RNA结合能力. 而CTD高度无序, 并且与朊病毒一样, 具有容易聚集的倾向, 因此也被称为TDP-43类朊病毒区域[94]. 自从在病理样本的不溶性包涵体中鉴定到TDP-43蛋白后, 人们逐渐发现它与ALS和FTD两种疾病高度相关, 已发现大约97%的ALS患者以及45% FTD患者的病理性不溶物中存在TDP-43成分[95].

TDP-43在生理浓度下就会发生相分离, 研究发现TDP-43的不同结构域对其相分离有着不同的贡献方式. Conicella等人[96]报道, 在TDP-43的CTD中, 有一段保守序列可以由原本无序的构象短暂形成α-螺旋, 不同分子间α-螺旋的相互作用驱动TDP-43相分离. 值得注意的是, 在TDP-43蛋白质分子间紧密相互作用下, 该区域的螺旋倾向可能增加, 并进一步导致聚集. 位于这段区域内的病理性突变将加速这种从液态到固态的转变. Wang等人[97]报道, TDP-43的NTD二聚化介导的分子间相互作用同样对相分离十分重要. NTD-NTD相互作用导致TDP-43寡聚体动态头尾相接, 拮抗TDP-43的病理性聚集. TDP-43的RRM主要介导了它和RNA的分子间相互作用, RNA也被证明有拮抗TDP-43相分离凝聚体由液态向固态的转变趋势. RNA是细胞内相分离驱动形成的无膜细胞器的重要成分, TDP-43也在这些无膜细胞器, 如核仁[98]、核旁斑[99]、Cajal体[100]、应激颗粒[101,102]等中存在[103].

### 2.5 SOD1

超氧化物歧化酶1(Superoxide dismutase 1, SOD1)是一种普遍表达且在物种间高度保守的蛋白. SOD1是由153个氨基酸组成的金属酶, 也称为铜/锌超氧化物歧化酶. SOD1定位于线粒体的细胞质、细胞核、溶酶体和膜间隙等位置. 它可以通过序列中的金属结合区域结合铜和锌离子, 形成同二聚体. SOD1已知的主要功能是作为一种歧化酶, 通过将超氧化物自由基转化为分子氧和过氧化氢来清除它们. 1993年, 关于ALS的第一个致病突变在编码SOD1的基因中被发现[104,105]. 此后, 目前已经有超过一百种SOD1突变被鉴定出来, 在20%的家族性ALS病例和3%的散发性ALS病例中可发现这些突变[106,107]. SOD1中的病理突变可能对其与金属的配位能力和蛋白结构产生影响, 导致蛋白质不稳定, 从而形成蛋白质折叠进而导致毒性.

2022年, Bidisha等人[108]发现不结合金属的SOD1蛋白可相分离形成液滴, 而随着体系中锌的浓度逐渐增大, 相分离的能力也逐渐丧失. 与ALS致病高度相关的两种突变体I113T和G85R降低了SOD1对锌的亲和力, 从而促进相分离的发生. 通过荧光相关光谱(FCS)和傅里叶变换红外光谱(FTIR)表征, 发现SOD1在相分离后发生了由无序到相对紧凑的折叠状态的构象转变, 从而从相分离转变为聚集状态[108]. 此外, Siyu等人[109]发现SOD1在拥挤环境下发生相分离, 并且残基Cys111和Trp32的异常氧化会加速SOD1相分离液滴的固化, 最终导致蛋白质聚集.

## 3 总结与展望

自从人类首次报道阿尔兹海默病等神经退行性疾病, 至今已有100多年. 截至目前, 我们还依然缺乏对这

些疾病发病机制的清晰认知和切实有效的治疗手段, 这给人类健康和社会资源带来了巨大的负担. 液-液相分离是最近十几年发现的在生物大分子中广泛存在的现象, 参与各种生理过程, 同时也与疾病的发生、发展密切相关. 最近研究发现, 生物分子相分离和异常相变可能是蛋白质聚集的一种潜在机制. 蛋白质的液滴环境非常有利于纤维聚集体的形成, 高度富集的相分离蛋白质通常表现出更大的聚集倾向. 包括本文所介绍的Aβ、Tau、α-突触核蛋白、TDP-43和SOD1等在内的许多神经退行性疾病相关蛋白可以组装成流动性较强的液滴, 随后变成富含低聚物和纤维聚集体的固态结构. 因此深入了解神经退行性疾病相关蛋白相分离和异常相变之间的关系对于理解相关疾病的发病机制具有重要意义. 然而, 在这个领域还有一些问题需要继续研究. 比如, 退行性疾病相关蛋白相分离和异常相变过程中形成的中间体和纤维在细胞水平和动物水平的毒性还需要进一步评估. 此外, 神经退行性疾病相关蛋白与其他蛋白质可能通过相互作用进一步形成共相分离或复合凝聚体, 这可能为与多种蛋白相关的神经病理学提供重要见解. 最后, 应该建立更加系统的机制, 以揭示神经退行性疾病相关蛋白相分离介导的聚集与疾病之间的联系.

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Summary for “神经退行性疾病相关淀粉样蛋白的液-液相分离”

# Liquid-liquid phase separation of amyloid-like proteins in neurodegenerative diseases

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Neurodegenerative diseases are diseases caused by the progressive death or loss of function of cells and neurons in the brain and peripheral nervous system, including Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) and others. Due to the incomplete understanding of the pathological mechanisms of neurodegenerative diseases, currently available treatment methods can only alleviate some related symptoms, and there remains a lack of effective treatment methods. Most neurodegenerative diseases share a common cellular and molecular mechanism, which is the formation of amyloid-like protein aggregates and inclusion bodies. The widespread presence of protein aggregates in neurodegenerative diseases suggests their special role in disease occurrence and progression. For a long time, nucleation and aggregation was considered as the only way for protein aggregate formation. However, recent studies suggest that these proteins may undergo another aggregation process, which is liquid-liquid phase separation mediated aggregation. Phase separation is the process by which biomolecules form dynamic condensates through weak multivalent interactions. In these condensates, the biomolecule concentration is highly enriched and still maintains dynamic exchange with the external environment. Phase separation is mediated by weak multivalent interactions such as electrostatic, π-related, hydrogen bonding, and hydrophobic interactions. For specific molecules, their phase separation behavior may be mainly mediated by one or some interactions. However, interactions in living systems are more complex. There has been a lot of work looking at the types of interactions that make major contributions in various systems. These findings may help us further understand how phase separation behaviors can be altered by small perturbatians on the sequences and why naturally occurring mutations produce significant physiological and biophysical effects. Proteins that undergo phase separation in living organisms usually contain intrinsically disordered regions (IDRs), or intrinsically disordered proteins (IDPs). Amyloid-like proteins usually have such disordered characteristics. Such IDRs/IDPs do not have stable folding structures and exist in a dynamic form in solution. Due to the lack of a clear three-dimensional structure, IDRs/IDPs have higher dynamism and flexibility, thus providing more opportunities for intermolecular contact and interaction. In recent years, researchers have shown that many neurodegenerative disease-related amyloid-like proteins can undergo phase separation, suggesting a potential association between the phase behavior of amyloid-like proteins and pathology. Here, we summarized recent studies on the phase separation and aggregation of several neurodegenerative disease-related amyloid-like proteins, including Aβ, Tau, α-synuclein, TDP-43 and SOD1. They are typical pathologic proteins associated with neurodegenerative diseases and have been shown to have a high correlation with related diseases over the past few decades. Their common feature is the amyloid aggregates found in the patients. Recent research has shown that they also have the property of phase separation, which may correlate to the formation of pathological aggregates. Therefore, we summarized the latest research on the phase behavior of these amyloid proteins, which may bring potential opportunities for regulating the associated pathological processes and treating diseases. We hope this article can help deepen the understanding of pathological mechanisms of proteins in neurodegenerative diseases and inspire new ideas for disease treatment.

**neurodegenerative diseases, amyloid-like protein, aggregation, phase separation**

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