PIAS? controls stability and facilitates SUMO-2 conjugation to CoREST family of transcriptional co-repressors

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CoREST family of transcriptional co-repressors regulates gene expression and cell fate determination during development. CoREST co-repressors recruit with different affinity the histone demethylase LSD1 (KDM1A) and the deacetylases HDAC1/2 to repress with variable strength the expression of target genes. CoREST protein levels are differentially regulated during cell fate determination and in mature tissues. However, regulatory mechanisms of CoREST co-repressors at the protein level have not been studied. Here, we report that CoREST (CoREST1, RCOR1) and its homologs CoREST2 (RCOR2) and CoREST3 (RCOR3) interact with PIAS? (protein inhibitor of activated STAT), a SUMO (small ubiquitin-like modifier)-E3-ligase. PIAS? increases the stability of CoREST proteins and facilitates their SUMOylation by SUMO-2. Interestingly, the SUMO-conjugating enzyme, Ubc9 also facilitates the SUMOylation of CoREST proteins. However, it does not change their protein levels. Specificity was shown using the null enzymatic form of PIAS? (PIAS?-C342A) and the SUMO protease SENP-1, which reversed SUMOylation and the increment of CoREST protein levels induced by PIAS?. The major SUMO acceptor lysines are different and are localized in nonconserved sequences among CoREST proteins. SUMOylation-deficient CoREST1 and CoREST3 mutants maintain a similar interaction profile with LSD1 and HDAC1/2, and consequently maintain similar repressor capacity compared with wild-type counterparts. In conclusion, CoREST co-repressors form protein complexes with PIAS?, which acts both as SUMO E3-ligase and as a protein stabilizer for CoREST proteins. This novel regulation of CoREST by PIAS? interaction and SUMOylation may serve to control cell fate determination during development. © 2018 The Author(s).