Tau Protein and Alzheimer's Disease

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ALZHEIMER'S Disease (AD) is a slow disease, specific for human brain, of unknown origin and not curable thus far. This review defines some of the boundary conditions of research.

Because AD is slow, its early stages are not noticed clinically. This hampers the development of drugs that might slow down or reverse the progression of the disease. Conversely, when the disease is noticed clinically, much of the brain damage is irreversible.

Because AD is restricted to human brain, it is not accessible to most methods of experimental analysis.

Because the origin of AD is unknown, it is difficult to search for diagnostic tools or for a medication.

The known correlations with genetic or environmental factors are, in most cases, not strong enough to determine a unique chain of cause and effect. This illustrates the need for the following: (a) Model systems easily accessible to experimentation and analysis, such as cell models or animal models (e.g., transgenic animals); (b) Assays for early detection, possibly from CSF, from sources other than brain (blood, biopsies from other tissues), or methods such as brain imaging (PET, MRI, etc.).

If experimental systems and early detection methods were available, it would be possible to search for treatment even before the origins of AD are known. However, ultimately, the origins will have to be found on the basis of cells or molecules to allow a rational diagnosis, prevention, or treatment.

At present, the search is restricted to a few markers that are thought to be characteristic of AD. This includes genetic linkages (implying proteins, e.g., APP or ApoE), or morphological markers (abnormal aggregates implying proteins, e.g., APP or tau). It is possible that these proteins are not at the root of the disease, but a promising avenue of research is to use these markers as a "sensaphone" to detect underlying abnormal events. The combined use of biochemical, cell biological, and molecular biological approaches has yielded several interesting results. In the case of APP, they point to abnormal proteolytic cleavage and/or accumulation of the protein that causes the fragments (Aβ) to aggregate. In the case of tau, they point to abnormal phosphorylation and an imbalance in signal transduction cascades, also with the result of abnormal aggregation.

TAU PROTEIN

The following discussion is restricted to tau protein. Tau is one of the microtubules associated proteins that are thought to have a role in the stabilization of neuronal microtubules; these in turn provide the tracks for intracellular transport. Tau appears to be one of the earliest markers of AD and forms the neurofibrillary changes (neuropil threads, neurofibrillary tangles, neuritic plaques). Tau protein in AD is distinct from normal brain in several ways:

1. It is aggregated into paired helical filaments (PHF) which coalesce into neurofibrillary tangles. These can be visualized and localized postmortem by special staining techniques.
2. Tau in AD is modified in several ways, e.g., by phosphorylation, proteolysis, and ubiquitination. Abnormal phosphorylation is probably the first and most critical modification; the other two modifications are likely to be secondary reactions by the body's defense system.
3. Abnormal tau spreads in a highly characteristic spatial and temporal sequence, starting in select neurons of the transentorial region. This provides the basis of subdividing the disease into 6 stages, of which only the late stages of 5 and 6 meet the clinical diagnosis of AD unambiguously (for review see ref. 2).

These observations prompt the following questions: (a) What causes the selective degeneration of certain neurons, especially at the early stages? What makes these neurons special in terms of function, differentiation, activity? Alternatively, are these neurons selectively exposed to some toxic factors (glutamate, Aβ, other stress-inducing substances)? Are these neurons particularly vulnerable? (b) Of all proteins in a cell, why is it that tau reacts in a pathological fashion? Or are there other proteins that become abnormal but are not visible by pathological aggregation? What causes tau to aggregate? Why does aggregation take place in selected regions of a cell? Why does abnormal tau become hyperphosphorylated? Because tau's function is linked to microtubules, are any of the microtubule-based processes impaired (e.g., intracellular traffic, neurite extension)? (c) What causes the spreading of the neurofibrillary changes in a reproducible fashion? Is there a gradient of toxic effects, a gradient of vulnerability? Or do affected cells communicate their degeneration to others? Do the body's defense mechanisms slow down or speed up the spreading?

The first two sets of questions call for a cell biological approach. If one could create cell models that mimic the behavior of the degenerating neurons one could assay for toxic substances or special properties. The cell models could be of neuronal origin or other cultured cells that are engineered to show "Alzheimer-like" behavior. Such engineering would involve, for example, the transfection with genes coding for tau protein, APP, ApoE receptors, or other proteins suspected to be involved (kinases, phosphatases). A number of labs are working on these issues and interesting results are beginning to emerge. The third set of questions is probably the most difficult to answer because they deal with whole brain tissue with a heterogeneous composition. These questions could possibly be addressed with suitable animal models, but even if they were available, the results are likely to be complex.

For the moment, the cell biological approach combined with the methods of biochemistry and molecular biology, seems to be
the most promising one for studying the etiology of AD. Even though the origins are unknown one can take the attitude that pathological tau may serve as a semaphore. It has revealed a potential link of pathological tau may serve as a pointer for searching in the right direction. In this regard, several important advances have been made in recent years (for recent reviews, 6, 9, 4, 10).

Tau has been identified as the primary component of abnormal neurofibrillary aggregates. Many of the normal and abnormal phosphorylation sites have been mapped, in particular, certain serine-proline or threonine-proline motifs because their phosphorylation leads to an Alzheimer-like antibody reactivity (8). Several protein kinases that are able to phosphorylate these motifs have been identified, including MAP kinase, GSK-3β, cdk5, and others (3). In addition, there are other kinases that can detach tau from its natural partner, microtubules; at least one of the sites (serine 262) is also characteristic of AD tau (5). The "abnormal" phosphorylation sites can be cleared again by certain phosphatases (calcineurin, PP-2A; ref. 3a). Some of the sites are transiently phosphorylated in foetal brain, suggesting that the degenerating neuron reacts to some stimulus in a fashion reminiscent of the fetal stage (7). Finally, the aggregation of tau into PHFs can be reconstructed in vitro (11).

The results on tau's phosphorylation all point to an imbalance in the signal transduction pathways involving cascades of phosphorylation and dephosphorylation. In this sense, tau has already fulfilled one role as a semaphore. It has revealed a potential link of the AD pathology to a general principle governing cell regulation. The field of signal transduction is complex, but it is evolving very rapidly. Because of its fundamental importance one can expect that it will serve as a guide for experiments in the field of AD research (as well as other disease states). For example, it is now possible to put a cell under stress such that the cell responds by activating certain kinases which could phosphorylate tau protein in a "pathological" fashion—this is the beginning of a cellular model system.

The etiology of Alzheimer's disease is still unknown. Because the disease is specific for human brain, a rational search for early diagnosis or prevention is very difficult. This calls for the development of cellular models that mimic the degeneration of neurons in AD. The brains of AD patients contain markers whose composition and location is characteristic of the disease; one of the most reliable markers is tau protein in its pathologically phosphorylated and aggregated form. This form of tau can serve as a guide to the origins of the pathology. One goal of research that should be feasible within the near future is to construct a cell that induces the same abnormal changes in tau protein in response to defined stimuli (extracellular signals, toxins, stress, etc.). This model can then be used to identify possible substances that might cause the disease, or identify strategies for preventing it. Once they are defined on a cellular level, the next step would be to test them on (transgenic) animal models which are being developed at present.

REFERENCES


