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研究论文

双拷贝*APP/BACE/DPsn*转基因果蝇模型的建立及基因功能的研究

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Construction and functional study of a transgenic *Drosophila* model with two copies of *APP*/*BACE*/*DPsn* genes

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摘要 阿尔茨海默症 (Alzheimer′s disease, AD)， 是一种以脑中β-淀粉样蛋白 (β-amyloid peptide， Aβ)沉积为主要病理改变的神经退行性疾病。在果蝇*Drosophila*模型中建立淀粉样蛋白前体蛋白 (amyloid precursor protein, APP)的剪切通路模拟Aβ的产生过程， 有望建立一种快速筛选治疗AD药物的动物模型。我们利用经典的Gal4/UAS系统， 将现有的*APP/BACE/DPsn*果蝇品系连续杂交， 通过同源重组的方法构建表达两个拷贝的*APP/BACE/DPsn*稳定可遗传的转基因果蝇新品系。进一步的实验结果表明：与不表达*APP/BACE/DPsn*的对照果蝇*w/y; APP/Cyo; BACE-DPsn/TM6BTb*相比， 表达两拷贝*APP/BACE/DPsn*的 *w/y; elav-APP; BACE-DPsn*果蝇的最长寿命为52 d， 比对照组(69 d)缩短了17 d， 为对照组果蝇的75%； 中位生存时间为39 d， 比对照组(49 d)缩短了10 d， 为对照组的80%； 平均寿命为37 d， 比对照组(47 d)缩短了10 d， 为对照组的79%。同时， 表达两个拷贝*APP/BACE/DPsn*的果蝇所产卵的羽化时间比对照果蝇延长了3 d； 其羽化成虫的理论值为1∶9 (11%)， 而实际羽化率仅为5.2%。结果提示， 由elav-Gal驱动在果蝇泛神经元内过表达*APP/BACE/DPsn*， 可以缩短果蝇寿命、 干扰果蝇胚胎正常发育。该果蝇有可能作为初步筛选AD治疗药物的动物模型， 为AD治疗新药的发现提供工具。

关键词： 转基因果蝇 APP基因 BACE基因 DPsn基因 阿尔茨海默症

Abstract: Alzheimer′s disease (AD) is a kind of cognitive dysfunction disease and β-amyloid (Aβ) generation is crucial for AD pathogenesis and plays a key role in disease progression. A transgenic fly expressing two copies of *APP/BACE/DPsn* to mimic the pathologic changes of AD might be useful for AD therapeutic drug screening. Using the classic *Gal4/UAS* system, we constructed the stable transgenic flies expressing two copies of *APP/BACE/DPsn* genes by consecutive crosses and homologus recombination. Further tests revealed that the lifespan and the medium survival time of flies expressing two copies of *APP/BACE/DPsn* genes were 52 d and 39 d, respectively, which were much shorter than the lifespan of 69 d and the medium survival time of 49 d of the control flies. Furthermore, the eclosion time of the flies expressing two copies of *APP/BACE/DPsn* genes was 3 d longer than that of the control flies, and the eclosion rate was 5.2% which was much less than the theoretical value 1∶9 (11%). The results suggest that the elav-Gal driven neuronal expression of two copies of *APP/BACE/DPsn* genes in flies leads to shorter lifespan and decreases viability of the offspring. These phenotypes of the transgenic fly might be used as a preliminary drug screen model for AD therapy.

Key words: Transgenic *Drosophila* *APP*; *BACE*; *DPsn* Alzheimer′s disease

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