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PTTG/securin induces and modulates p53 expression and function

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Pituitary tumor transforming gene (PTTG) is a novel oncogene that is highly expressed in most of the tumors. Overexpression of PTTG induces cellular transformation and promotes tumor formation in nude mice. PTTG has been implicated to play important role in various cellular processes including sister chromatid separation during cell division and induction of apoptosis in a p53 dependent and independent manner. However, the relationship between PTTG and p53 remains unclear. In this report, we studied the effect of overexpression of PTTG on expression and function of p53 gene. Our results indicate that overexpression of PTTG modulates p53 expression at both transcription and translational levels and that this induction is dependent upon the p53 status of the cells. Deletion analysis of the p53 gene promoter revealed that only a small region of p53 promoter is required for its activation by PTTG. This action of PTTG is, however, indirect and is mediated through the regulation of c-myc expression, which further interacts with p53 promoter sequence. Our results also indicate that overexpression of PTTG stimulates expression of Bax gene, one of the known downstream targets of p53, and induces apoptosis in breast tumor cell line (MCF-7). Stimulation of Bax expression by PTTG is indirect and is mediated through modulation of p53 expression. We conclude that overexpression of PTTG induces expression and function of p53 gene, and this action of PTTG is mediated through the regulation c-myc expression. Induction of p53 by PTTG might serve as one of the key processes that transformed cells undertake to prevent aneuploidy, this process however is not perfect and some cells might escape this mechanism and later manifest themselves as tumors.

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PTEN regulates differential Fas apoptosis in Type I and Type II cells

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The molecular basis to account for the differential Type I/Type II CD95 (Fas) death receptor signals has hitherto remained elusive. Here we show that the PTEN tumour suppressor plays a key role in regulating Fas signals in Type I /Type II cells. PTEN expression analysis revealed that Type I (H9 and SKW6.4) cells, expressed functional PTEN whereas Type II (Jurkat and CEM), cells were PTEN null, with constitutive Akt activation. Analysis of PTEN expression in the NCI-60 tumor panel revealed a very high correlation between PTEN expression and Type I signaling and PTEN deficiency and Type II signaling. Expression of DN-PTEN in Type I cells led to delayed Type II-like PARP cleavage kinetics and enhanced sensitivity to CD95/FasL, S2, which selectively kills Type II cells. In contrast, re-expression of PTEN in Type II cells resulted in mitochondrial independence and accelerated kinetics of CD95/Fas induced caspase activation.