NO CORRELATION BETWEEN LEVELS OF SECRETED B-AMYLOID, DYSREGULATION OF CELL CYCLE AND AGE OF ONSET OF ALZHEIMER'S DISEASE PATIENTS WITH DIFFERENT PRESENILIN1 FAD MUTATIONS

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The central role of β-amyloid in Alzheimer's disease pathogenesis has a solid base in analysis of familial cases with presenilins or APP mutations. However, there are several problems with the amyloid hypothesis. To shed more light on the role of presenilin mutations in AD pathology we analyzed several properties of cells bearing different presenilin1 mutations, which were identified in Polish FAD patients. Some mutations were very penetrative (P117R, S170F, F177L, I213F) with age of onset between 29-36, other were moderate (L153V, M139V, H163R, E318G), with age of onset between 39-50 years old. All mutations, except one (P117R) in two different clones, did not induce any significant differences in proliferating rates as well as in the cell cycle phases of immortalized lymphocytes. HEK-293 cells stably co-expressing presenilin1 with analyzed FAD mutations and APP with Swedish mutation had unchanged cell cycle properties except clones with P117R mutations. On the other hand these cell lines secreted different levels of Aβ₁₋₄₀ and Aβ₁₋₄₂ peptides. The clones with wild type presenilin1 or with E318G mutation secreted high level of Aβ₁₋₄₀ and low of Aβ₁₋₄₂. Other clones secreted higher levels of both amyloid peptides and the ratio was about 1. Thus, there was no correlation between the age of onset of the disease and neither of the level of secreted amyloid nor the change of cell cycle. This suggests complex effects of presenilin1 mutations on the development of AD pathology not necessarily related to β-amyloid production and cell cycle dysregulation.