

Interplay between Inflammation and Degeneration: Using Inclusion Body Myositis to Study “Neuroinflammation”

In primary inflammatory or autoimmune neurological disorders, such as primary or secondary progressive multiple sclerosis and chronic inflammatory neuropathies and myopathies, the chronic persistent inflammation leads to degeneration and irreversible cell loss. In other disorders considered neurodegenerative, such as Alzheimer's disease or amyotrophic lateral sclerosis, there is “neuroinflammation” characterized by gliosis, macrophage activation, and cytokine upregulation. Although in most of these conditions inflammatory mediators coexist even from the outset with cell stress and degeneration, the interrelationship between inflammatory and degeneration-associated molecules has not been studied *in vivo*, and the clinically relevant markers connected with disease progression remain unclear.

Perhaps one of the typical human neurological disorders in which inflammation and degeneration coexist from the outset is inclusion body myositis (IBM), the most common acquired myopathy for individuals older than 50 years.^{1–3} The muscles of IBM patients have the following characteristics: (1) clonal expansion of CD8⁺ cells that invade major histocompatibility complex class I (MHC-I)–expressing muscle fibers; (2) persistent upregulation of cytokines, chemokines, adhesion molecules, and MHC-I, which induces cell stress; (3) vacuolization; (4) mitochondrial and nuclear abnormalities; (5) promiscuous deposits of degeneration-associated molecules, identical to those seen in Alzheimer's disease, such as β -amyloid, tau, ubiquitin, presenilin, α -synuclein, and apolipoprotein E; and (6) involvement of the ubiquitin-proteasome system, including the disposal of unwanted proteins by macroautophagy, as seen in neurodegenerative disorders.⁴ Because of these features, the IBM muscle is a useful tool to investigate *in vivo* the interplay between inflammatory and degenerative molecules.

Toward this goal, Kitazawa and colleagues' study⁵ is a significant contribution that complements recent work from our laboratory.⁶ Using an IBM-transgenic mouse model, the authors found that acute and chronic inflammation induced by lipopolysaccharide (LPS) increased the steady-state level of amyloid precursor protein and phosphorylated tau in skeletal muscle by inducing glycogen synthase kinase-3 β (GSK-3 β), a tau kinase. The cytokines interleukin-1 β , interleukin-6, and tumor necrosis factor- α upregulated

GSK-3 β , whereas antibodies against them effectively attenuated the inflammation-induced tau phosphorylation. The GSK inhibitor, lithium, had a similar effect. The authors conclude that suppression of inflammation in IBM may slow disease progression. The findings are interesting and support previous studies^{1,6,7} even though they are only indirectly related to human IBM for several reasons. First, the MCK-amyloid precursor protein mouse is not a satisfactory IBM model because the muscles have atypical histology, no inflammation, and minimal weakness; second, lipopolysaccharide is an artificial and transient inflammatory inducer; and third, the myofibers in MCK-amyloid precursor protein mice express MHC-I only transiently after lipopolysaccharide administration. These limitations do not, however, diminish the impact of Kitazawa and colleagues' observations.⁵ To the contrary, the mice offer a strong glimpse on the magnitude of alterations occurring in the human muscle where inflammation is profound, MHC-upregulation persistent, vacuolization prominent, and β -amyloid deposition pronounced.

The scholars in the field of IBM are divided into two camps; one believes that inflammation is the primary culprit and liken the disease to primary progressive multiple sclerosis, which, like IBM, does not respond to immunotherapies^{1,7}; the other considers the disease degenerative² and the inflammation secondary to accumulation of β -amyloid–driven molecules, one of which may be driving antigen-specific T cells. We have favored the autoimmune hypothesis for the following reasons: (1) IBM is frequently seen with autoimmune disorders and increasingly with human immunodeficiency virus and Human T cell Lymphotropic Virus infection^{1,7,8}; (2) T-cell invasion of nonnecrotic fibers is found early and in greater frequency than the Congo red–positive fibers⁹; (3) the cytotoxic T cells, at the immunological synapses, do not recognize amyloid-related proteins as antigens; (4) the cytokine-induced upregulation of MHC-I occurs early and is capable of triggering cell stress and degeneration;^{1,11} and (5) cytokines, especially IL1 β , can induce amyloid aggregates (6). Most importantly, endomysial inflammation alone can cause muscle destruction and clinical weakness, as seen in polymyositis; whether the tiny β -amyloid deposits are sufficient alone to trigger muscle degenera-

Proposed Mechanisms linking Degeneration with Inflammation

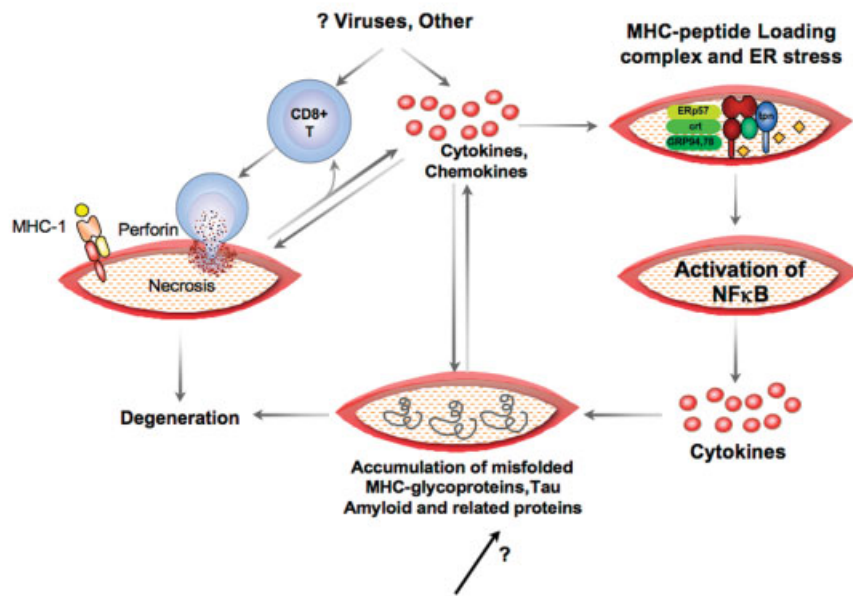


Fig. Proposed mechanism on the interplay between inflammation and degeneration in inclusion body myositis (IBM). Viral or inflammatory triggers lead to clonal expansion of CD8⁺ T cells and T-cell-mediated cytotoxicity via the perforin pathway. The released cytokines upregulate major histocompatibility complex (MHC) class I molecules and increase levels of the MHC-peptide loading complex, because the abundance of generated peptides cannot be conformationally assembled with the MHC to exit the endoplasmic reticulum (ER).¹ As a result, there is an ER stress response, which leads to activation of the transcription factor nuclear factor-κB (NF-κB) and further cytokine release with subsequent accumulation of misfolded MHC glycoproteins, including phosphorylated tau and amyloid-related proteins.¹ Regardless of whether the primary triggering event is inflammation or protein dysregulation, the released cytokines released during this process, even from the stimulated muscle fibers themselves, are in concert with the accumulated misfolded proteins in a self-sustaining inflammatory and degenerative process that promotes the expression of inflammatory and degenerative molecules. crt, calreticulin; ERp57, glucose-regulated protein, 58kDa; GRP78, glucose-regulated protein, 78kDa; GRP94, glucose-regulated protein, 94kDa; tpn, tapasin.

tion in humans remains unclear especially because the same molecules accumulate in various vacuolar myopathies and muscular dystrophies caused by genetic mutations,^{12–14} whereas in other conditions, these deposits appear innocuous.^{15,16} Regardless of whether the primary event is a disimmune or protein dysregulation process, these two new studies^{5,6} provide strong evidence that in IBM proinflammatory cytokines not only correlate with the intramuscular accumulation of amyloid, phosphorylated tau, ubiquitin, and αB-crystallin,⁶ but also induce tau phosphorylation and amyloid aggregates. Cytokines also stimulate myofibers to produce inflammatory mediators in an autoamplificatory mechanism, enhancing further the chronicity of inflammation, amyloid formation, and cell stress (Fig).

At the translational level, these interrelationships can generate novel therapies. Kitazawa and colleagues⁵ tried lithium, a drug increasingly explored as a neuroprotective agent, because it can modulate tau phosphorylation or amyloid processing. The results, although disappointing in their IBM model, were informative. Lithium inhibited tau phosphorylation, a downstream

event, but did not significantly affect the motor function of the treated animals and had no effect on interleukin-1β or the intramuscular production of Aβ-amyloid, suggesting that amyloid formation and inflammation occur upstream to tau pathology. Treatment with anti-cytokine antibodies also attenuated tau phosphorylation,⁵ but their long-term effect on amyloid production was not studied.

IBM is a complex and disabling disorder. There is an urgent need for new trials to stop disease progression. Understanding the molecules that drive muscle degeneration is not an easy task. The aforementioned interrelationships, however, make IBM an ideal model to study “neuroinflammation” and examine serially in vivo the clinical importance of the main players driving inflammation and degeneration. Because effective anti-degenerative agents as treatment options are not in the offing, focusing on antiinflammatory mediators is more realistic. The results from the trial with alemtuzumab, a T-cell-depleting monoclonal antibody against CD52, in the treatment of IBM patients, support this view.¹⁷ Alemtuzumab significantly reversed disease progression,

improved the strength of some patients, and reduced the inflammatory and degeneration-associated molecules in the patients' muscles.¹⁷ The observations are encouraging and necessitate further study. In Alzheimer's disease, intravenous immunoglobulin suppressed β -amyloid and improved cognition,¹⁸ prompting a large National Institutes of Health-sponsored trial. A subset of new non-steroidal anti-inflammatory drugs are potent modulators of γ -secretase, reducing amyloid production.¹⁹ Although using novel antiinflammatory agents to stop degeneration is a reasonable way to proceed at least for now, the future will tell whether we are following the right path.

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