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A genetic screen for novel regulators of *cep-1/p53* in *C. elegans*

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The tumour suppressor p53 is mutated in approximately 50% of all human cancers and a majority of tumours with wild type p53 contain mutations in other proteins that result in loss of p53 activity. One such protein is the key negative regulator, Mdm2, which binds and ubiquitinates p53, resulting in loss of activity and degradation of p53. A primordial ancestor of p53 has been identified in invertebrate species, including *C. elegans* where it is known as CEP-1 (Current Biology 2001 11:1722-7, Science 2001 294:591-5). Activation of these homologues results only in induction of apoptosis and not of cell cycle arrest. Careful examination of the *C. elegans* genome has failed to identify a Mdm2 homologue, which implies that there are other negative regulators present, homologues of which may play important roles in regulating human p53. To identify these regulators, we have performed a forward genetic screen using the *C. elegans* germline in which apoptosis is readily observed. This screen identified candidates based on their heightened apoptotic response to low doses of ionising radiation. A pilot screen has identified *gld-1* as a translational repressor of *cep-1* (Cell 2005 120:357-68), demonstrating the validity of this approach. Further analyses enabled us to sort candidates into distinct phenotypic classes based on a number of assays. The class that is of most interest includes candidates that (i) have increased apoptosis only upon DNA damage, (ii) and which is dependent upon *cep-1*, (iii) result in increased CEP-1 activity, and (iv) are not due to DNA repair defects. Progress on the characterisation and identification of these candidates will be presented. It is anticipated that the identification and characterisation of these candidates will aid in the understanding of p53 regulation, ultimately leading to potential therapeutic strategies.