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Mutated tau, amyloid and neuroinflammation in Alzheimer disease—A brief review

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ABSTRACT

This review discussed the importance of mutated tau, amyloid and neuroinflammatory factors and microglia in Alzheimer disease. In particular tau, CD4 and TNF alpha were included in the review and the colocalizations of these factors were highlighted. It is important to realize the Alzheimer disease may result from the interactions of these factors. Some of these factors may coexist at the same region and at the same time e.g. mutated tau and amyloid in plaques. A summary scheme of etiology leading to the disease was included.

Alzheimer disease presently affects at least 30 million patients around the world (Burns and Iliffe, 2009; Querfurth and LaFerla, 2010), with only 5% of patients with early onset and related to genetic factors (Blennow et al., 2006) while, majority of patients were sporadic and of late onset (65 years old or over) (Burns and Iliffe, 2009; Mendez, 2012). The disease was discovered more than a hundred years ago by Alois Alzheimer in the year 1906 (Berchtold and Cotman, 1998). Dementia is one of the major manifestations of the disease, starting initially with the loss of short term memory (Carlesimo and Oscar-Berman, 1992; Forstl and Kurz, 1999). In fact, the short term memory loss was associated with spatial memory and large numbers of cell loss was observed in the entorhinal cortex in these patients (Zhu et al., 2007). The disease then progressed to various other parts of the brain leading to language difficulties, motor apraxia, loss of long term memory, inability to take care of himself or herself and finally patients had changes in personality, mode, behavior and judgement (Forstl and Kurz, 1999; Taler and Phillips, 2008; Burns and Iliffe, 2009). As early as the Alzheimer days, plagues and tangles in brains were described to be neuropathological features of the disease (Forstl and Kurz, 1999). To this day, the many suggested possible etiologies rendered the clarification of the mechanism of the disease foggy. Examples of etiology included (1) amyloid precursor protein induced cell death receptor resulting in cell death (Lacor et al., 2007) and amyloid itself could be detrimental and acted on synapses (Nikolaev et al., 2009). (2) Lack of acetylcholine disturbed cell transmission and formed the cholinergic hypothesis (Francis et al., 1999). (3) Oxidative stress produced global effect on neuronal survival (Zhang et al., 1997; Su et al., 2008).

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(4) Metallic excess or deficiency might also play a role, especially for zinc and copper. (5) In the recent ten years, the role of neuroinflammatory changes during Alzheimer onset became a hot topic (Blennow et al., 2006).

When getting down to basic, we have known for many years that (1) plaques would lead to formation of death enzymes in neurons, e.g. the caspases (Yew et al., 2004). (2) Dying cells in brains of Alzheimer patients were predominately neurons and they died by apoptosis (Li et al., 1997). (3) Dying cells contained caspases 3 and 6 and had downregulated levels of brain derived neurotrophic factor (Yew et al., 2004; Lorke et al., 2010). (4) Alzheimer patients further had downregulation of adhesion molecules which were important for maintenance of synapses (e.g. neuronal cell adhesion molecule) (Yew et al., 1999) and (5) Alzheimer brains had indeed a depletion of neurotransmitters, not only acetylcholine, but catecholamine and serotonin and their receptors as well (Yew et al., 1999; Lorke et al., 2006; Yeung et al., 2010a). (6) Mutated tau protein also existed in activated caspases positive neurons, in other words dying cells (Wai et al., 2009).

With these in mind, we would take a brief look at the amyloid, mutated tau and their relationships with neuroinflammation to update and to collate into a comprehensive picture for this disease.

It has been known for more than a hundred years that Alzheimer disease has two markers—amyloid beta and mutated tau. These notions still hold true in this fatal disease. The interaction between mutated tau and amyloid is always interesting and elusive. In one recent study, it was reported that overexpression of tau protein could actually curb amyloid beta initiated apoptosis via targeting caspase 3 pathway in Neuro-2a (N2a) culture cells (Liu et al., 2010). Again in culture cells, the reverse might not be true and that hyperphosphorylation of tau could be initiated instead by accumulated amyloid beta (Huang and Jiang, 2009). A study by Colle et al. (2000) on the loss of isocortical presenilin 1 immunoreactivity in Alzheimer disease looking for correlation between amyloid beta and neurofibrillary tangles, revealed that presenilin 1 immunoreactivity was not present in neurons with neurofibrillary tangles. Since presenilin relates to amyloid production, this appears to indicate gene controlled amyloid production does not coexist with production of fibrillary tangles and this did not associate with tangle formation. In another study on the human aging brainstem of two groups of Alzheimer patients of ages between 65 and 67 years and between 91 and 96 years, with both groups at end stages (equivalent to Braak stage V to VI) and had mini–mental state examination (MMSE) scores between 12 and 16, it was found that activated caspases 3 or 6 were colocalized in mutated tau neurons but those neurons that had colocalizations of caspase 6 and mutated tau together in the same neuron was much more in number than those neurons with caspase 3 and mutated tau colocalization. Likewise, there were much more cells with colocalization of mutated tau and caspases in the older patients (Wai et al., 2009). These finding suggested that caspase 6, rather than caspase 3 might appear with mutated tau together more frequently and concomitantly in neurons at end stage of Alzheimer. This alone delineated that tau by itself could lead to neuronal cell death, with and without beta amyloid, in addition to mutated tau's ability to form tangles. Mutated tau, separately and individually, could downregulate cell survival and affected neuronal function (Buerger et al., 2005). As normal tau is the component of the neurotubules of the nerve cell which forms the internal cellular railway, thus any mutated tau would result in a "twisted" and inoperable rail system of cell transport. As a consequence, the twisted conducting system and filamentous network would affect both cellular function and synaptic transmission seriously (Maccioni et al., 2001). Even more important was that the microtubules also form the cytoskeleton of the cell and abnormal tau will lead to an aberrant and weak cytoskeleton, which in the long term predisposes to cellular damage and cell death. Further, chaperone interacts with mutated tau and amyloid beta (Blair et al., 2015), probably causing eventual misfolding and misalignment of amyloid and mutated tau themselves.

On the other hand, it has been well known that amyloid beta or its precursors would lead to neuronal cell death. For example, Susanto et al. (2015) reported that in human parietal atrophy of Alzheimer patients, decrease of MRI volumes could be related to amyloid deposits. It was long believed for decades that most neuronal cell deaths were apoptosis (Li et al., 1997). Furthermore, amyloid beta did not seem only to lead to cell death but also loss of postsynaptic protein (PSD 95) and synaptophysin (Liu et al., 2010). These changes were mediated via the *N*-methyl-D-aspartate (NMDA) receptors, suppression of NMDA receptor subunit 1a (NR1a) and activation of NMDA receptor subunit 2B (NR2B) induced cyclooxygenase (COX) and caspase 3 formation on top of being toxic to the synaptic proteins. Those composite events led to cell death and disturbance of synaptic function. Indeed, soluble amyloid beta peptides when injected into rat hippocampus in vivo, did disrupt synaptic plasticity (Hu et al., 2008). In transgenic mouse overexpressing amyloid precursor protein, the hippocampal excitatory transmission was disrupted and this could block long-term potentiation (LTP) at nanomoler concentrations (Rowan et al., 2003). Nonsteroidal anti-inflammatory drugs (NSAID) improved amyloid suppression on memory and synaptic plasticity, probably via the blocking of COX (Morihara et al., 2002). It is further interesting to note that some abusive drugs, in particular, ketamine used in experimental animals for a period of more than 3 months, would result in mutated tau and amyloid formation (Yeung et al., 2010b; Sun et al., 2011).

There had always been a question on whether amyloid beta or mutated tau could induce cell death individually or they must act in combination. Using a culture model of human neuroblastoma cells with deoxycline regulated expression of truncated tau, Zilka et al. (2011) concluded that neuronal death correlated with neurofibrillary density. The dying cells exhibited cell shrinkage, DNA fragmentation similar to that of apoptosis initiated by caspase 3. This is interesting but did not align with an observation by our group that mutated tau was colocalized in caspase 6 positive neurons more often than those of caspase 3 (Wai et al., 2009), signifying perhaps there were detours from the classical induction of neuronal cell death via the traditional caspase 3 cascade. Apart from the induction of apoptosis, caspases 9 had been associated with the cleavage of normal tau to a truncated tau, thus facilitating the formation of neurofibrillary tangle (Rohn et al., 2002). From another angle, caspase 8 was also present along in amyloid plaques (Yew et al., 2004) suggesting caspase 8, 9 contributed in both tau and amyloid mechanisms directly or indirectly involved in apoptosis. In our studies, mutated tau and amyloid