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

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The author has hypothesized that cytoskeletal abnormalities may underlie the mental deficiency seen in Down's syndrome and may predispose persons with Down's syndrome to the eventual development of Alzheimer's disease (AD) [J Neurol Sci 1987;79:91–100; Down's Syndr. Papers Abst 1987;10:1–3]. To investigate this hypothesis directly an electron microscopic (EM) study was undertaken. It has not been possible for the author to obtain adequate human material; therefore fetal murine trisomy 16 central nervous system was used. Trisomy 16 is an excellent model of human Down's syndrome [Br Res Bull 1986;16:767–771]. EM observations were made of the cortical plate within the developing telencephalic vesicle at the gestational age of E17. The cytoskeletal EM observations revealed microtubular profiles that were more coiled and curved in the trisomic condition than in normal. Other observations included: increased neuronal membrane fragility in trisomy 16; increased nuclear contour irregularity in trisomic neurons; and notable decrease in the cross-sectional area of neuronal nuclei in trisomy 16 ($p < 0.01$). The observations concerning nuclear morphological differences in trisomy 16 may be related to the reported differences in nuclear histone expression in AD [Ann Neurol 1984;15:329–334]. The EM cytoskeletal, cellular membrane, and nuclear contour observations strengthen the role of the trisomy 16 mouse as a model for Down's syndrome and potentially for AD.

38. Expression of the 210-kDa Neurofilament Subunit in Cultured Central Nervous System from Normal and Trisomy 16 Mice: Regulation by Interferon

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The author has hypothesized that cytoskeletal abnormalities may underlie the mental deficiency seen in Down's syndrome (DS) and may predispose persons with DS to the eventual development of Alzheimer's disease [J Neurol Sci 1987;79:91–100; Down's Synd Papers Abs 1987;10:1–3]. Results using autopsy-derived, formalin-fixed central nervous system (CNS) tissue from subjects with DS and control subjects have substantiated this hypothesis by revealing precocious neurofilament antigen expression in subjects with DS during the first few months of life [J Neurol Sci 1987;79:91–100]. A possible explanation for abnormal regulation of cytoskeletal components in DS may be enhanced sensitivity to endogenous interferon. The purpose of this investigation was to study the effects of interferon on cultured fetal CNS neurons taken from normal mice and those with trisomy 16, an excellent model for DS [Br Res Bull 1986;16:767–771]. When applied to CNS cultures taken from normal fetal mice, interferon increases the immunohistochemical expression of the 210-kDa neurofilament subunit. This effect can be blocked by the application of oxyphenbutazone, which inhibits interferon-mediated metabolic pathways. CNS cultures taken from fetal mice with trisomy 16 express greater intensity of the 210-kDa neurofilament subunit immunohistochemical staining than do normal mice. Application of oxyphenbutazone normalizes trisomy 16 CNS neurofilament expression. These results demonstrate that interferon has a regulatory effect upon CNS neuronal neurofilament immunohistochemical expression. Also, there is differential expression of the 210-kDa neurofilament subunit in normal and trisomic cultured CNS neurons. Finally, and possibly most significantly, an interferon inhibitor has been shown to normalize trisomy 16 CNS neurofilament expression. These results may open the door for further investigations of potential therapeutic modalities in DS and Alzheimer's disease. (Supported in part by a grant from the Physicians' Services Incorporated Foundation.)