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新 视 点

多因素异常修饰导致体内蛋白质选择性错误折叠和功能丧失的假设*

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摘要 蛋白质异常修饰导致错误折叠的机制目前尚不清楚. 提出如下设想：细胞内的蛋白质分子可能发生多种异常修饰，引起蛋白质选择性错误折叠和聚积而导致神经退行性疾病.

关键词 蛋白质异常修饰，蛋白质错误折叠，神经退行性疾病，选择性错误折叠
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蛋白质异常修饰所导致的错误折叠与神经退行性疾病之间有密切关系，是当今蛋白质科学领域的研究热点[1]，化学修饰与微环境因素异常所导致的蛋白质错误折叠机制尚未得到阐明. 迄今为止，大量研究主要局限在单因素化学修饰与错误折叠的关系，如神经 tau 的异常磷酸化[2]、APP (β-amyloid precursor protein)的异常酶切[3]、prion 的异常糖基化[4]，以及一些蛋白质的醛基化等[5]. 实际上，由于体内蛋白质处于复杂的微环境中，因而可能与多种化学因素相互作用.

我们知道，蛋白质翻译后修饰有百多种方式，一个蛋白质分子可能存在多个化学修饰位点，如神经 tau 可以在其不同的位点进行磷酸化、糖基化等[2,6]，分子中一种侧链基团可以接受多种化学修饰[7~10]，如赖氨酸的 ε- 氨基可以发生氨基化、非酶促糖基化、羟基化、Sumoylation 以及泛素化等修饰，半胱氨酸的巯基可被烷基化、氧化生成二硫键、亚硝基化等[11~14]. 现在也已经发现体内某些神经退行性疾病患者或动物模型的特定脑区，存在多种异常化学修饰的蛋白质或多肽分子聚积[6,15,16]，一种错误折叠蛋白存在一种以上不同方式的异常修饰[6,17,18].

Brooks 和 Gu[19](2003 年)的工作表明，在抑癌蛋白 p53 蛋白的化学修饰中，乙酰化能够竞争并抑制泛素化修饰 ε- 氨基. 我们已有的实验观察也表明，只有在肝素和糖基化试剂两种因素的共同作用下，神经 tau 才发生明显的错误折叠与分子聚积(图 1)，诱导微管装配的功能也丧失. 而在相同实验

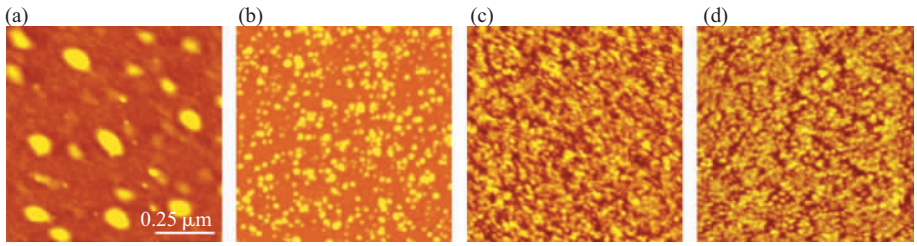

Fig. 1 AFM images of tau aggregation in the presence of glucose and heparin
Protein tau23 (3 g/L), glucose (1.5 mol/L), and heparin (0.6 g/L) were incubated at 37℃ for 7 d and then aliquots were taken for observation by tapping-mode AFM in air. Protein tau23 with heparin (panel b, (35.4 ± 4.4) nm, horizontal diameter), glucose (panel c, (30.5 ± 3.5) nm) or alone (panel d, (21.9 ± 1.2) nm) were used as controls. Compared with these three groups, the size of protein tau23 with glucose and heparin together (panel a, (127.5 ± 11.9) nm) was obviously larger.

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条件下，肝素或糖基化试剂单独作用的 tau 表现稳定. 暗示在同一蛋白质氨基酸残基侧链基团上，不同方式的化学修饰之间可能存在竞争作用，也可能存在协同作用.

在以上认识的基础上，我们提出如下假设：细胞内的蛋白质分子可能发生多种异常修饰，引起蛋白质选择性错误折叠和聚积而导致神经退行性疾病. 这可能是散发型(非家族遗传性)神经退行性疾病的一种重要发病机制. 但是，蛋白质修饰与疾病之间的内在联系[17,20]尚要大量的实验进一步阐明.

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Hypothesis: a Combination of Modifying Factors Induces Misfolding and Dysfunction of Selected Proteins *In vivo**

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Abstract Although the relationship between abnormal chemical modification and protein misfolding has been widely studied, most work is focused on the effect of a single factor on the structure and function of a protein. Here, it is proposed that a combination of multiple factors may modify selected proteins *in vivo*, and lead to their misfolding and aggregation in certain cell types.

Key words combinative protein modification, protein misfolding, neurodegenerative diseases, selective misfolding

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