Novel way to diagnose Alzheimer's disease by blood analysis

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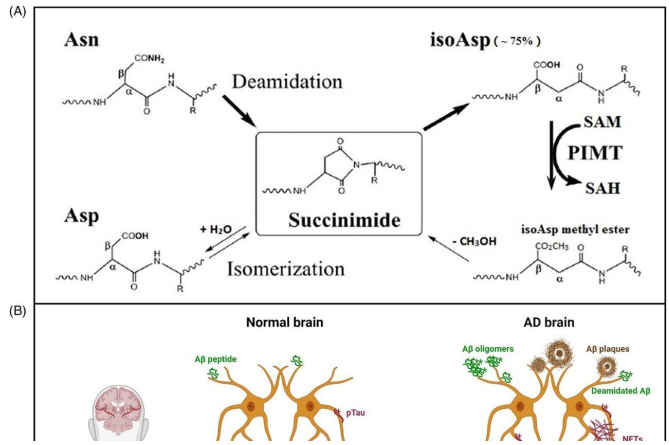

IsoAsp formation and the updated isoAsp hypothesis of AD. (A) Formation of isoAsp via succinimide intermediate by deamidation of Asn or isomerization of Asp residues, and its “repair” by the enzyme PIMT that methylates isoAsp using SAM as a methyl donor, converting it to SAH. Methylated isoAsp spontaneously loses a methanol molecule to become either normal l-Asp (in ?25% cases) or isoAsp again. (B) The updated isoAsp hypothesis of AD: A? peptide and p-tau protein produced in brain are cleared by passing via the blood-brain barrier and being carried by HSA to kidneys and liver. Spontaneously deamidated HSA is repaired in liver; failure of repair leads to HSA aggregation, with a lost ability to bind A? and p-tau. The anti-isoAsp antibodies remove deamidated HSA, and newly synthesized HSA molecules restore homeostasis. Due to a combination of insufficient repair and reduced removal of deamidated HSA, the diminished clearance of A? and p-tau causes their accumulation in brain, with the A? oligomers and ultimately plaques as well as neurofibrillary tangles formed, resulting in AD. Image was created via BioRender. Abbreviations: IsoAsp, isoaspartate; Asn, asparagine; Asp, aspartate; PIMT, l-isoaspartyl methyltransferase; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; AD, Alzheimer's disease; HSA, human serum albumin; A?, amyloid beta; p-tau, phosphorylated tau; NFTs, neurofibrillary tangles; Ab, antibody. Credit: *Alzheimer's & Dementia* (2022). DOI: 10.1002/alz.12735

Using proteomics and other advanced tools of molecular biology, an international team of researchers led by a group from Karolinska Institutet have found a novel way to diagnose Alzheimer's disease by blood analysis, with a potential to uncover the underlying cause of the disease and prevent its development.

When we age, so do proteins in our body, including long-lived proteins in our blood, such as albumin. One of the major manifestations of protein aging is the loss of ammonia, known as deamidation. As deamidation products accumulate, the protein molecule loses its structure, function and solubility, and starts aggregating.

The link between deamidation and neurodegeneration has long been postulated, but only now has decisive evidence been obtained. As discovered by an international group of researchers led by Roman Zubarev, MBB, development of Alzheimer's disease (AD) is not only associated with build-up of deamidated albumin, but also with diminished defenses against deamidation in form of natural deamidation-specific antibodies. As deamidation of blood proteins appears to precede all other damaging processes in AD, fighting its build-up may prevent neurodegeneration and prolong healthy life. The study is published in *Alzheimer's & Dementia*.

More information: Jijing Wang et al, Testing the link between isoaspartate and Alzheimer's disease etiology, *Alzheimer's & Dementia* (2022). DOI: 10.1002/alz.12735

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