Sporadic inclusion body myositis (sIBM) is the most prevalent muscle wasting disorder in the elderly with unknown etiology. Endoplasmic reticulum stress and abnormal deposition of Myostatin precursor protein MstnPP and amyloid precursor protein APP or metabolites thereof have been implicated in disease pathology. Here, the aggregation states and cellular effects of overexpressed MstnPP and APP in a human muscle cell line were systematically analyzed. It was found that ectopic expression of both MstnPP and APP induced endoplasmic reticulum (ER) stress. Overexpressed MstnPP but not APP metabolites were predominantly retained within the ER. Biochemical analysis revealed that the proteolytic fragments of MstnPP, which are pro-Mstn and inhibitory propeptide, formed insoluble aggregates that were increased upon experimentally induced ER stress. Importantly, ER stress also impaired secretion of pro-Mstn and Mstn growth factor. These findings support the hypothesis that a vicious cycle of accelerated ER stress and MstnPP metabolite aggregation contribute to sIBM progression. Moreover, these data suggest that increased expression of MstnPP does not necessarily correlate with increased secretion of Mstn growth factor.