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细胞环境因素异常导致的蛋白质结构和功能变化可能是诱发散发性阿尔茨海默病（AD）的重要原因．探索 AD 关键蛋白（如 Tau 蛋白）异常修饰的细胞环境触发因素和机制，可能是实现 AD 预警、早期诊断和干预的重要途径．

——刘缨

环境因素与 Tau 蛋白的异常磷酸化 *

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摘要 神经纤维缠结是阿尔茨海默病(Alzheimer's disease，AD)的重要病理特征之一，其发生发展因素一直是相关研究领域的热点问题．神经纤维缠结由异常磷酸化的 Tau 蛋白错误折叠、聚集所形成，因此对诱发 Tau 蛋白异常磷酸化的因素进行探究显得尤为重要．Tau 蛋白异常磷酸化逐渐形成神经缠结是 AD 早期发生的病理过程之一，本文就 Tau 蛋白异常磷酸化发生的环境影响因素进行了讨论．

关键词 环境因素，阿尔茨海默病，Tau 蛋白，异常磷酸化
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阿尔茨海默病(Alzheimer's disease，AD)的发病因素和机制十分复杂，已知的相关因素包括基因变异[1–2]、表观遗传学[3–5]和内外环境因素[6–7]导致的蛋白质异常修饰[8–9]及在脑内的沉积[10–12]、神经营养及可塑性改变[13–14]、氧化应激[15–17]、离子通道[18]、金属离子代谢[19]及能量代谢紊乱[20–23]等等．目前国内外同行公认，环境因素是诱发散发性 AD 的重要原因，AD 发生发展是环境因素与基因相互作用的结果．对 AD 痴呆前阶段(pre-MCI、MCI)的早期预警、发现和干预有希望阻止或延缓疾病的发生发展．因此，对诱发 AD 环境危险因素的探索具有十分重要的意义．

尽管 AD 的发病机制尚无定论，但 Aβ 在细胞外聚积所形成的淀粉样沉淀及细胞内异常磷酸化 Tau 蛋白形成的神经纤维缠结(neurofibrillary tangles，NFTs)[24–25]是 AD 典型的病理改变．这些变化损伤神经突触可塑性、破坏神经环路、导致疾病的发生[26]．异常磷酸化促进 Tau 蛋白聚集，形成配对螺旋样二聚体(paired helical filaments，PHFs)，最终形成 NFTs．NFTs 在 AD 病人脑内的含量与认知功能损伤程度成正相关[27–28]，而 Tau 蛋白的聚集在痴呆前期已经发生[29–30]．因此，探索 AD 早期 Tau 蛋白异常磷酸化的触发因素，有可能发现新的生物标记物，有助于 AD 的早期诊断和干预．

1 Tau 蛋白的异常磷酸化

蛋白质磷酸化修饰是指磷酸基团加成到蛋白质氨基酸残基上的反应，主要发生在丝氨酸(serine, S)、苏氨酸(threonine, T)、酪氨酸(tyrosine, Y)三种氨

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基酸残基上．磷酸化修饰是 Tau 蛋白最常发生的翻译后修饰[31]．Tau 蛋白的过度磷酸化修饰会降低其微管结合能力，从而导致细胞骨架的稳定性降低[32-33]．据统计，目前已发现的 Tau 蛋白磷酸化修饰位点已多达 85 种以上[34-35]．很多激酶和磷酸酶参与了 Tau 蛋白磷酸化修饰的调节，Tau 蛋白的每个磷酸化位点都由一个或多个蛋白激酶进行调控[35-36]．Sergeant 等[37]将 Tau 蛋白磷酸化修饰的激酶分为 3 类：PDPKs 蛋白激酶 (proline-directed protein kinases)、非 PDPKs 蛋白激酶 (non-proline- directed protein kinases)和酪氨酸特异的蛋白激酶．当这些蛋白激酶的酶活异常升高时就能导致 Tau 蛋白的异常和过度磷酸化．而磷酸酶能催化 Tau 蛋白产生去磷酸化反应[38-39] (表 1)．Tau 蛋白的磷酸化水平在磷酸化激酶和磷酸酶的共同作用下保持一种动态平衡 (图 1)．Tau 蛋白磷酸化系统的激活和去磷酸化系统的抑制都能导致 Tau 蛋白过度异常磷酸化，引起 Tau 疾病．

Table 1　The catergories of protein kinases phosphatases in Tau phosphorylation

表 1　参与 Tau 蛋白磷酸化调控的酶

1. Tau 蛋白磷酸化激酶	(1) PDPKs 蛋白激酶 (proline-directed protein kinases) GSK3β (glycogen synthase kinase-3β); CDK1/5 (cyclin-dependent kinase-1/5); MAPKs(mitogen-activated protein kinases); SAPKs (stress-activated protein kinases) (2) 非 PDPKs 蛋白激酶(non-proline-directed protein kinases) TTBK1/2(tau-tubulin kinase 1/2); CK1α/1δ/1ε/2 (casein kinase 1α/1δ/1ε/2); DYRK1A(dual-specificity tyrosine phosphorylation and regulated kinase 1A); MARKs (microtubule affinity-regulating kinases); PKA(Protein kinase A); PKB/AKT (Protein Kinase B); PKC (Protein kinase C); PKN(protein kinase cAMP-dependent/B/C/N)); CaMKⅡ (Ca^{2+}/Cal-Modulin-dependent protein kinase Ⅱ) (3) 酪氨酸特异的蛋白激酶 SFKs (Src family kinases); c-Abl kinase
2. Tau 蛋白去磷酸酶	PP2A (protein phosphatase-2A); PP5 (protein phosphatase-5)

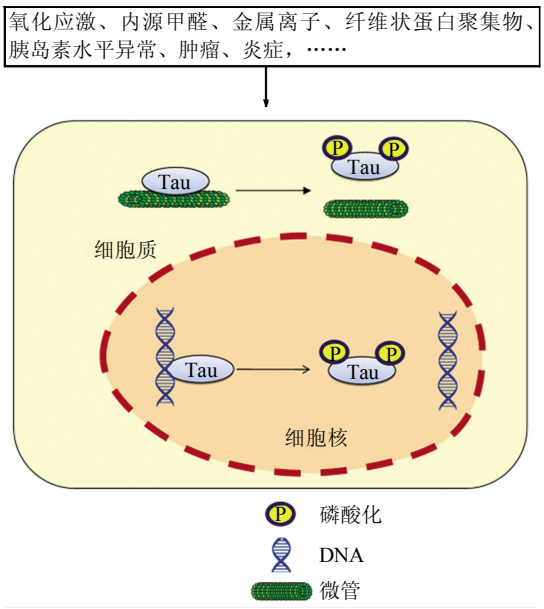

Fig. 1　Inducing factors of Tau hyperphosphorylation and dysfunction

图 1　导致 Tau 蛋白过度磷酸化的因素

很多因素能导致 Tau 蛋白的过度磷酸化，错误折叠及聚集，从而引发神经退行性疾病(如 AD). Tau 蛋白的异常磷酸化使其与微管和 DNA 结合能力下降，丧失正常的生理功能[5, 40].

2　导致 Tau 蛋白异常磷酸化的细胞内外环境因素

2.1　氧化应激

氧化应激是机体内氧化和抗氧化作用失衡，产生大量氧化中间产物(reactive oxygen species，ROS)的过程．ROS 通过细胞内生物化学反应产生，能够导致细胞的损伤．氧化应激与很多疾病有关，如神经退行性疾病等．

氧化应激能够导致 Tau 蛋白的过度磷酸化．Melov 等[41]通过敲除小鼠的 SOD_2 基因而形成线粒体氧化应激的模型，他们的研究表明线粒体 SOD_2 基因缺失的小鼠脑内出现明显的淀粉样斑块和 Tau 蛋白 Ser396 位的超磷酸化．内质网应激也能导致 Tau 蛋白的过度磷酸化，可能由磷酸化激酶 ERK 介导，而 Tau 蛋白的过度磷酸化也能引发内质网应激，这种恶性循环继而引起 AD 样的神经退行性变[42]．作为氧化应激的标志之一，脂质过氧化也可以导致 Tau 蛋白的过度磷酸化．发生脂质过氧化

时，花生四烯酸(arachidonic acid)被降解成有毒性的小片段，进而引起 Tau 的过磷酸化和聚集[43]. Filipcik 等[44]报道了急性固定应激(IMO)通过促肾上腺皮质激素的释放导致 Tau 蛋白过度磷酸化. Su 等[45]报道了慢性氧化应激导致 Tau 蛋白的过度磷酸化，且 Tau 蛋白过度磷酸化由 JNK、p38 以及 PP2A 的作用导致.

但也有研究发现，在 Tau 疾病的果蝇模型中，氧化应激虽然能够导致神经退行样改变，但是并未导致 Tau 蛋白的过度磷酸化，而是通过 Tau 蛋白诱导的细胞周期的激活介导[46]. 因此，氧化应激效应对 Tau 蛋白磷酸化的作用还需要进一步的研究和阐明.

2.2 内源甲醛

中国科学院生物物理研究所赫荣乔等针对 AD 发病的环境因素提出了中枢神经系统“甲醛慢性损伤”的学说[6]，强调“伴随老龄化而出现的内源性甲醛代谢功能下降，甲醛浓度在体内的逐渐升高是造成老年认知功能慢性损伤的重要原因之一”. 甲醛具有很强的毒性，不但广泛存在于人类的生活环境中，同时机体内也在不断地产生和利用甲醛. 甲醛浓度的异常升高能够引起 Tau 蛋白等聚集并具有较强的细胞毒性[47-48]，引起神经细胞的变性甚至死亡. 甲醛可以触发细胞内 Tau 蛋白异常磷酸化，而且过度磷酸化导致 Tau 蛋白错误折叠，分子聚积，并且与 DNA 的亲和力下降，使 DNA 失去保护，易被活性氧等自由基攻击而破坏[28]. 在临床试验中，他们观察到尿甲醛含量与老年人认知功能损伤程度成正相关，并探讨了甲醛诱发记忆衰退的神经分子机制[3, 49]. 这些研究结果表明，甲醛应激是引起 Tau 蛋白异常磷酸化、产生蛋白质分子聚积以及细胞变性死亡的重要因素.

2.3 Tau 蛋白激酶活性影响因子

Tau 蛋白的磷酸化修饰是通过多种蛋白激酶如 GSK3β、CDK5、PKA、MAPK、DYRK1A 等[31, 50]的催化实现的，一些能够影响 Tau 磷酸化激酶活性的分子就能够影响 Tau 蛋白的磷酸化水平. 如：某些磷酸酶可以降低 GSK-3β 的抑制性位点(Ser9)的磷酸化水平，从而提高 GSK-3β 的激酶活性，提高 Tau 蛋白的磷酸化水平[51]. 另有报道称，CDK5 可能作为起始激酶，进而激活 GSK-3β，最终引起 Tau 蛋白磷酸化水平的升高[52]. 腺苷酸环化酶激活剂毛喉素(forskolin)能够增加细胞内 cAMP 的含量，从而间接影响 Tau 蛋白的磷酸化. 采用磷酸二酯酶抑制剂和 forskolin 处理，能够激活 PKA，从而导致 PKA 活性增加，使得 Tau 的相应位点磷酸化，但同时抑制了 MAPK 激酶的活性，从而降低了 Tau 蛋白上受 MAPK 调控的位点磷酸化水平的降低(多为 Ser/Pro 基序)[53]. 在衰老机体内，NMDA 受体的激活会活化 ERK/MAPK 蛋白激酶通路，从而使 Tau 蛋白过度磷酸化[54].

PP2A(protein phosphatase 2A)是调控 Tau 蛋白去磷酸化的重要磷酸酶，其活性可受多种因素的影响，如磷酸酶抑制剂[55]、蛋白亚基的构型[56]、甲基化修饰[57-58]. Zhou 等[59]的研究表明，雌激素缺乏致 PP2A L309 位的去甲基化，导致 PP2A 的活性下降，继而影响 Tau 蛋白的磷酸化水平.

2.4 金属离子

研究表明细胞内外一些金属离子水平的变化也可以导致 Tau 磷酸化异常. Cai 等[60]采用 PC12 细胞模型研究了锰离子对 Tau 蛋白磷酸化的影响，发现金属锰离子可通过激活 ERK/MAPK 导致细胞内 Tau 蛋白的超磷酸化. Sun 等[61]的研究表明突触释放的锌离子能够导致 Tau 蛋白的过度磷酸化：他们首先采用螯合剂螯合锌离子，再采用谷氨酸盐处理原代海马神经元以增加突触活性，结果表明神经元内 Tau 蛋白被过度磷酸化. 进一步的实验表明锌离子导致 Tau 的过度磷酸化是通过抑制 PP2A 激酶的活性来介导的. 在培养的神经元细胞外加入 KCl 使细胞膜产生去极化，可以引起由钙离子介导的瞬时 Tau 蛋白磷酸化[62]，同时也能导致淀粉样前体蛋白(amyloid precursor protein，APP)的磷酸化. 这个磷酸化过程由 GSK3β 和 CDK5 两种激酶介导.

与上述金属离子的作用不同，铁离子和锂离子却能引起完全相反的结果. 铁离子能够诱发氧化应激，导致 CDK5/p25 复合物活性的降低及 Tau 蛋白磷酸化的减少[63]. 锂离子则可以抑制 GSK-3β 的活性，从而降低 Tau 蛋白的磷酸化水平[64].

2.5 细胞外纤维状蛋白聚集物

Aβ 淀粉样蛋白沉积和 Tau 蛋白聚集形成的神经纤维缠结，是 AD 的两大典型病理特征，这两者之间的联系和相互作用也是相关领域的研究热点. 研究表明，经纤维状 Aβ 处理，神经元内的 Tau 蛋白可以出现异常磷酸化和聚集现象，同时 Tau 蛋白丧失其与微管结合的功能[65].

Waxman 等[66]发现，在培养细胞外加入人源 α-Synuclein 蛋白形成的纤维，能够导致细胞内 Tau 蛋白的过度磷酸化，并形成 NFTs 样的聚集物.

2.6 胰岛素水平异常

越来越多的证据表明 AD 与胰岛素失调相关．AD 病人的脑脊液中胰岛素含量减少，葡萄糖代谢水平下降[67-68]．Planel 等[69]采用链脲霉素(streptozotocin)诱导形成糖尿病小鼠模型并检测小鼠体内 Tau 蛋白的磷酸化情况．结果表明，小鼠脑内出现 Tau 蛋白过度磷酸化现象，这种现象的发生是由两种不同的机制产生：体温过低和磷酸酶活性的降低．

2.7 肿瘤及炎症因子

慢性炎症反应是肿瘤发生与 AD 发病二者共同的病理特征．有报道表明，由肿瘤引起的炎症反应所释放出的相关因子，如白介素 1a (IL-1a)、IL-1b、IL-6、IP-10 及肿瘤坏死因子 α(TNF-α)等，加速了 Tau 蛋白的过度磷酸化及 AD 的病程进展，后者反过来又促进了肿瘤的发展[70]．另外，对肿瘤和 AD 患者的临床研究中都发现体内甲醛的异常升高．这些线索提示有必要进一步探索肿瘤与 AD 之间的关系．

2.8 其他

除以上几种细胞环境因素外，Tau 蛋白异常磷酸化也出现在其他条件下，如 Wnt 通路的改变[71]、细胞自噬功能紊乱[72]、麻醉[73-74]、手术应激[75]、饥饿[76]、药物使用[77-78]、游离脂肪酸[79]、羰基化合物[80]、磺基黏多糖[81]以及醌类[82]等化学物质的诱导．

2.9 小结

影响 Tau 蛋白磷酸化的细胞内外环境因素很多，这些因素都能导致 Tau 蛋白的过度磷酸化，从而引起 Tau 蛋白与微管和 DNA 结合能力下降，微管系统与 DNA 的稳定性降低(图 1)．但是哪些因素与神经退行性疾病的发生直接相关，尚需要进行大量的研究．针对以上环境因素和 Tau 蛋白异常磷酸化，发展新的技术和方法早期诊断 AD 发生，将有可能实现 AD 的有效干预．

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Endogenous and Exogenous Factors in Hyperphosphorylation of Tau in Alzheimer′s Disease*

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Abstract Neurofibrillary tangles (NFTs) are regarded as one of the major pathological features of Alzheimer's disease, and are composed of misfolded and aggreagted Tau protein with hyperphosphorylation. But the mechanism of Tau hyperphosphorylation still remains to be clarified. This review summarized the roles of endogenous and exogenous factors in the induction of Tau hyperphosphorylation. The level of some factors and the hyperphosphorylation of Tau could be used as biomarkers for the early processing of AD.

Key words endogenous and exogenous factors, Alzheimer's disease, Tau protein, abnormal phosphorylation
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