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Abstract title:

Threshold concentrations for BPDE-induced cell death are characterised by altered DNA damage signalling and associated with unrepaired double-strand breaks

Abstract text (incl. figure legends and references):

The environmental carcinogen benzo(a)pyrene (B[a]P) is not carcinogenic unless metabolically activated to benzo(a)pyrene 9,10-diol-7,8-epoxide (BPDE). In our previous work, we showed that exposure of human VH10tert fibroblasts to non-toxic concentrations of BPDE induces p53-dependend transcriptional activation of the nucleotide excision repair as well as p53/p21-dependent induction of senescence, leading to cellular survival. In contrast, high BPDE concentrations result in p53 mediated cell death via apoptosis, suggesting the existence of specific thresholds at which the p53-dependent pro-survival signalling turns into p53-dependent pro-death signalling. The initial activation of the DNA damage response does not differ between toxic and non-toxic BPDE concentrations, whereas at later time points toxic concentrations cause complex changes in the DNA damage response resulting in cell death. In summary, protective ATR-CHK1-p53Ser15-p21 dependent signalling changes upon toxic concentrations into ATM-CHK2-p53Ser46-NOXA dependent signalling, mediating induction of apoptosis. Preliminary data further suggest that this threshold is caused by unrepaired DNA double-strand breaks.