Brain Research Bulletin, Vol. 22, pp. 233–243. © Pergamon Press plc, 1989. Printed in the U.S.A. 0361-9230/89 $3.00 + .00

Murine Trisomy 16 Model of Down's Syndrome: Central Nervous System Electron Microscopic Observations

AUDRIUS V. PLIOPLYS[1] AND H. MELANIE BEDFORD

Surrey Place Centre and Division of Neurology, Department of Pediatrics
Hospital for Sick Children and University of Toronto

Received 11 July 1988

PLIOPLYS, A. V. AND H. M. BEDFORD. *Murine trisomy 16 model of Down's syndrome: Central nervous system electron microscopic observations.* BRAIN RES BULL **22**(2) 233–243, 1989.—Murine trisomy 16 is an excellent model for the human Down's syndrome (DS) (13). Electron microscopic (EM) observations were made of the cortical plate within the developing telencephalic vesicle at the gestational age of E17. The EM observations revealed: (A) microtubular profiles which were more coiled and curved in the trisomic condition; (B) poor cell-to-cell apposition and increased cellular membrane fragmentation in trisomy 16; (C) increased nuclear contour irregularity in trisomic neurons; (D) significant decrease in the cross-sectional area of neuronal nuclei in trisomy 16 ($p<0.01$). The microtubular observations lend credence to the hypothesis that abnormal cytoskeletal interactions may underlie the mental deficiency seen in DS and may predispose to the eventual development of Alzheimer's disease (AD) in DS individuals (39,40). The cellular membrane findings may be related to reported CNS membrane lipid abnormalities in DS (1,2). The nuclear morphologic observations may be related to the reported differences in chromatin and nuclear histone expression in AD (7,8). These results strengthen the role of the trisomy 16 mouse as a model for DS and potentially for AD.

Down's syndrome Membranes Microtubules Nucleus Trisomy 16

DOWN'S syndrome (DS) is the most common identified cause of mental retardation. Even though the trisomic 21st chromosome is a marker for DS, it is not clearly understood how this genetic material causes neurologic impairment (5).

The published literature suggests that cytoskeletal abnormalities may underlie the neurobiologic cause of the mental deficiency associated with DS. The cytoskeleton is composed of three major polymeric protein systems: microtubules, intermediate filaments and microfilaments, as well as interconnections that link these systems together. These cytoskeletal components are important in developing and maintaining cell shape, allowing cell motility, moving organelles and molecules throughout the cell, and may be involved at the synaptic level in the process of learning (15, 25, 27). With Golgi staining techniques, DS cerebral cortical neurons have been shown to have abnormalities in dendritic arborization and in dendritic spine shape and distribution (29, 30, 56, 57), suggestive of an underlying cytoskeletal defect. Human neuropathologic results have shown a decreased number of cortical neurons in DS (48, 61); this may be caused by slowed neurogenesis due to defective cytoskeletal interactions. Also, anomalous expression of the 210 Kdalton neurofilament subunit has recently been reported within the first few months of life in DS individuals (39).

The hypothesis of an underlying cytoskeletal defect in DS is strengthened by the association of DS with Alzheimer's disease (AD). Aging individuals with DS develop the neuropathological hallmarks of AD and a large proportion display evidence of decreasing mental abilities (9, 28, 60). Furthermore, cerebral cortical dendritic abnormalities similar to those found in DS have been described in AD (43, 50, 58). These morphologic changes seen in AD may be due to underlying abnormalities in neuronal microtubules (38).

Pathologically, AD is typified by the accumulation of paired helical filaments which share antigenic determinants with microtubules and neurofilaments (15,42). Abnormalities in microtubular biochemical assembly and ultrastructural appearance have been reported in AD (19,38). The microtubule-associated protein tau has also been shown to be aberrantly distributed in AD (23), and is incorporated into paired helical filaments of AD (18). It is possible that DS neuronal cytoskeletal components or their expression are intrinsically different from normals, thus predisposing DS individuals to the development of AD.

Other lines of research suggest a strong association between DS and AD: extra copies of 21st chromosome genetic material are found in nonfamilial AD (11); genetic polymorphisms in genes coded on the 21st chromosomes have been found in families with familial AD (49); the gene for beta amyloid, one of the abnormally stored materials in AD, has

[1]Requests for reprints should be addressed to Dr. A. V. Plioplys, Surrey Place Centre, 2 Surrey Place, Toronto, Ontario, Canada M5S 2C2.