*TACSM Abstract*

# DEPTOR Expression Correlates with Muscle Protein Synthesis

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Mammalian target of rapamycin (mTOR) has long been declared a focal point of muscle protein synthesis. mTORC1 (an mTOR complex consisting of mTOR, raptor, PRAS40, and mLST8) has been associated with regulation of protein translation in muscle, altering expression and activity levels of key downstream targets S6K1 and eIF-4E-BP1. mTORC1 has been shown to be affected by various stimuli, including nutritional status, growth factors, and mechanical loading. But in past incidents we have found disconnects in muscle protein synthesis and mTOR signaling, stimulating discussions that mTOR content and activation alone may not be able to fully account for muscle protein synthesis. Gaining popularity as a target for anti-cancer therapies, we became interested in DEPTOR, an endogenous inhibitor of mTORC1. Pharmacological inhibition of DEPTOR in cell culture and mouse studies has displayed increases of anabolic signaling in response to atrophic circumstances. We present two unique catabolic conditions in which we explore DEPTOR expression and muscle protein synthesis and demonstrate the first known data proposing that DEPTOR expression is not only influenced by physiological stimuli, including mechanical loading and insulin sensitivity, but that DEPTOR expression strongly correlates with 24-hr cumulative muscle protein synthesis rates.

In one study, male Sprague Dawley rats were subjected to various conditions of musculoskeletal unloading, reloading, and overload, in which hindlimb unloading (HU) was utilized to mimic chronic disuse atrophy (28-d), followed by ambulatory reloading (56-d post HU) with and without the addition of resistance exercise prescribed to assist in recovery (3 sessions/wk for 7-wks; progressive increases in added resistance up to ~60% BW). DEPTOR expression was assessed via Immunoblotting. 24-hr cumulative muscle protein synthesis (FSR) was measured via stable isotope labeling and quantified by gas chromatogram/mass spectrometry. DEPTOR demonstrated a strong negative correlation with FSR in the gastrocnemius ($r = -0.93261$; $p < 0.01$). In our second study, male obese Zucker rats were divided into their lean and obese phenotypes, as well as placed into sedentary and resistance exercised groups. DEPTOR and FSR were assessed as described above following operant conditioning and four progressive exercise sessions over 9-d. Gastrocnemius DEPTOR/FSR was again significant ($r = -0.75723$; $p<0.01$). Collectively, these results are the first to associate physiologic changes in DEPTOR expression with alterations of FSR, which may have important implications towards the design of therapeutic targets for the control of muscle mass or in evaluating muscle anabolism.