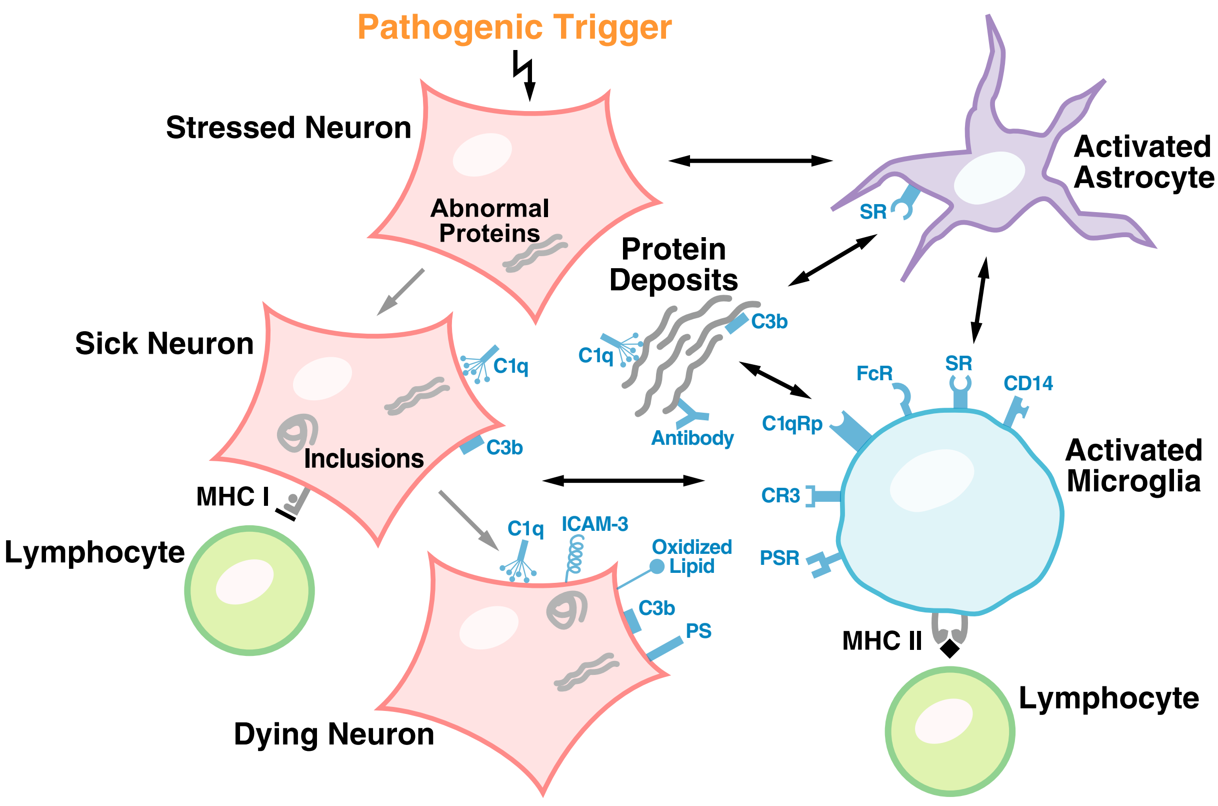
Inflammation and Alzheimer's Disease

The Gladstone Connection

Alzheimer's disease (AD), the most common dementia in the elderly, is characterized by a relentless loss of higher cognitive function. With the rapid increase of the aging population, industrial societies face a burgeoning epidemic of AD. The number of people with AD is predicted to triple in the next 50 years. Thus, there is an urgent need to further our understanding of AD pathogenesis and to identify novel therapeutic targets for treating this devastating disease. To find such targets, researchers at the Gladstone Institute of Neurological Disease focus on elucidating the mechanisms underlying AD.

In AD, the brain regions responsible for learning, memory, and emotional behaviors become severely damaged as a result of biochemical and structural changes resulting from the accumulation of abnormal proteins. Although the exact cause of AD is unknown, most studies of AD pathogenesis have focused on two pathological hallmarks, senile plaques and neurofibrillary tangles, both of which involve abnormal protein deposits. Senile plaques are extracellular deposits of beta amyloid (Aβ) peptides that result from



Some components of the inflammatory response to central nervous system (CNS) degeneration. Pathogenic triggers, such as accumulation of abnormal proteins in cells or extracellular spaces, elicit cellular stress responses and can result in progressive degeneration and eventual death of neurons. Many soluble factors are involved in promoting or inhibiting these processes. For example, cytokines and other mediators of the innate immune response are released by astrocytes and microglia to orchestrate defense mechanisms and initiate the removal or sequestration of the pathogenic triggers. Some of the molecules and receptors involved in the recognition of abnormal proteins and degenerating cells are illustrated. Receptors on glial cells recognize ligands and initiate inflammatory responses. C1qRp, C1q receptor for phagocytosis; CR3, complement receptor 3; FcR, Fc receptor; PSR, phosphatidyl serine receptor; SR, scavenger receptor.

the proteolytic cleavage of the amyloid precursor protein (APP). Neurofibrillary tangles are intracellular aggregates of an abnormal form of the microtubule-associated protein tau. Considerable evidence supports the hypothesis that Aβ accumulation in the brain triggers a complex pathological cascade leading to neuronal dysfunction and ultimately dementia.

Inflammation in AD

A key event in this cascade is an inflammatory response involving glial cells, a specialized type of injury-responsive brain cell. Normally, glial cells nourish and communicate with neurons. In AD brains, however, the accumulation of Aβ peptides and the presence of injured neurons appear to trigger glial cell activation and proliferation in an attempt to return the brain to a normal state. One type of glial cell, microglia, produce inflammatory cytokines that summon other immune cells into action. In addition, complement, a multiprotein network that is part of the immune system, is also activated.

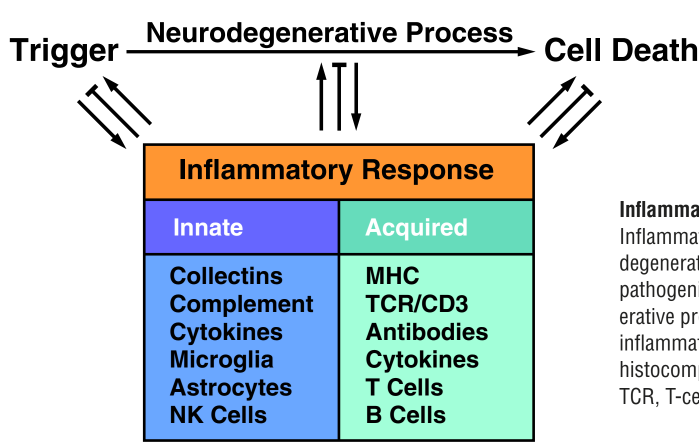
A Double-Edged Sword

What is the purpose of the inflammatory response? In many tissues, it is the body's first defense against infection. Most of the time, inflammation is a lifesaver. A complex combination of cells and secreted protein factors marshals a defensive attack against disease-causing bacteria, viruses, and parasites. However, if inflammation goes awry, it can lead to a host of diseases, including rheumatoid arthritis and ulcerative colitis.

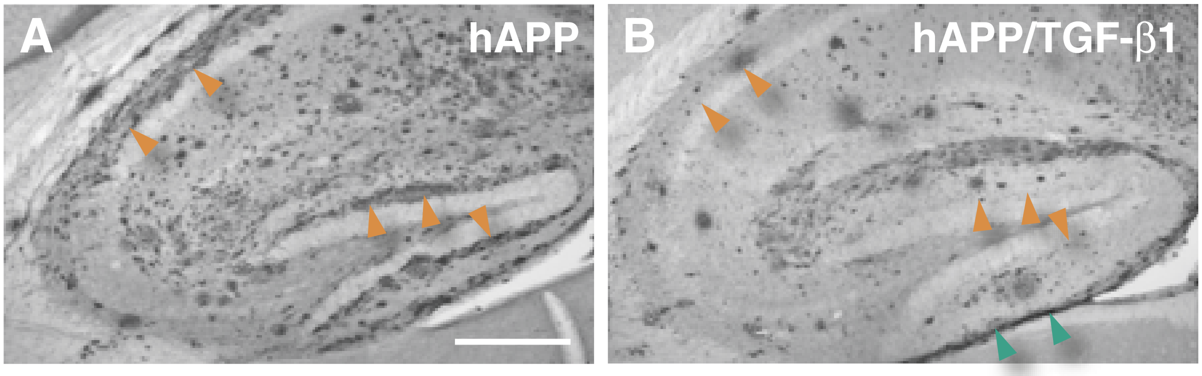
The inflammatory response triggered by the accumulation of Aβ may result in removal of Aβ aggregates and thereby decrease the harmful effects of chronic Aβ accumulation. For example, when aged transgenic mice expressing human APP were vaccinated with Aβ, the size and number of amyloid plaques were drastically reduced, possibly through phagocytosis by microglia. Clinical trials of Aβ immunization were halted because some patients developed meningoencephalitis, a pathological inflammation of the brain and the thin sheets of tissue that enwrap it. However, trials have now resumed after intensive efforts were made to design immunization regimens to avoid these detrimental side effects.

On the other hand, there also is evidence that Aβ-induced inflammation can damage the central nervous system. In cultured cells, Aβ stimulates microglia to release cytokines and other neurotoxic factors. Supporting the idea that chronic inflammation has a damaging effect in AD, nonsteroidal anti-inflammatory drugs such as ibuprofen appear to reduce the risk of developing the disease.

Because the inflammatory response can either promote or counteract the neurodegenerative processes in AD, it is critical to pinpoint its role in specific pathophysiological situations.



Inflammatory responses and neurodegeneration. Inflammatory responses associated with neurodegeneration are probably attempts to remove the pathogenic trigger and to inhibit the neurodegenerative process. However, uncontrolled or chronic inflammation may promote the process. MHC, major histocompatibility complexes; NK, natural killer; TCR, T-cell receptor; ↑, stimulation; ⊥, inhibition.



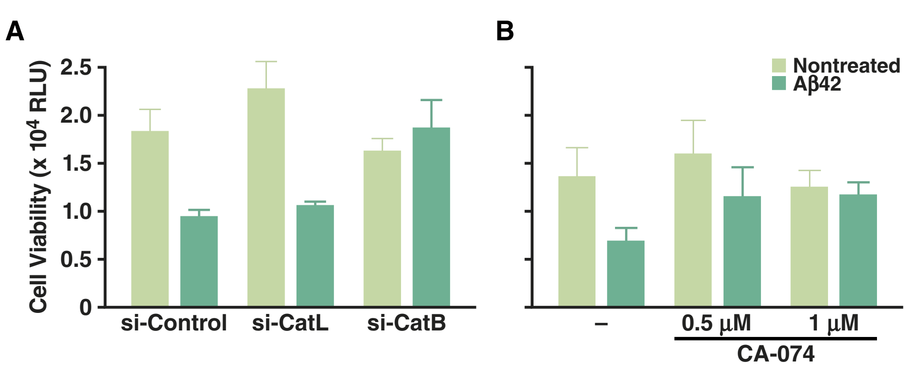
Change in distribution and overall decrease in Aβ deposits in human APP (hAPP)/TGF-β1 mice. Sagittal brain sections of mice transgenic for human APP (A) and hAPP/TGF-β1 (B) were immunostained for human Aβ deposition, and antibody binding was visualized with the immunoperoxidase method. Aβ deposition in the hippocampal stratum oriens and in the molecular layer of the dentate gyrus (orange arrowheads) is much more prominent in the hAPP brain (A) than in the hAPP/TGF-β1 brain (B). The latter showed dense staining in the hippocampal fissure and the meninges (green arrowheads). Scale bar indicates 500 mm (A and B).

TGF-β1 and the Clearance of Aβ

Dr. Lennart Mucke and his colleagues have unraveled how transforming growth factor β1 (TGF-β1), a key cytokine regulator of the brain's responses to injury and inflammation, promotes the removal of Aβ aggregates. In transgenic mouse models overexpressing human APP and carrying mutations linked to familial AD, elevated production of TGF-β1 reduced the number of amyloid plaques by 67% and the overall Aβ load by 50%, and also decreased the number of plaque-associated distortions of neuronal branches called neuritic dystrophy. Plaque reduction in these mice was associated with a strong activation of microglia and an increase in inflammatory mediators. In cell culture, recombinant TGF-β1 directly promoted Aβ clearance by microglia. These findings provide strong evidence that TGF-β1-associated microglial activation may play a beneficial role by reducing the accumulation of Aβ in the brain.

Cathepsin B and Aβ Toxicity

Focusing on the interaction of microglia and Aβ, Dr. Li Gan and her colleagues showed that cathepsin B, an enzyme released from microglia, is essential for neuronal death resulting from the reaction of microglia to Aβ. When cathepsin B expression was inhibited, this form of neuronal death was abolished. What is more, a highly specific pharmacological inhibitor of extracellular cathepsin B also protected neurons from Aβ toxicity.



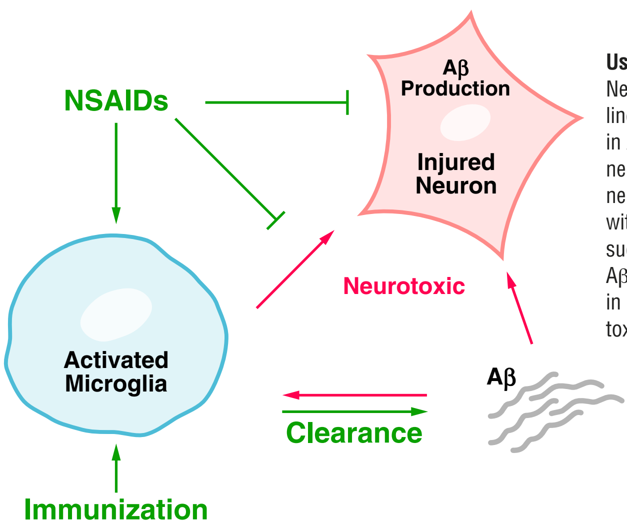
Cathepsin B may have a key role in mediating the toxic effects of Aβ. Aβ causes microglial cells to secrete factors that are toxic to neurons. (A) Small interfering (si) RNAs were used to inhibit cathepsin B or cathepsin L expression in microglia. Cathepsin B siRNA resulted in greater protection from the toxic factors than did cathepsin L or control siRNA. (B) Inhibiting microglial cathepsin B activity with the cathepsin B inhibitor CA-074 at concentrations of 0.5 μM and 1 μM protected neurons from the toxic effects of factors secreted from microglia.

Active cathepsin B has been observed in association with neuritic plaques in AD brains. Cathepsin B can degrade a variety of extracellular matrix proteins and associated signal transduction molecules, thereby triggering apoptosis (“programmed” cell death) and contributing to neuronal and synaptic loss in AD.

Interestingly, extracellular cathepsin B has been implicated in various diseases involving tissue-remodeling states, such as rheumatoid arthritis and tumor metastasis. Potent cathepsin B inhibitors were developed to target those devastating diseases. Studies by Dr. Gan and her colleagues suggest that these agents may also have therapeutic value for AD.

Future Studies

Chronic inflammation has emerged as a clear pathological hallmark of AD. While some inflammatory responses can damage the brain, others have potent beneficial effects. A better understanding of specific molecular pathways in activated glial cells may help reconcile the apparently contradictory outcomes of inflammatory responses. By dissecting the pathways that lead to beneficial or damaging outcomes, Gladstone scientists hope to learn how to direct the inflammatory machinery to exert only beneficial functions. These studies will provide the basis for the development of better therapies for AD patients and contribute to ending the scourge of AD and possibly other diseases.



Using the inflammatory response against AD. Neurotoxic assemblies of Aβ peptides (gray wavy lines) presumably injure neurons and activate glia in AD brains. While some glial products can be neurotoxic, other glial products and activities protect neurons and help remove Aβ aggregates. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, or vaccination with Aβ may promote beneficial glial activities (depicted in green) and inhibit detrimental effects such as Aβ toxicity in the brain (depicted in red).