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Trace Amyloid Back to Precursor Protein

And then go farther down that pathway to find Alzheimer's cause, a reader suggests

- by Wes Ashford MD, PhD

The following was submitted in response to a MedPage Today *series by staff writer Kristina Fiore about the role of beta-amyloid protein in Alzheimer's disease.*

Thank you for your series that raises questions about the amyloid hypothesis in Alzheimer's disease.

There is a more extreme view that amyloid itself has almost nothing to do with dementia in the human, unlike the brain of the mouse models which are overloaded with abnormal beta-amyloid protein.

As I've expressed in a commentary in the *Journal of Alzheimer's Disease*, I do not think it is a stretch to consider that amyloid, senile plaques, neurofibrillary tangles, and neuronal death are just various end-points indicative of a process that is actually causing the dementia, but have no role in causing dementia.

From a molecular neurobiological perspective, it is more reasonable to take amyloid, predominantly an extracellular protein, out of the causal cascade leading to dementia and instead follow its intracellular complement of the gamma-secretase cleavage. This protein, so-called amyloid precursor protein (APP) intracellular domain (AICD), is actually in a better position to affect conditions inside the neuron.

AICD is known to cause hyperphosphorylation of tau, which will continue the cascade leading to dementia: formation of paired helical filaments, which aggregate to form neuropil threads (which are found only in those amyloid plaques associated with dementia and a diagnosis of Alzheimer's disease), and the neuropil threads amputate axons and dendrites, leading to massive synapse loss -- the direct cause of dementia.

The subsequent events, retrograde transport of neuropil threads to neuronal cell bodies, accumulation of neuropil threads to form neurofibrillary tangles, and resulting cell death are not part of the cause of dementia, either -- instead, they are just late effects. All of the well-known pathological stigmata of Alzheimer's disease, plaques, tangles, neuron death, inflammatory response, are all visible but secondary consequences of the underlying process leading to the dementia and should not be mistaken for treatment targets.

The real line to follow for prevention is to understand the APOE genotype and how age leads to the progressive breakdown of the serotonin and norepinephrine neurons, finally ending up damaging the

cholinergic neurons. The loss of the basic brainstem projections is associated with an imbalance in the memory mechanisms involved in processing the APP, specifically, failure to activate the alpha-secretase cleavage of the APP, with default excess cleavage by beta-secretase and gamma-secretase, leading to increased production AICD, leading to synapse loss and dementia.

I am hopeful that the field can look to the critical neurobiological processes beyond the amyloid cascade hypothesis so it can quit wasting billions of dollars and realign behind some promising directions.

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Ashford is a consultant to Neurotez and MemTrax

COMMENTS

08.28.2015

— Reeta Griffin

This sounds very logical. Is research being done with this pathway? Any funding from Rx companies? Would love to hear the answers or why someone else thinks this isn't where research needs to be.

08.30.2015

— Sanjay W. Pimplikar

In a series of papers starting with Ghosal et al., 2009, my group has shown that AICD transgenic mice recapitulate major AD-pathological features, including memory deficits and neurodegeneration, in an age-dependent manner (Vogt et al., 2011; Ghosal et al., 2011; Ghosal et al., 2010; Margevicius et al., 2015). Several other groups have independently shown neurotoxic effects of AICD in vitro in neuronal and non-neuronal cells. So, the idea that AICD can be an important factor (if not the only one) in causing AD is supported by considerable data.

Most of these publication can be accessed in PubMED by searching for "Pimplikar".

1. Ghosal K, Vogt DL, Liang M, Shen Y, Lamb BT, Pimplikar SW. Alzheimer's disease-like pathological features in transgenic mice expressing the APP intracellular domain. Proc Natl Acad Sci U S A. 2009 Oct 27;106(43):18367-72.