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ER Stress Impairs Myogenic Cell Growth By Inhibiting Amino Acid Activation Of mTORC1

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PURPOSE: To test whether endoplasmic reticulum (ER) stress impairs the response to growth factors and leucine in muscle cells. METHODS: C2C12 muscle cells were grown and fully differentiated into myotubes. After 4 days of differentiation, tunicamycin (TN) or thapsigargin (TG), known inducers of ER stress, were added for 17h before stimulation of the mTORC1 pathway with insulin or IGF-1 (10-50nM) for 15min or leucine (2.5-5mM) for 30min. Cells were harvested for mRNA or protein expression analyses or used for leucine uptake measurements. RESULTS: TN (0-5000ng/ml) and TG (0-2000nM) induced ER stress in a dose-dependent manner. At the end of the 17h-incubation, BiP and IRE1 expression and PERK and eIF2· phosphorylation were increased proportionally to TN and TG concentrations. At the same time, TN and TG repressed basal phosphorylation of PKB and S6K1. Growth factor-induction of PKB was repressed by low and high concentrations of TN but only by high concentrations of TG. Leucine-induction of S6K1 was repressed by low concentrations of both TN and TG. Leucine-induction of S6K1 was repressed at lower TG concentrations than growth factor-induction, indicating that TG inhibits leucine and growth factors activation of mTORC1 by different means. The activation/amount of several targets known to inhibit the mTORC1 pathway was determined. TN and TG did not change the phosphorylation state of AMPK or JNK. Both increased TRB3 mRNA expression and only TG increased REDD1 mRNA. TN and TG decreased the basal phosphorylation state of PRAS40. Interestingly, neither TN nor TG prevented the activation of PRAS40 by insulin. In contrast, PRAS40 phosphorylation did not increase with amino acids and TN and TG treatment further reduced its phosphorylation. Since non-phosphorylated PRAS40 inhibits mTORC1, this could impair downstream signaling by the mTORC1 complex. Finally the inhibition of leucine-induced phosphorylation of S6K1 could not be explained by a reduced entry of leucine into the cells as leucine uptake tended to increase with TN and TG. In summary, these data indicate that inhibition of PRAS40 by TN and TG could result in impaired activation of mTORC1 in response to leucine. CONCLUSIONS: TN and TG repressed the activation of mTORC1 by leucine and growth factors in muscle cells. As ER stress is triggered by high-fat feeding in skeletal muscle, we speculate that ER stress could be one mechanism impairing the response to load-induced hypertrophy in high-fat fed models.