NDRG2, a novel player in the control of skeletal muscle mass?

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The N-myc downstream-regulated genes (NDRG1-4) represent a family of molecules linked to cell growth, differentiation and stress (Melotte *et al*,, 2010); however, how they function and their protein partners are poorly described. Recently, we identified that the knockdown of NDRG2 affected myoblast proliferation and differentiation (Foletta *et al.*, 2009). In addition, we identified that NDRG2 expression increased markedly with muscle differentiation and that its gene expression increased also following treatment with catabolic agents, and conversely, decreased under hypertrophic conditions in myotubes. Furthermore, the profile of NDRG2 gene expression closely matched the mRNA profiles of the E3 ligases atrogin-1/MAFbx and MuRF1, key regulators of the ubiquitin proteasome pathway and skeletal muscle mass. This outcome suggests that these three genes are regulated by related factors and that they may have connected roles during changes in muscle mass. Here, we sought to characterize further the potential relationship of these molecules in differentiated muscle cells.

Protein synthesis and degradation as measured by ^{3}H-tyrosine incorporation and release, respectively, was assessed in mouse C2C12 myotubes following the knockdown of NDRG2 protein levels by siRNA under basal, 10 nM insulin and 1 μM dexamethasone treatments. Co-immunoprecipitation analyses of overexpressed NDRG2, atrogin-1 and MuRF1 proteins in C2C12 myoblasts in the presence or absence of the proteasome inhibitor MG132 also were performed.

A 20% increase in insulin-mediated protein synthesis ($p<0.01$) was found in myotubes lacking NDRG2 although no effect on protein degradation was measured. Co-immunoprecipitation analyses also revealed an ability of NDRG2 to interact with both atrogin-1 and MuRF1. Moreover, the interaction between NDRG2 and atrogin-1 was enhanced by 20 μM MG132, but not for the NDRG2 and MuRF1 interaction, suggesting that the inhibition of atrogin-1 activity may promote NDRG2-atrogin-1 binding.

These data provide corroborative evidence of a relationship between NDRG2 and the ubiquitin proteasome regulators, atrogin-1 and MuRF1, and that NDRG2 may also impact on the control of skeletal muscle mass. Currently, we are characterising the signaling pathways through which NDRG2 may affect protein synthesis. These studies will help provide greater insight into the complex molecular mechanisms governing muscle mass regulation.

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