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Functional Medicine

QUOTE GM #14

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ON THE PATHOGENESIS OF ALZHEIMER'S DISEASE: THE MAM HYPOTHESIS

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On the Pathogenesis of Alzheimer's Disease: The MAM Hypothesis.

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Abstract

The pathogenesis of Alzheimer's disease (AD) is currently unclear and is the subject of much debate. The most widely accepted hypothesis designed to explain AD pathogenesis is the amyloid cascade, which invokes the accumulation of extracellular plaques and intracellular tangles as playing a fundamental role in the course and progression of the disease. However, besides plaques and tangles, other biochemical and morphological features are also present in AD, often manifesting early in the course of the disease before the accumulation of plaques and tangles. These include altered calcium, cholesterol, and phospholipid metabolism; altered mitochondrial dynamics; and reduced bioenergetic function. Notably, these other features of AD are associated with functions localized to a subdomain of the endoplasmic reticulum (ER), known as mitochondria-associated ER membranes (MAMs). The MAM region of the ER is a lipid raft-like domain closely apposed to mitochondria in such a way that the 2 organelles are able to communicate with each other, both physically and biochemically, thereby facilitating the functions of this region. We have found that MAM-localized functions are increased significantly in cellular and animal models of AD and in cells from patients with AD in a manner consistent with the biochemical findings noted above. Based on these and other observations, we propose that increased ER-mitochondrial apposition and perturbed MAM function lie at the heart of AD pathogenesis.-Area-Gomez, E., Schon, E. A. On the pathogenesis of Alzheimer's disease: the MAM hypothesis.

KEYWORDS: cholesterol; endoplasmic reticulum; lipid rafts; mitochondria; phospholipids

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