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P311 Downregulates TGF-β1 and TGF-β2 Expression but not TGF-β3 During Myofibroblast Transformation

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We identified P311 by screening for genes differentially expressed during smooth muscle myogenesis. P311, also referred to as PTZ17, is an 8-kDa protein previously found in neurons and muscle. P311 does not belong to any known family of proteins and its function remains largely undetermined. P311 has a conserved PEST domain (sequences rich in Pro, Glu, Ser and Thr) which serves as a rapid degradation signal for the ubiquitin/proteasome system. We recently showed that expression of P311 in fibroblast cell lines NIH-3T3 and 10T1/2 induced phenotypic changes consistent with myofibroblast transformation (Pan et al. *submitted*). The P311-induced changes differed however from the well-characterized fibrogenic myofibroblast phenotype in that P311 inhibited expression of TGF-β1, TGF receptor II and TGF-β1-activating MMP-2, with the resultant decrease in collagen expression. This further study on the three TGF-βs confirmed that during myofibroblast transformation P311 downregulates TGF-β1 expression. In addition we found that P311 inhibited TGF-β2 mRNA but it had no effect on TGF-β3 message. Deletion of the PEST domain (P311ΔPEST) reversed the effect of P311 on TGF-β isoforms. P311ΔPEST upregulated TGF-β1 and TGF-β2 mRNA while TGF-β3 mRNA levels decreased. Furthermore, we found that P311 interacts with TGF-β2 in a yeast two hybrid system through a sequence conserved among the three TGF-β species. P311-TGF-β2 interaction was confirmed by glutathione-S-transferase pull-down studies. Using this assay we determined that P311 also interacts with TGF-β1 but not with TGF-β3. Our studies therefore suggest that P311 modulates TGF-β by acting at several levels of regulation and involves participation of its PEST domain.