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A Glycated core of Alzheimer's Pathology

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For decades, a great deal of public attention has followed the search for cures for cancer, heart disease and viral infections, but the single most expensive, and seemingly intractable, medical challenge in the industrialized world is Alzheimer's disease [1]. The history of Alzheimer's clinical trials has been notoriously disappointing [2], but are we truly doomed to continue repeating this futility?

In fact, there are grounds for hope. In recent years, in a focal areas distinct from the clinical failures, we have seen fascinating progress on several potentially convergent fronts of that may afford promising new therapeutic opportunities.

One front has focused on diagnostics and biomarker development, and entails identifying and assessing a significantly number of pathological risk factors. For Alzheimer's these include diabetes [3-5], hypertension[3,5], obesity[5,6], rheumatoid arthritis[5,7], glaucoma[5,8], macular degeneration[5,9], multiple sclerosis[5,10], and other disorders [5]. A second, highly complementary, front has involved breakthrough insight into the biochemistry underlying these risk factors, as well as progress on new therapeutics that productively exploits this new mechanistic understanding.

Logically, if an array of different diseases are statistically connected to (and may help to cause) Alzheimer's, then it is likely that some of the causative molecular processes characterized for the risk factors should also be relevant to Alzheimer's itself. Yet, however clear this concept may seem, it has remained largely under-represented in the foci of clinical investigations.

By contrast, the numerous anti-amyloid monoclonal antibodies, and small molecule secretase modulators being put forward as Alzheimer's drug candidates are rooted the heavily beaten path of trying to mitigate Amyloid β and tau misfolding – a strategy littered with failure. There are, admittedly, some advantages in the conservative approach since many pitfalls are already known, and each failure tends to illuminate possible corrective strategies to try, but at a certain point one seems faced with the question of leaving the beaten path and experimenting with the unknown.

Yet, there is actually a third option – a 'new conservatism', where we may re-use old approaches that have actually worked for diseases other than Alzheimer's. In other words, perhaps we can leverage practical experience and therapeutic successes for diseases such as diabetes, COPD, hypertension, and so forth, to successfully treat Alzheimer's disease.

In fact, these seeming disparate pathologies are actually quite similar. For example, Alzheimer's has long been regarded as a protein misfolding disorder, but so are many of these other diseases. In type 2 diabetes, the islet amyloid polypeptide (a metabolic regulator) tends to accumulate and oligomerize into beta-cell cytotoxins [11]. Similarly in COPD, it is serum amyloid A that tends to pathologically oligomerize and fibrilize [12], whereas a key marker for many cases of hypertension is overexpression and amyloidogenic aggregation of light chain immunoglobulins [13].

The strong thread of amyloidogenic misfolding in both Alzheimer's pre-morbidity risk factors and Alzheimer's itself might seem to be in keeping with hypotheses of a prion-oriented initiation of neuropathologies [14]. Specifically, evidence of significant misfolding in peripheral pre-morbidities might imply that the misfolds spread to amyloidogenic central nervous system proteins like Amyloid β and tau in a pseudo-infectious manner [15]. However, this model has been dealt a significant blow by recent work from the Stanley Prusiner lab, which reports, counter-intuitively, that in non-familial Alzheimer's (which constitutes nearly 90% of cases) there is a pronounced inverse correlation between pathological progression and the prion-propagation capacity of amyloidogenic proteins like Amyloid β and tau [16]. In order words, the rate of prionic plaque and fibril formation is significantly slower in later stages of the disease when most neuron death occurs.

How then should we interpret pre- and co-morbidity evidence that points toward misfolding of different proteins as a strong commonality with Alzheimer's, in light of with evidence that neurodegeneration likely is not actually caused by the large-scale protein misfolding that is so characteristic of Alzheimer's disease?

To answer this question, consider the analogy of an electrical storm, where the sky first grows dark, then one notices distant thunder and lightning, followed then by heavy rain. Does this sequence imply that the rain is caused by lightning which, in turn, was originally caused by the dark sky? No, in fact all three of these phenomena are independent symptoms arising from a same root cause – a cumulonimbus cloud, which ultimately forms under specific conditions of pressure and temperature differential, and an abundance of moisture. Likewise, in Alzheimer's pathology, it is perfectly reasonable to assume that amyloid formation and neurodegeneration are similarly independent symptoms of some common root cause, where that common root may also (in earlier pathology stages) help to cause preceding risk factors.

If so, what is that common root cause?

A variety of hand-waving arguments have begun to emerge, including the vague notion that inflammatory mediators [17] or dysregulated metal ions [18] may cause both microscopic protein misfolding and macroscopic health disorders. The unfortunate weakness in this argument comes with competing evidence that misfolded proteins cause inflammation [19] and metal ion dysregulation [20]. This leads to 'chicken and egg' causal loops that hinder the identification of a druggable intervention point, and often suggest that the true cause is something else entirely.

Fortunately, another common thread runs through Alzheimer's disease and a great many pre- and co-morbidity risk factors – glycation. These pathologies all are marked by the covalent binding of small plasma carbohydrates (in particular, glucose, fructose and methylglyoxal) to basic amino acids lysine and arginine. This glycation process generally neutralizes the charge of cationic lysine or arginine, which then alter the protein conformation in the vicinity of the bound carbohydrate, and may further disrupt salt bridge interactions and thus interfere with tertiary stabilization within the affected protein, or alter protein-protein interaction profiles.

Interestingly, glycation also tends to alter protein secondary structure, leading to a pronounced increase in the abundance of beta strand character in proteins [21-23], which also substantially increases the propensity for intermolecular amyloid aggregates to assemble as extended beta sheets.

Among the three Alzheimer's risk factors exemplified earlier, the islet amyloid polypeptide (IAPP; a marker for type 2 diabetes), serum amyloid A1 (SAA1; a marker for COPD) and immunoglobulin light chains κ and λ (IgLk, IgLl; markers for hypertension) all have distinct glycation motifs (lysine or arginine residues immediately flanked by proton shuttling amino acids, such as histidine, aspartate, glutamate or serine). IAPP has been specifically verified as a protein that is vulnerable to glycation [24], while IAPP, SAA1, IgLk and IgLl are all known to be ligands for the receptor for advanced glycate end products (RAGE) [25-27].

In Alzheimer's itself, both the amyloid β peptide [22] and the tau protein [28] are known to become glycated upon exposure to pathologically significant concentrations of plasma carbohydrates. For both amyloid β and tau, there are two lysine-glycation motifs immediately adjacent to hairpin-forming beta strands [22,29], which may imply that glycation not only spatially coincides with the beta-rich pathological forms of these molecules, but actually causes the associated beta conformational shift.

The glycation-induced functional alteration of amyloid β and tau may not be limited to conformational effects, however. From the perspective of fully characterizing pathological mechanism, it is worth noting that both amyloid β and tau have a third glycation-vulnerable motif that is independent of the two hairpin-associated lysines. Tau has a glycatable Arg 723 within the serine-rich phosphorylation C-terminal region, whose hyperphosporylation is significantly correlated with pathological effect in a substantial number of neurological syndromes. This coincides nicely with observations that methylglyoxal (a dicarbonyl known to glycate arginines) tends to modify tau to promote hyperphosphorylation [30]. Meanwhile, for amyloid β, Arg 5 manifests in a classical glycation motif that may help to rationalize extensive evidence (e.g., [31-33]) that the N-terminal coil of amyloid β complexes with metal ions in a manner that is potentially pathological [34]. Mechanistically, this metal ion complexation is explained by an arginine modification that alters the N-terminal electrostatics (i.e., neutralizing a metal-repelling positive charge) and, more specifically, methylglyoxalation of the arginine produces an additional imidazolone moiety that can collaborate with existing histidines to achieve polydentate ligation of polarizable cations such as Cu^{2+} and Zn^{2+}.

The above two paragraphs suggest at least four different ways that glycation chemistry may produce Alzheimer's-relevant pathology. Is it thus possible that the multi-faceted nature of Alzheimer's actually arises not so much from polyfactorial effects of aging, but rather from a single biochemical process that is capable of distorting fundamental physiology in a myriad of ways? This would seem to be a more hopeful scenario than the growing pessimistic view that the complexity of Alzheimer's can only be explained by the coincidental development of multiple unrelated pathologies [35].

Indeed, it would be incredibly daunting if, to effectively treat Alzheimer's, we needed to develop one drug to correct the flawed immune signaling of a hairpin-misfolded amyloid β, another to phagocytose oligomeric tau that can no longer provide robust microtubule stabilization, a third to correct deviant metal ion sequestration by modified amyloid β, and a fourth to control Caspase 3 over-activation arising from hyperphosphorylated tau. It would be far easier if we, instead, could instead block multiple modes of prospective pathology by simply finding, and correcting, the right upstream biochemical risk.

Could therapeutic or prophylactic schemes aimed at reducing protein glycation afford us that upstream leverage? Current literature already hints at distinct targeting strategies. Favorable preliminary results have been observed for both Nrf2/glyoxalase activators which enzymatically repair protein glycation [36], and scavengers such as creatine [37] which remove problematic carbohydrates in the first place.

Are there yet other novel targeting opportunities waiting to be found?

Well, that may take work to answer, but perhaps it too may be simpler and more productive than continuing to re-sample old failed Alzheimer's strategies.

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