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Sporadic inclusion body myositis: evidence of a link between inflammation, cell stress and β -amyloid deposition

Frank Mastaglia

Sporadic inclusion body myositis (sIBM) is the most important muscle disease associated with aging which is usually unresponsive to treatment and results in progressive disability with a selective pattern of muscle wasting and weakness of the quadriceps and forearm muscles.^{1,2} There has been longstanding debate as to whether sIBM is a primary inflammatory myopathy or a myodegenerative disorder with secondary inflammation. The relationship between the T cell predominant inflammatory response which tends to predominate in the earlier stages of the disease and the myofibre degeneration and amyloid deposits which become more prominent as the disease progresses remains uncertain.¹⁻³ The study by Muth *et al*⁴ (see page 1344) has provided the most convincing evidence yet linking the amyloid deposition and vacuolar degeneration of myofibres to the inflammatory milieu in the muscle and a state of cell stress. Using immunohistochemical techniques they have shown very elegantly that in sIBM biopsies the cell stress protein α B-crystallin and the amyloid

precursor protein (APP) are co-expressed in muscle fibres, together with major histocompatibility complex I and other molecular markers of degeneration and regeneration (neural cell adhesion molecule and desmin), even before the fibres show β -amyloid deposits and other overt degenerative changes such as rimmed vacuole formation, and even in fibres which are not invaded by inflammatory cells. While this observation per se does not necessarily exclude an endogenous derangement as the cause of cell stress and presentation of antigenic peptides to the immune system, the in vitro experiments which they also performed, showing that exposure of human myotubes to the cytokines interleukin 1β and interferon γ leads to co-expression of α B-crystallin and APP, favours the view that the changes found in biopsies could also be due to the effects of inflammatory mediators. Their findings therefore support the view that the primary process in sIBM is inflammatory and are in keeping with various other lines of evidence which point to sIBM being a primary autoimmune disease of muscle.¹⁻⁵

The findings of Muth and colleagues⁴ are particularly important as they provide further impetus to the search for more effective therapeutic agents to control the dysimmune process in sIBM. Although the majority of cases of sIBM fail to

respond to treatment with glucocorticoids and other conventional immunosuppressive agents, this does not necessarily diminish the importance of the immune process in the pathogenesis of the disease but may simply reflect the inadequacy of current therapies and the need to find other therapeutic targets. To date, cytokine based therapies such as β -interferon and tumour necrosis factor α inhibitors have not proved to be effective. However, of greater promise are approaches targeting T cells, such as anti-CD52 (alemtuzumab) which has recently been reported to reduce muscle inflammation and expression of α B-crystallin and other cell stress molecules, with improvement in muscle function and slowing of disease progression.⁶

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