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Amyloid: From Starch to Finish

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In 1639, Nicholas Fontanus examined an unusual specimen: a recently deceased young man whose abdomen sloshed with excess fluid and whose skin had turned the deep yellow of severe jaundice. During the autopsy, Fontanus found large white stones in his spleen. In 1722, Jeremiah Wainewright autopsied a patient whose swollen neck suggested thyroid disease, but an unexpected finding challenged the diagnosis: tucked underneath the patient's ribcage, his liver had swelled to between two and three times its normal size to make room for a mysterious, clay-colored substance. In 1789, Antoine Portal opened the body of a deceased elderly woman to discover a liver with the texture of rendered fat.

Soon, the terms "lardaceous" and "waxy" began appearing in medical textbooks to describe livers and kidneys suffering from this strange malady. Eventually, Rudolph Virchow, chair of pathologic anatomy at the University of Bavaria in Würzburg, weighed in. Virchow, a scientist most famous for his work on cell division, disapproved of both descriptors. He believed that the strange substance was starch, a linear sugar molecule typically found in plants. But other researchers disagreed, thinking that a more accurate comparison might be cellulose, starch's fibrous, indigestible cousin. So Virchow forced the debate. In 1854, he applied a relatively new term – one created in 1838 by German botanist Matthias Schleiden to describe a normal, starchy plant component – to the strange material depositing in human tissues (1). The mysterious substance still defied explanation, but at last received a unifying name: amyloid.

Researchers continued to delve further, as the name alone offered no insight into the provenance of the mysterious substance. Five years later, scientists resolved the debate: amyloid was neither starch nor cellulose, but a protein. At the same time, researchers developed iodine stains and aniline dyes to search for amyloid deposits throughout the body. Everywhere they looked, they found amyloid – not only in the liver, kidneys, and spleen, as had been reported in the 1600s, but also the aorta, smaller arteries, and the entire intestinal tract (1). Having identified the makeup of this still-mysterious protein, and having tracked it throughout the body, the obvious question remained: where did amyloid come from? Without advanced microscopy or other tools of modern molecular biology, the question was unanswerable – and it would remain so for generations.

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In the meantime, medicine carried on. And, in 1901, a German neurologist by the name of Alois Alzheimer met a 51-year-old woman named Auguste Deter. Deter suffered from memory loss, paranoia, and psychological changes. As the story goes, Alzheimer had never seen a case like this. Following her death in 1906, he obtained permission to perform an autopsy. The examination revealed severe neuronal loss throughout her brain. He also found peculiar intracellular tangled fibrils and extracellular plaques of an unknown substance (2). He published his findings in 1907 and, several years later, his colleague and mentor, Emil Kraepelin, conferred the name Alzheimer's disease (AD).

(History has largely overlooked that Alzheimer was not the first or only contributor to the discovery of the characteristic histopathological findings. One account appears to have been published five months earlier by Solomon Carter Fuller, the first African American psychiatrist, who was working at the time in Alzheimer's lab (3). Historians still debate the intention behind Kraepelin's decision to name the disease after his protégé (4).)

Over the ensuing decades, researchers identified the composition of the extracellular plaques as a type of amyloid (eventually termed amyloid-β, or Aβ) (5). We now know that Aβ is one of more than 40 proteins that form pathogenic amyloid (2). Many years later, following the advent of electron microscopy, scientists discovered that the other telltale sign of the disease – tangled fibrils – were also a form of amyloid (in this case, hyperphosphorylated tau protein, or p-tau) (1). Once again, amyloid was everywhere. And now the question came into new focus: what actually caused the disease?

The role of Aβ rose to the fore when scientists discovered the gene for amyloid precursor protein (APP) on chromosome 21. It was already known that having three copies of chromosome 21 leads to Down syndrome – a condition in which 50% of individuals in their 60s will develop AD. Later work showed that mutations of APP and the proteins that process it (e.g. presenilin 1 and presenilin 2) all cause forms of autosomal dominantly inherited AD. These data offered clear proof that excess Aβ *could* play a key role in the pathogenesis of AD. But the proportion of cases caused by these mutations was actually relatively small.

While it was easy to view Aβ as pathogenic, it turns out that it plays a key role in healthy individuals (as a regulator of synaptic activity) (6). Moreover, the same thing appears to be true of p-tau – while it may be pathogenic when found in excess, it, too, is integral to healthy neuronal functioning (as a regulator of axonal integrity and axonal transport) (6).Thus, rather than identifying a pathological molecule, per se, research shifted towards trying to understand how these molecules are normally processed and what factors might disrupt the homeostatic balance.

In 1994, researchers found a clue in a seemingly unrelated process: autophagy. Autophagy is a highly regulated process that wraps cellular components in pockets of membrane filled with digestive enzymes (autophagosomes), and delivers them, neatly packaged and partially digested, to lysosomes for breakdown. Through this process, cells can degrade pathogens, protein aggregates, and even damaged organelles. This system may be used to help cells conserve energy in times of stress. It turns out that, among its many other functions,

autophagy also plays a crucial role in amyloid processing – and perhaps in AD (see Di Meco, et al. in the current issue (7)).

And here's where it gets complicated: under ordinary circumstances, autophagosomes bring APP, Aβ, and other amyloid products to the lysosome for destruction; at the same time, the autophagosomes may contain beta-secretase – thereby increasing the conversion of APP to Aβ (8). Both destruction and creation exist in balance — a delicate equilibrium. (For this reason, the system is sometimes referred to as the autophagy-lysosome-amyloid axis.)

Given the complexity of this pathway, small perturbations could have a significant impact. One new idea is the "traffic jam hypothesis" of AD (8). Several genetic risk factors (e.g. the gene *APOE*) are thought to impede the autophagosome's journey to the lysosome. This may lead to both decreased destruction *and*, by increasing the amount of time APP is exposed to beta-secretase, increased production of Aβ.

The same pathway may also help explain the connection between Aβ and p-tau pathology in AD. In normal homeostasis, autophagy regulates p-tau clearance. The disruption of autophagy (whatever the cause) could lead to an accumulation of p-tau. Once p-tau begins to accumulate it can lead to further disruption in autophagy, thus creating a positive feedback cycle. Meanwhile, as autophagy slows down, APP may become trapped in an environment that promotes its cleavage into pathologic Aβ. Essentially, once autophagy goes awry, the entire system can enter into a spiral that leads to the accumulation of misfolded protein aggregates and, ultimately, clinically appreciable disease.

The autophagy model may help answer why other treatment approaches for AD have come up short. In recent years, the most public trials have involved agents that try to decrease the burden of Aβ or p-tau (e.g. via targeted antibodies) (9, 10). Other strategies include trying to design small molecules that might inhibit the downstream toxicity of Aβ. One reason that these trials have not succeeded may be that they are targeting an end product of a disease pathway rather than the core pathological process.

If AD pathology starts with autophagy, could a cure start there as well? As promising as such an approach may seem, so far clinical trials with drugs thought to modulate autophagy have reported modest or no effect on AD. For example, memantine, a drug currently approved by the FDA to treat AD, has a stated mechanism of action via NMDA receptor antagonism but is also thought to alter autophagy. Many other drugs not currently approved for AD (e.g. the mood stabilizer lithium and the antiepileptic carbamazepine) have been studied because they activate autophagy – sadly, none has yielded positive results. While these findings are frustrating, they are only an initial foray into the field. The societal burden of AD demands our continued attention: researchers need to focus on the gaps in our knowledge and examine the places where our hypotheses break down. More than ever, we need to expand our search for novel therapeutic strategies.

When Virchow named amyloid after starch, he did not yet know about the lysosome or any other organelle. The concept of autophagy could not exist, since the light microscope guided research into whole cells, not organelles. Centuries later, we still cannot yet tell the tale of amyloid from start to finish and a cure for Alzheimer's disease remains out of reach. One

hope may be that with a new understanding of the amyloid-autophagy-lysosome axis, the next decade may produce answers we cannot yet imagine.

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