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DIABETES

Peripheral Aβ linked to pathogenesis of T2DM

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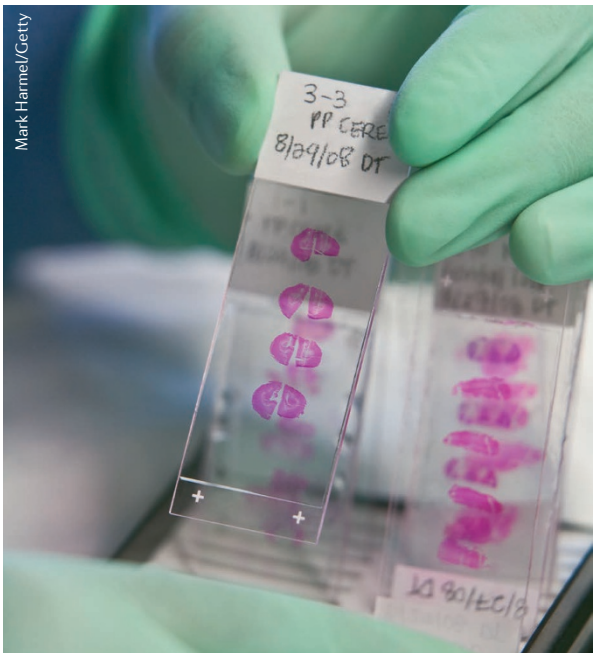
Epidemiological studies suggest that patients with type 2 diabetes mellitus (T2DM) are at increased risk of developing Alzheimer disease, but the mechanistic underpinnings of this relationship remain unclear. In a new study, Nadeeja Wijesekara and colleagues investigated the link between these two diseases in a novel double transgenic mouse model that expresses both human amyloid-β42 (Aβ42) and human islet amyloid polypeptide (IAPP).

Amyloid aggregation and deposition is a common pathology in patients with T2DM and in patients with Alzheimer disease. IAPP accumulates in islets of patients with T2DM, and Aβ42 forms insoluble plaques in the brains of patients with Alzheimer disease. In addition, T2DM and Alzheimer disease share many pathophysiological features, such as insulin resistance, inflammation and oxidative stress.



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"Studies that have previously examined the relationship between Alzheimer disease and T2DM have used Alzheimer disease-related murine models on a high-fat diet, on hyperlipidaemic genetic backgrounds or with acute models of streptozotocin-induced β-cell death," explains Wijesekara. "However, these models lack the presence of islet amyloid deposition because rodent IAPP does not aggregate."

To investigate the role of Aβ42 and IAPP in the interplay between Alzheimer disease and T2DM, Wijesekara and colleagues developed a novel mouse model that exhibits both neuronal and islet amyloid pathologies. The mice were created by crossing an Alzheimer disease-related human amyloid precursor protein transgenic mouse that has enhanced Aβ42 production with mice expressing β-cell-specific human IAPP. The authors reported that, compared with single transgenic Alzheimer disease or T2DM transgenic mouse models, the double transgenic mice were markedly more hyperglycaemic and glucose intolerant, and displayed exacerbated pancreatic and cerebral amyloid pathology, as well as increased synaptotoxicity.

Interestingly, the double transgenic mice also had Aβ42-mediated peripheral insulin resistance. The authors confirmed this finding by immunizing the double transgenic mice against Aβ42 and showing that immunized mice were not insulin resistant. In addition, Wijesekara and colleagues observed the co-deposition of Aβ42 and IAPP in islets of the double transgenic mice. The team believe these data show that Aβ42 might have a central role in the pathogenesis of T2DM. Finally, the islets of the double transgenic mice contained elevated levels of abnormally phosphorylated tau — a common pathology in the brains of patients with Alzheimer disease — highlighting another shared molecular mechanism between T2DM and Alzheimer disease.

"Our data suggest that peripheral Aβ42 could be a major factor contributing to the development of T2DM and that Aβ42 immunization might be a promising therapeutic strategy for improving glucose homeostasis in individuals who have elevated levels of peripheral Aβ42," concludes Wijesekara. "We now want to further elucidate the role of Aβ42 and tau in the periphery and continue to investigate the link between peripheral Aβ42 and neurodegeneration. Such studies could steer translational research in a direction that will be beneficial for both patients with Alzheimer disease and patients with T2DM."

Alan Morris

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