Poster Presentation

MS16.P03

Structural Studies of TREM-2 Mutants Linked to Neurodegenerative Diseases

D. Kober[1,2], T. Brett[2]

[1]Washington University in St. Louis, Molecular Microbiology and Microbial Pathogenesis Program, St. Louis, USA, [2]Washington University in St. Louis, Department of Internal Medicine, St. Louis, USA

Triggering Receptor Expressed on Myeloid Cells-2 (TREM-2) is an extracellular surface protein expressed on myeloid cells of the monocyte/macrophage lineage including dendritic cells, macrophages, osteoclasts, and microglia. Recent genetic studies have revealed point mutations in TREM-2 that correlate with a dramatically increased risk for the development of neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia, and Parkinson's disease. This represents the first molecular link between inflammatory processes and neurodegenerative disease. TREM-2 modulates the innate immune inflammatory response; however, the biological ligand for TREM-2 remains elusive. As a first step towards understanding the role of TREM-2 in neurodegenerative disease, we have undertaken structural and biophysical studies of wild-type and mutant TREM-2 proteins. We developed a mammalian-cell based expression system for the successful production of TREM-2 in quantities suitable for structural studies. We have crystallized the TREM-2 Ig domain and determined the structure at 3.3 Å resolution. Analysis of this structure reveals the location of disease-linked mutations and produces hypotheses about their involvement in structural stability and ligand binding. In addition, we are studying the affect these mutations have on the stability of the protein using biochemical stability and surface expression assays. We are also pursuing structural studies of the point mutants to elucidate any structural changes caused by mutation. These studies are crucial to understanding the functional consequences of TREM-2 point mutations linked to the development of neurodegenerative diseases and, ultimately, to develop patient-specific molecular therapies to treat them.

Keywords: Alzheimer's Disease, Inflammation, Innate Immunity