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DEFECTIVE SIGNALING PATHWAYS IN VCP ASSOCIATED INCLUSION BODY MYOPATHY (IBMPFD)

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Purpose of Study: Inclusion body myopathy associated with Paget's disease of the bone and frontotemporal dementia (IBMPFD) is caused by mutations in the Valosin Containing Protein (VCP) gene resulting in progressive muscle weakness, malfunction in the bone remodeling, and premature frontotemporal dementia. The purpose of our study was to clarify molecular and cellular consequences of VCP mutations in patients' and control subjects' primary myoblasts and muscle tissues.

Methods Used: Western blotting, immunocytochemistry, microarray, qRTPCR, pathway analyses.

Summary of Results: Patients' myoblasts accumulated large vacuoles that were able to fuse with lysosomes. Lysosomal membrane proteins Lamp1 and Lamp2 were defectively N-glycosylated in patients' myoblasts, and the maturation processes were affected. Additionally, mutant myoblasts demonstrated increased autophagy and apoptosis. Expression profiling revealed that 279 genes were differentially expressed in patients' muscle ($p < 0.001$). Down-regulation of Platelet-Derived Growth Factor Receptor Alpha (PDGFR-α, –7.5x) was specific to IBMPFD when compared to other muscle dystrophies. This finding was confirmed by qRT-PCR and Western blotting.

Conclusions: Our findings suggest that patients' myoblasts and muscle biopsies can be used to clarify the molecular pathogenesis of IBMPFD. Additionally, PDGFR-α may play a role in the development of progressive muscle pathology in IBMPFD patients. Affected PDGFR-α signaling may alsoresult in defective autophagy and accumulation of storage material in patients' cells. This may be associated with increased apoptosis and defective myotube formation, which eventually result in muscle weakness in IBMPFD patients.