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Activation of autophagy and suspended apoptosis in skeletal muscle of inclusion body myositis

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Inclusion Body Myositis (IBM) is characterized by rimmed vacuole formation and misfolded protein accumulation, both depending on lysosome dysfunction. In skeletal muscle, selective protein degradation is allowed by macroautophagy. A proper balance in degradation and accumulation of proteins and organelles is critical for cell survival. Extracellular signal-regulated protein kinase (ERK1/2) is essential in cell survival, but recent evidence suggests that it is also necessary for autophagy. Alteration in subcellular localization of ERK promotes cell death either via autophagic death or via apoptosis upstream caspase-3. Moreover, in IBM myocytes there is no convincing evidence for apoptosis. Here, we correlated the expression level of autophagic and apoptotic molecules with that of ERK2 by analysing, with immunohistochemistry (IHC) and western blot (WB) methods, immunolocalization and expression of a panel of molecules directly involved and/or associated with the disease histopathogenesis: coated vesicles protein clathrin, mannose-6-phosphate receptor (M6PR), autophagy related proteins Beclin1 and ATG5, microtubule associated protein light chain LC3a and LC3b, Apoptotic Protease Activating Factor 1 (APAF1), Caspase-3, ERK2, and the specific IBM marker SMI31. Muscle biopsy specimens were obtained from 10 patients with sporadic IBM, 1 familial IBM patient, 1 amyotrophic lateral sclerosis patient, 1 patient with polymyositis with prominent mitochondrial pathology and 9 non myophatic patients as control specimens. IHC studies of expression and colocalization revealed an increase of clathrin, Beclin1, ATG5, and LC3 immunoreactivity, mainly observed in the sarcoplasm of small, atrophic fibres in all diseased specimens compared to controls. By WB analysis, expression level of both APAF1 and Caspase-3 did not significantly change between patients and controls, whereas the level of expression of ERK2 and autophagy markers seemed to inversely correlate. The results demonstrated that transport of newly synthesized lysosome enzymes and formation of autophagic vacuoles are both activated in IBM muscle. ERK2 phosphorylating activity is probably involved in rescue attempt to overcome the cell injury rather than directly stimulating the cell death. During IBM, the apoptotic cascade seems to be suspended, however,under the effect of cytotoxic stimuli, protective autophagy may switch to autophagic programmed cell death.

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