

In **Alzheimer's disease** (AD), **white matter degeneration** begins early, increases with disease progression, and contributes to cognitive impairment, yet the mechanisms are poorly understood.

Myelin loss impairs axonal function and its breakdown promotes **oxidative stress**, **inflammation**, and **lipid peroxidation**, further compromising the structure and function of **axons**. **Oligodendrocyte** dysfunction impairs homeostatic mechanisms needed to maintain myelin. Microvascular disease with **endothelial cell** pathology leads to thrombin activation and pro-inflammatory **cytokine** release, oxidative stress, and increased vascular permeability. Progressive fibrotic replacement of smooth muscle cells reduces vaso-responsiveness to metabolic demands. Fibrotic thickening of vessel walls narrows the lumens, rendering them more susceptible to occlusion, endothelial cell injury, and thrombin activation. Since normal physiological functions of oligodendrocytes and microvascular endothelial cells rely on intact **insulin**/insulin-like growth factor (**IGF**) signaling through cell survival, metabolic and anti-inflammatory pathways, conceivably, WM degeneration in AD is mediated by insulin and IGF resistance with attendant pathogenic targeting of **oligodendroglia** and **endothelial cells**. The **APOEε4** genotype may serve as a cofactor in AD-associated glial-vascular WM degeneration due to its role as a mediator of insulin resistance ¹⁾.

¹⁾

de la Monte SM, Grammas P. Insulin Resistance and Oligodendrocyte/Microvascular Endothelial Cell Dysfunction as Mediators of White Matter Degeneration in Alzheimer's Disease. In: Wisniewski T, editor. Alzheimer's Disease [Internet]. Brisbane (AU): Codon Publications; 2019 Dec 20. Chapter 8. Available from <http://www.ncbi.nlm.nih.gov/books/NBK552145/> PubMed PMID: 31895517.

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