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Original Research Article

Lipofuscin Hypothesis of Alzheimer's Disease

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Abstract
The primary culprit responsible for Alzheimer's disease (AD) remains unknown. Aβ protein has been identified as the main component of amyloid of senile plaques, the hallmark lesion of AD, but it is not definitively established whether the formation of extracellular Aβ deposits is the absolute harbinger of the series of pathological events that hit the brain in the course of sporadic AD. The aim of this paper is to draw attention to a relatively overlooked age-related product, lipofuscin, and advance the hypothesis that its release into the extracellular space following the death of neurons may substantially contribute to the formation of senile plaques. The presence of intraneuronal Aβ, similarities between AD and age-related macular degeneration, and the possible explanation of some of the unknown issues in AD suggest that this hypothesis should not be discarded out of hand.

Unresolved Issues in the Pathogenesis of Alzheimer's Disease

One of the major obstacles to understanding the pathogenesis of Alzheimer's disease (AD) is the difficulty of relating its highly specific neuropathological hallmarks (extracellular amyloid β, Aβ, deposition and τ protein-based intraneuronal neurofibrillary tangles) to the series of generally harmful events that occur in patients' brains and may play a major role

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in the process of neuronal degeneration (including oxidative stress, the activation of inflammation, and the deregulation of a number of basic mechanisms of cell function), or to acknowledged risk factors such as head injury, altered cholesterol homeostasis, a particular isoform of apolipoprotein E, and cerebrovascular disease.

Although the amyloid cascade hypothesis [1] sequences the two basic lesions of AD, it does not explain what triggers the accumulation of Aβ protein in the brain. Furthermore, many other pathogenic aspects remain largely unknown. Why does Aβ deposition usually begin in late adulthood or during aging? Why does its focal aggregation lead to a myriad of discrete lesions (the senile plaques) rather than diffuse involvement of the neuropil? Why do senile plaques form almost exclusively in the grey matter and spare the white matter even though the Aβ protein precursor is highly expressed in neurites? Why are brain regions such as the cerebral cortex affected much earlier and more severely than other regions?

Not even the revised version of the Aβ hypothesis, which considers oligomers as the most detrimental factor for neuronal and synaptic functions, adds anything that can help to answer these questions [2].

The Morphogenesis of Senile Plaques: A Role for Lipofuscin?

We advance a hypothesis that may provide some clues relating to the first steps in the genesis of senile plaques.

Our idea is that following the death of neurons during aging (due to several unrelated causes), lipofuscin is set free in the neuropil, where it cannot be rapidly degraded due to its biochemical characteristics. Therefore, the fate of this waste product may be to linger in the extracellular milieu, giving rise to a focal impairment in the tissue that may represent the starting point of the senile plaque. In other words, just as the young Holden Caulfield in *The Catcher in the Rye* was puzzled as to where the ducks of Central Park go when the lake freezes over, we wonder what happens to the lipofuscin built up in a neuron when the cell dies.

Why should we imagine that the brain starts to accumulate insoluble aggregated proteins focally and extracellularly from a certain point in life when the process actually begins with the formation of lipofuscin in the cytoplasm of neurons at birth? By middle age, the brain is already overloaded with a large amount of this insoluble material, which consists of cross-bound oxidized proteins and lipid degradation products that are highly resistant to cellular proteolysis [3].

Unlike previous theories concerning the possible involvement of lipofuscin in the pathogenesis of AD [4], our hypothesis does not imply that intraneuronal lipofuscin is intrinsically harmful to neuronal cells, but that it may become so when it is released into the extracellular space.

Differences in the tinctorial properties and structure of lipofuscin and the amyloid of senile plaques would seem to argue against our proposal. However, it must be borne in mind that lipofuscin contains Aβ and its precursor [5, 6], and that its relocation from the intra- to the extracellular compartment (together with the intervention of microglia, astrocytes and a robust neuroinflammatory response) could greatly modify its morphological, tinctorial and biochemical characteristics. This scenario would also reverse the most commonly held concept that the Aβ peptide self polymerize over years to form senile plaques. Following our view, the lipofuscin released into the extracellular space may act as a source of Aβ oligomers for a prolonged period of time.

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Lipofuscin as a Possible Link between Aβ, the Innate Immune System and Oxidative Stress

The hydrophobic and insoluble characteristics of lipofuscin correspond closely to those of substances that are most effective in inducing an innate immune response [7]. Furthermore, it is worth noting that mitochondrial autophagocytosis is believed to be a major contributor to lipofuscin formation [8] and that mitochondria are the remnants of ancient bacterial intruders that have become symbionts of eukaryotic cells [9]. Finally, the rate of lipofuscin formation is also closely related to oxidative stress [3].

Lipofuscin may therefore provide the missing link between the factors that are known to be involved in the pathogenesis of AD (such as oxidative stress, mitochondrial dysfunction and the activation of innate immune responses) [10] and the senile plaques that represent its earliest and most specific, microscopically visible structural alterations.

Recent evidence indicating that vascular factors play a substantial role in the genesis of AD [11] may be interpreted in this context because hypoperfusion is a potential cause of damage of neurons and may therefore be capable of initiating neuronal death and lipofuscin release. Furthermore, the general anesthesia and perioperative procedures that have been shown to be associated with an increased risk of AD may act in a similar way [12].

Our hypothesis is not supported by experimental evidence, but there are also no published data that substantially argue against it. It would therefore be very interesting to establish whether there are any differences in the biochemical composition of lipofuscin between AD brains and brains that are relatively resistant to developing Aβ deposition and AD-associated changes. Lipofuscin, which means 'dark fat' and is also known as 'age pigment' or 'lipopigment', is currently defined operationally rather than structurally [3, 8]. Its biochemical composition varies in different animal species, different brain structures and different ages [13], thus indicating that there is not just one but many types of lipofuscin with similar tinctorial characteristics (autofluorescence). It is also conceivable that some types of lipofuscin have more deleterious effects than others when released extracellularly, and have more propensity to induce the formation of senile plaques.

It is not known whether the composition of lipofuscin is different in subjects with or without apolipoprotein ε_4 alleles. It would also be significant to determine the effect of experimentally inoculated lipofuscin on the brains of mice, and whether it induces Aβ formation.

Of note, Aβ deposition in AD occurs not only in the neuropil but also in vessel walls, and this distribution is consistent with the release of debris or waste products that follow the perivascular spaces when they are extruded from the cellular compartment.

Lipofuscin in Other Age-Related Degenerative Diseases

Lipofuscin has long been considered inert, but various lines of evidence indicate that it plays a major role in another neuronal degenerative process that is very common in elderly people: age-related macular degeneration (AMD) [14]. Lipofuscin accumulation in the cells of the retinal pigmented epithelium is involved in the pathogenesis of AMD, together with the formation of abnormal extracellular deposits (or drusen) that accumulate along the basal surface of the pigmented epithelium. It has been shown that drusen contain a number of molecules and, most significantly, these include Aβ protein [15]. The fact that drusen arise from material released by lipofuscin-rich retinal pigmented epithelial cells and contain a substantial number of proteins that are also components of senile plaques suggest unexpected analogies between the pathogenetic mechanisms of AMD and AD.

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Conclusions

We propose that the primary culprit responsible for sporadic AD may be the release of neuronal lipofuscin in the extracellular compartment, an event that should not be harmless since the neuron carries the weight of keeping this substance segregated inside its cytoplasm for decades.

The above-mentioned 'lipofuscin hypothesis of AD' considers Aβ deposition as a downstream phenomenon which is critical and essential but not the absolutely and invariably causative event in determining the onset of AD. It could be that in sporadic AD, Aβ is more than an epiphenomenon because it is tightly linked to the release of lipofuscin in the neuropil, but that the scenario differs when Aβ deposition is induced artificially per se, e.g. in the transgenic mouse model of AD where large quantities of Aβ do not determine significant neuronal degeneration [16].

Lipofuscin is a matrix that recapitulates the insults and damage a neuron receives during the life of an individual. It is therefore likely that its composition and characteristics are influenced by various genetic and environmental factors that may reinforce or weaken each other and, in combination with factors that alter the chance in age-related neuronal death, may modulate the overall individual risk of developing AD.

Our hypothesis may open up new lines of research in addition to those currently focused on Aβ and τ, and thus contribute to more decisive advances in our understanding of the pathogenesis of AD, and in the identification of effective preventive or therapeutic strategies.

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