Speculations on the Role of Transmissible Agents in the Pathogenesis of Alzheimer’s Disease

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ABSTRACT: Unconventional agents and conventional viruses provide model systems to investigate the pathogenesis of Alzheimer’s disease (AD). The essay which follows examines the hypothetical role of herpes simplex in AD and presents some generally applicable experimental approaches to detecting genes in brain tissues. The concluding section, on parallels between AD and diseases of the brain caused by unconventional viruses, defines strategies for isolating genes related to pathology.

RESUME: Speculation sur le rôle des agents transmissibles dans la pathogénèse de la maladie d’Alzheimer. Les agents non-conventionnels et les virus conventionnels fournissent des systèmes modèles pour l’investigation de la pathogénèse de la maladie d’Alzheimer (MA). Nous analysons dans cet article le rôle hypothétique du virus de l’herpes simplex dans la MA et nous présentons des approches expérimentales d’application générale pour déterminer les gènes dans le tissu cérébral. La conclusion qui traite des parallèles entre la MA et les maladies du cerveau causées par des virus non-conventionnels élabore des stratégies pour isoler des gènes qui sont en rapport avec un état pathologique.

Hybridization Tests of the Virus Hypothesis

The strong prediction of the virus hypothesis is the presence of the HSV genome in the appropriate anatomic locations. This can be tested by in situ hybridization, a technique which localizes viral or other sequences in single cells in tissue sections; and by macroscopic-microscopic hybridization, a method which combines in situ hybridization with large-scale screening of sections to enhance the sampling power of the technique. These methods currently can detect the equivalent of 0.02 HSV genomes per cell in tissue sections fixed in formalin to preserve cellular morphology. Because these techniques detect viral DNA in the relatively rare latently infected cell, they are considerably more sensitive than methods which depend on nucleic acids extracted from the whole tissue where viral sequences may be diluted beyond the limits of detection. This dilution effect may be responsible for the negative results obtained thus far for HSV in AD. We have undertaken a survey of ganglionic and brain tissues in collaboration with Dr. Ball to evaluate the proposed spread of HSV to the human brain and the relationship of this event to the pathological changes in AD. As a first step we have optimized the hybridization procedures and demonstrated that we can detect HSV DNA in the sensory neurons.
in the trigeminal ganglion of man (Figure 1). With this encouraging result in hand, we have begun the examination of brain tissues from AD patients and controls.

Unconventional Agents and the Pathogenesis of AD

Unconventional scrapie and other virus-like agents can cause pathological alterations analogous to those seen in AD. We reasoned that these parallels, such as the formation of neuritic plaques, might reflect activation of the same set of genes. Thus, cloning of genes of this type might shed some light on the basis for the tissue lesions. We looked for genes whose expression increases in scrapie and AD by cloning DNA copies of mRNAs obtained from the brains of infected animals. We screened this library with probes copied from mRNAs of infected and uninfected animals to identify clones which gave a higher signal with the scrapie probe indicating a greater abundance of a particular mRNA in the infected brain. The first such clone, Scr-1, identified by differential screening, turns out to be a single copy gene whose expression increases about twenty-fold in scrapie infection. By in situ hybridization Scr-1 mRNA is increased in a focal pattern particularly prominent in areas adjacent to the ventricles of infected animals. The increased binding in AD of Scr-1 is confined to neuritic plaques, largely in cellular processes. The precise nature of this transcript is under investigation, but from the sequence of the clone we know that the 3' untranslated portion of Scr-1 mRNA is closely related to glial fibrillary acidic protein.

Prospectus

The underlying premise of the investigations of scrapie and AD is the concept that degenerative, infectious, or other kinds of pathological developments reflect dysregulation of gene expression. Pathological changes in AD are hypothesized to be the result of an increase or decrease in gene expression which bears a plausible spatial and temporal relationship to the tissue lesions or loss of function. To identify these genes a cDNA library is constructed from the mRNAs extracted from the brains of patients with AD. This library is screened differentially with probes from AD and controls to detect clones which give an enhanced or diminished signal as a result of the increase or decrease of abundance of the respective mRNAs. Their relevance to the pathological state is then assessed by sequencing and hybridization to see if they are brain specific and localized in cells and anatomic regions which could account for the particular tissue change or loss of function. Clones which meet these criteria of "interest" are then evaluated further as to genomic localization (e.g., to chromosome 21, because of the greatly increased incidence of AD in Down’s syndrome).
expression. Identifying those genes whose expression increases or decreases in pathological conditions should therefore prove to be a general approach to the analysis of these conditions. We hope that this analysis, and the experimental strategy which supports it summarized in Figure 2, will provide insight and reagents for prevention, diagnosis and treatment of AD and other degenerative diseases.

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