LETTER TO THE EDITOR

Comment on ‘Interrelation of inflammation and APP in sIBM: IL-1β induces accumulation of β-amyloid in skeletal muscle’

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Sir, Dr Schmidt and colleagues report that in muscle from patients with inclusion body myositis (IBM) there is a correlation between measures of inflammation and ‘β-amyloid-associated degeneration’ (Schmidt et al., 2008). They found that the number of immune system cells visible in hematoxylin/eosin stained muscle sections and the amount of certain transcripts produced by immune cells correlated with the abundance of β-amyloid precursor protein (APP) transcript. These and other data are interpreted as supporting an hypothesis suggested a decade ago in which in IBM muscle, interleukin-1-beta (IL-1β) secreted by immune system cells results in APP production by myofibres, and APP production by myofibres results in IL-1β secretion by immune cells (Dalakas, 1998). This hypothesis is expanded here to one in which other inflammatory molecules, such as interferon-gamma (IFN-γ), also result in APP and β-amyloid production by myofibres.

What should be considered in the interpretation of these results is the previously published data that immune cells produce abundant APP transcript and produce and secrete APP protein (Monning et al., 1990; Monning et al., 1992; Schlossmacher et al., 1992; Schubert et al., 1993; Askanas et al., 1995; Schubert et al., 1997; Suh et al., 1997). A correlation between the abundance of immune system cells and immune system transcripts in muscle with the amount of APP transcript would be expected simply because APP transcript is produced and carried into muscle by the very same immune cells producing the other immune transcripts.

The authors also report in the Discussion that not in PM or DM but only in sIBM, there was a significant and consistent correlation between the mRNA expression of β-amyloid-associated molecules and the major inflammatory markers. Actually, the PM data show a high correlation between APP transcript and inflammatory cell numbers and transcripts after a single outlier is removed.

The Supplementary Figure shows removal of this outlier; for the grade of inflammation correlation with APP transcript abundance, the Pearson correlation coefficient for all PM samples graphed is −0.19 (P = 0.56) in FIGURE 3A, but after removal of one outlier, it is 0.69 (P = 0.02) in the Supplementary Figure. Similarly, the correlation of IL-1β and APP transcript abundance is −0.08 (P = 0.81) for all PM samples but after removal of one outlier, the correlation is 0.75 (P = 0.007). The IL-1β transcript correlation with APP is in fact significant only for PM, after removal of the outlier, and not for IBM (P = 0.16). The authors report in the Results that ‘after removal of outliers, there was a significant correlation in the group of PM-patients between the mRNA-expression of APP and the grade of inflammation and the mRNA-expression of IL-1β’. The high correlation of APP transcript with inflammatory cells and transcripts present in PM weakens the hypothesis that the same relationship present in IBM relates to β-amyloid-mediated myofibre degeneration, given such degeneration is not hypothesized to occur in PM.

Lastly, the investigators state that a ‘hallmark of sIBM is accumulation of aberrant molecules, most of all β-amyloid, within the myofibres’. The claim that β-amyloid accumulates in IBM myofibres has been directly contradicted in published articles by three independent laboratories studying a combined 35 patients with IBM. These studies found no immunohistochemical evidence for the presence of either APP or β-amyloid protein in any myofibres in 28 of these patients and found five or less affected myofibres in each of the remaining seven patients (Leclerc et al., 1993; Nalbantoglu et al., 1994; Sherriff et al., 1995). One of these laboratories found immunoreactivity that remained after pre-absorption of antibody by synthetic β-amyloid, concluding that some anti-β-amyloid antibodies that have been interpreted as showing β-amyloid presence immunostain diseased muscle non-specifically (Sherriff et al., 1995). Dr Schmidt and colleagues...
found that APP transcript abundance was even higher in dermatomyositis muscle than in IBM muscle, in agreement with previous reports that APP transcript and protein are abnormally increased in myofibres (called ‘regenerating’ based on their staining for desmin) in a wide range of muscle diseases other than IBM (in 29 and 43 patients in six and seven disease categories) (Sarkozy et al., 1994; Askanas et al., 1995). In the current study by Dr Schmidt and colleagues, β-amyloid was reported present in 15.3% of IBM myofibres. However, the 6E10 antibody used and interpreted as reactive to β-amyloid reacts to APP as well (confirmed in western blot experiments shown in Figure 2 from Howland et al. (1998) and Figure 7b from Wojcik et al. (2007)), as the β-amyloid peptide sequence is a subsequence of APP. It therefore seems uncertain as to whether any β-amyloid protein is being seen in IBM myofibres in these experiments. More generally, given that no western blot study of IBM muscle demonstrating a 4 kDa band (the approximate mass of β-amyloid) immunoreactive with any anti-β-amyloid antibody has ever been published, together with multiple immunohistochemical studies that have failed to see β-amyloid in IBM muscle and the inability of any antibodies that have been used to discriminate β-amyloid from APP, it is important to consider the possibility that no β-amyloid protein has ever been demonstrated in any IBM patient muscle sample, let alone demonstration that its presence is disease specific. These issues should be kept in mind with regard to the view that the accumulation of β-amyloid is an IBM ‘hallmark’.

References


