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THE TRANSCRIPTOME OF CANCER METASTASIS

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Defining the molecular strategies that integrate diverse signaling pathways in expression of specific gene programs critical in homeostasis and disease remains a central issue in biology. In cancer biology, this is particularly pertinent, because down-regulation of tumor metastasis suppressor genes that normally inhibit tumor metastases is a common occurrence, and the underlying molecular mechanisms are not established. Recently, we have reported that the down-regulation of a metastasis suppressor gene, KAI1, in prostate cancer cells involves the inhibitory actions of beta-catenin, along with a reptin chromatin remodeling complex (Kim et al., Nature 434, 921). This novel inhibitory function of beta-catenin/reptin requires both increased levels of beta-catenin expression and recruitment of histone deacetylase activity, and results in down-regulation of a subset of NF-kB target genes. The coordinated actions of beta-catenin/reptin components that mediate the repressive state serve to antagonize a Tip60 coactivator complex, required for activation, with the balance of these opposing complexes controlling the expression of KAI1. Here we found an intriguing signal recognition code of which signaling factors cause reptin chromatin remodeling complex to confer repressive function to control expression of KAI1. Biochemical purification of a reptin-containing complex revealed that it unexpectedly contains SUMO processing enzymes. This work provides a novel insight for linking SUMO modification of chromatin remodeling complex to cancer metastasis.
Key Words: Metastasis suppressor gene, KAI1, SUMO, Beta-catenin/reptin, Tip60