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Titel des Beitrags: Inhibition of Cullin-RING E3 ubiquitin ligase 7 by simian virus 40 large T antigen.

Abstract: Simian virus 40 (SV40) large tumor antigen (LT) triggers oncogenic transformation by inhibition of key tumor suppressor proteins, including p53 and members of the retinoblastoma family. In addition, SV40 transformation requires binding of LT to Cullin 7 (CUL7), a core component of Cullin-RING E3 ubiquitin ligase 7 (CRL7). However, the pathomechanistic effects of LT-CUL7 interaction are mostly unknown. Here we report both in vitro and in vivo experimental evidence that SV40 LT suppresses the ubiquitin ligase function of CRL7. We show that SV40 LT, but not a CUL7 binding-deficient mutant (LT(?69-83)), impaired 26S proteasome-dependent proteolysis of the CRL7 target protein insulin receptor substrate 1 (IRS1), a component of the insulin and insulin-like growth factor 1 signaling pathway. SV40 LT expression resulted in the accumulation and prolonged half-life of IRS1. In vitro, purified SV40 LT reduced CRL7-dependent IRS1 ubiquitination in a concentration-dependent manner. Expression of SV40 LT, or depletion of CUL7 by RNA interference, resulted in the enhanced activation of IRS1 downstream signaling pathways phosphatidylinositol-3-kinase/AKT and Erk mitogen-activated pathway kinase, as well as up-regulation of the downstream target gene c-fos. Finally,
SV40 LT-positive carcinoma of carcinoembryonic antigen 424/SV40 LT transgenic mice displayed elevated IRS1 protein levels and activation of downstream signaling. Taken together, these data suggest that SV40 LT protects IRS1 from CRL7-mediated degradation, thereby sustaining high levels of promitogenic IRS1 downstream signaling pathways.

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