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Pro-Inflammatory Cytokine Overproduction: A Contributor to Pathophysiology

Candidate for 2009 Zenith Fellows Award

The protein called p38alpha mitogen-activating protein kinase (p38alpha MAPK) has been shown to play a key role in brain inflammation. Research has found associations between this protein and the increased production of inflammation-related molecules called cytokines. However, little is known about how the association between p38alpha MAPK and cytokines may affect the progression of Alzheimer's disease, a disorder partly characterized by brain inflammation.

Linda Jo Van Eldik, Ph.D., and colleagues hypothesize that p38alpha MAPK contributes to both the brain inflammation and brain cell damage involved in Alzheimer's. In an earlier study with mice engineered to develop Alzheimer-like symptoms, the researchers found that a molecule called compound 069A could inhibit the activities of p38alpha MAPK. This treatment also moderated the overproduction of cytokines in the animals' brains, and it reduced the severity of brain damage. Specifically, the animals showed less damage to their synapses, the specialized junctions through which brain cells send and receive chemical messages.

For this grant, Dr. Van Eldik's team hopes to conduct a more thorough study to test how p38alpha MAPK is involved in brain disease. The researchers will use genetically engineered mice to compare the effects of p38alpha MAPK and a related molecule called p38beta MAPK on cytokine overproduction and synaptic damage. They expect to find that the p38alpha form is more closely associated with these pathologies than is the p38beta form. Dr. Van Eldik's group also hopes to verify that compound 069A can ameliorate brain inflammation and synaptic loss by inhibiting p38alpha MAPK activities. The findings of this study could shed new light on how Alzheimer's progresses, and they could lead to novel drug therapies for the disease.