62 Trisomy 16 Mouse Model of Alzheimer's Disease

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Aging individuals with Down's syndrome (DS) develop the neuropathologic hallmarks of Alzheimer's disease (AD) and a large proportion display evidence of decreasing cognitive abilities (1-3). In addition, other lines of research suggest an association between DS and AD: extra copies of 21st chromosome genetic material are found in nonfamilial AD (4); genetic polymorphisms in genes coded on the 21st chromosome have been found in families with familial AD (5); the gene for β-amyloid, one of the abnormally stored materials in AD, has been mapped to the 21st chromosome (6). Cerebral cortical dendritic abnormalities similar to those found in DS have been described in AD (7-9). These morphologic changes may be due to underlying abnormalities in neuronal microtubules (10). Furthermore, cytoskeletal abnormalities are common to both DS and AD. A microtubule-dependent event, lymphocyte capping in response to concanavalin A, has been shown to be defective in both DS and AD (11). Similar findings have been made in cultured DS and AD fibroblasts (12). These DS and AD cytoskeletal related findings may be due to abnormal phosphorylation, suggestive of a defect in post-translation modification (13). The highly phosphorylated 210-kDa neurofilament subunit is redistributed to aberrant locations in AD (13) and is precociously expressed in DS (14). Nonphosphorylated neurofilament proteins are markers for vulnerable cortical neurons in AD (15). The Alz-50 antigen which is specific for AD (16) has kinase activity and may be involved in abnormal cytoskeletal phosphorylation (17). In AD protein kinase C dependent phosphorylation is abnormal (18). Early stages of AD are typified by the loss of neurofilament-rich axonal systems (19).

The proposed cytoskeletal abnormalities in DS may be on the basis of the enzymes coded on the 21st chromosome and this may be related to the interferon α and β receptors which are coded by this chromosome (20). In DS, cellular responsiveness to interferon is exaggerated such that a given dose of interferon elicits not a 1.5-fold antiviral response but a 3- to 15-fold response (21). In the initiation of the antiviral state, interferon treatment decreases the rates of cell mitosis, locomotion, membrane ruffling and saltatory movements of intracellular granules (22,23). Fibroblasts treated with interferon contain three times the number of actin fibers when compared to untreated cells (23). Interferon treatment of normal cells produces defective

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