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TUMOUR SUPPRESSION

Shedding light on degradation

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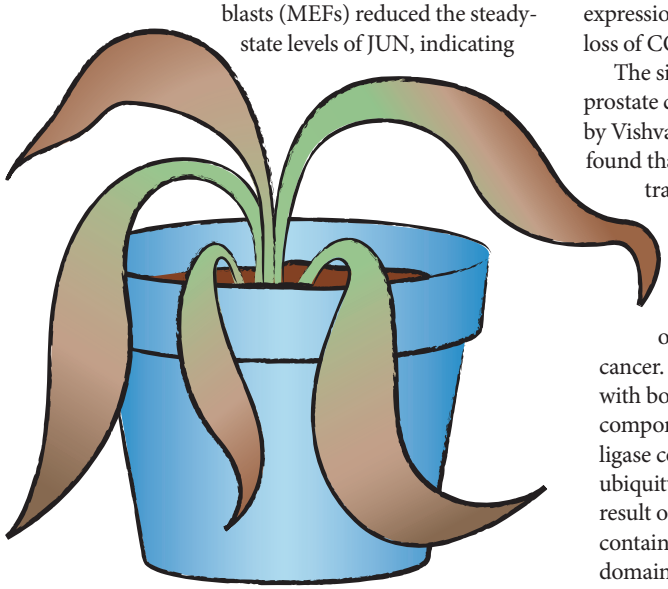
Constitutive photomorphogenesis protein 1 (COP1) can function as an E3 ubiquitin ligase and has been associated with the degradation of the oncoprotein JUN and the tumour suppressor p53. Using different approaches, two recent papers have shown that COP1 can suppress tumorigenesis.

Jean-Christophe Marine and colleagues investigated the function of COP1 *in vivo* using *Cop1*-null mice (which are embryonic lethal) and *Cop1* hypomorphic ($Cop1^{hypo/hypo}$) mice. $Cop1^{hypo/hypo}$ mice have a 90% reduction in COP1 expression levels and are smaller than their wild-type counterparts, but are viable and fertile. Marine and colleagues found no evidence that the function of p53 was compromised by either the loss or the reduced expression of COP1. JUN protein levels, however, were substantially increased in *Cop1*-null embryos, and the half-life of JUN was increased in specific tissues in $Cop1^{hypo/hypo}$ mice. The re-expression of COP1 in $Cop1^{hypo/-}$ mouse embryonic fibroblasts (MEFs) reduced the steady-state levels of JUN, indicating that COP1 regulates JUN stability *in vivo*. Further experiments using MEFs indicated that although the loss of COP1 increases JUN expression levels, JUN is not phosphorylated and is inactive. However, the excess pool of JUN was phosphorylated when p53 expression was ablated, which was consistent with the finding that $Trp53^{-/-}$;$Cop1^{hypo/-}$ MEFs have increased rates of proliferation. By 1 year of age, around 50% of the $Cop1^{hypo/hypo}$ mice developed tumours — mostly T cell lymphomas — and this rate increased substantially when 7–12-week-old mice were exposed to 4 Gy whole-body γ-irradiation. Using the Tumourscape database the authors found that *COP1* deletion was fairly rare in human tumours, but reduced expression levels of COP1 were evident in the Oncomine array comparative genomic hybridization (CGH) database, particularly in prostate cancer. The examination of COP1 levels in prostate cancer cell lines indicated an inverse relationship between COP1 expression and JUN expression, suggesting a role for the loss of COP1 in prostate cancer.



The significance of COP1 loss in prostate cancer was also examined by Vishva Dixit and colleagues. They found that COP1 binds to the E26 transformation-specific (ETS) family members ETV1, ETV4 and ETV5. These transcription factors are often rearranged and overexpressed in prostate cancer. Like JUN, ETV1 interacts with both COP1 and another component of a large ubiquitin ligase complex, DET1, and it is ubiquitylated and degraded as a result of this interaction. ETV1 contains three COP1-binding domains, two of which are often lost during gene rearrangements, preventing its interaction with COP1 and its degradation. Using a conditional $Cop1^{flox/flox}$ allele that is deleted only in mouse prostatic epithelium, these authors showed that COP1 loss induced prostatic hyperplasia, and that this correlated with increased levels of proliferation and expression of ETV1, ETV4 and JUN. Crossing these mice with mice lacking the tumour suppressor gene *Pten* in the prostate (a common lesion in prostate cancer) resulted in invasive prostate cancer and increased expression of ETV1, ETV4 and JUN. Array CGH data from 166 human prostate cancers indicated that loss of *COP1* expression does occur, albeit in a small proportion of cases (five of 166), and three of these showed increased ETV1 expression. Immunohistochemical screening of an additional 120 prostate cancer samples showed that four had increased levels of ETV1 or JUN, three of which had also lost expression of COP1. These findings indicate that the oncogenic function of translocated genes, such as *ETV1*, might arise as a result of the loss of sequences that normally ensure protein degradation. In a few cases in which these oncogenes are not translocated, the half-lives of these genes are increased through an alternative mechanism — the loss of COP1.

Both papers suggest that COP1 can function as a tumour suppressor by regulating the stability of known oncoproteins.

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ORIGINAL RESEARCH PAPERS Migliorini, D. *et al.* Cop1 constitutively regulates c-Jun protein stability and functions as a tumor suppressor in mice. *J. Clin. Invest.* **121**, 1329–1343 (2011) | Vitari, A. C. *et al.* COP1 is a tumour suppressor that causes degradation of ETS transcription factors. *Nature* 15 May 2011 (doi:10.1038/nature10005)