Published in final edited form as:

Clin Neurosci Res. 2006 December ; 6(5): 225.

INTRODUCTION: Immune mechanisms of neurodegeneration

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While inflammation is well established as a primary mechanism in diseases such as multiple sclerosis, recent work has shown that inflammation may also contribute to several other types of neurological disorders. While inflammatory infiltrates have long been observed in conditions such as brain injury and ischemia, neurodegenerative diseases such as Alzheimer's and Parkinson's diseases are now recognized to have an immune component as well. The significance of this inflammatory response was not widely appreciated until recently, when anti-inflammatory treatment strategies, mostly at laboratory level, were recognized to be effective interventions.

Peripheral immune cells, primarily leukocytes, are known to accumulate in the injured central nervous system under conditions of ischemia or trauma where the blood brain barrier is disrupted. An endogenous inflammatory response, characterized by activated microglia, is also present in these disorders, as well as in several neurodegenerative diseases. There is now a substantial body of work indicating that both exogenous and endogenous immune responses can exacerbate central nervous system injury in these conditions. The immune system, while involved in protecting the organism from invading pathogens, is also thought to be a means by which organs, including the brain, can recover and regenerate after various noninfectious insults by eliminating necrotic debris or unnecessary material and supporting regeneration. However, under certain circumstances, it is clear that inflammation can also cause significant tissue damage and inhibit recovery including neurogenesis. In support of this concept, several studies suggest that preventing peripheral inflammatory cell infiltration or activation of endogenous microglia can reduce neurological damage. Such has been the case in studies of experimental Alzheimer's disease, Parkinson's disease, stroke, and trauma.

This endogenous immune response may also be mediated through astrocytes, which are being increasingly recognized as being capable of functions similar to that of more conventional immune cells. Even neurons in certain settings have been documented to generate immune mediators such as inflammatory cytokines. Such observations have led to the study of immune modulating therapies for diseases not typically thought of as inflammatory.

It is also possible that certain anti-inflammatory environments can limit certain beneficial effects of inflammation such repair and debris clearance. Recent work has shown that part of the degenerative process in Alzheimer's disease is due to an impaired clearance of amyloid, and microglia in some model systems actually seem to support neuron survival. A further layer of complexity is posed by the concept of microglial activation, now seen to encompass several different functional states. Recent work also suggests the existence of different populations of microglia with differing reparative or destructive properties. It is clear that this field is still in

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its infancy, and many questions remain. Is all neuroinflammation necessarily “bad”, and if not, when is it “good”? Do the trophic versus damaging functions of inflammatory cells change with the acuity or timecourse of the disease? How do various cell populations interact under disease conditions? In this issue, we review the current state of knowledge with regard to immune responses and how they may participate in a variety of neurodegenerative diseases. We also discuss the various therapeutic strategies employed both in the laboratory and at the clinical level.