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COMMENTARY

Axin bridges Daxx to p53

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The death domain-associated protein Daxx exerts many reported functions that include mediating the signaling from FasL to apoptosis via activating the c-Jun N-terminal kinase (JNK) [1], induction and inhibition of apoptosis [2-5], and regulation of chromatin remodeling. It was originally cloned from a yeast two-hybrid screen using the intracellular tail of the Fas receptor as the bait [1]. Whereas many of the initial reports remain controversial, it is clear that Daxx plays important roles in the regulation of apoptosis triggered by a series of stress signals including UV irradiation, hydrogen peroxide treatment and TGF-β treatment [2, 3]. In this Commentary, we focus on Axin being a tethering factor linking Daxx to p53.

A possible functional linkage of Daxx to p53 was first reported by Ohiro *et al*. [6]. In that study, it was shown that some tumorigenic mutants of p53, but not wild-type p53, interact with Daxx and inhibit Daxx-induced cell death by blocking Daxx-dependent activation of the JNK kinase, suggesting that mutant p53 in tumor cells may contribute to tumorigenesis by inhibiting stress-induced kinase pathways. However, another group showed that Daxx interacts with wild-type p53, both *in vitro* and *in vivo*, and differentially modulates p53 target genes, with activation of PUMA and inhibition of p21 and Mdm2 [4]. Recently, Lin and colleagues have found that Axin, a scaffold protein that plays an architectural role in the assembly of the degradation complex for β-catenin in Wnt signaling, forms a ternary complex with the ser/thr kinase HIPK2 to enhance p53-dependent cell death [7], and have provided further evidence that the Axin/HIPK2/p53 complex co-exists with Daxx. Axin thus serves as a bridge to tether Daxx to the p53-activating complex [8]. It is important to stress that in this model Daxx does not directly interact with p53 (Figure 1). Daxx association results in higher HIPK2 kinase activity towards p53 compared to that occupied by Axin alone. In addition, they also showed that Daxx exhibits higher affinity with Axin in cells irradiated by UV which promotes the translocation of Axin from cytoplasm to the nucleus, and that specific knockdown of Daxx or Axin diminished UV-induced p53 phosphorylation and cell death. These findings have established a novel pathway linking UV irradiation to the p53 phosphorylation complex consisting of Daxx, Axin, HIPK2 and p53, and to the ultimate induction of cell death in response to the UV damage.

It is also interesting to note that Daxx seems to have opposite roles in modulating p53 function before and after stress stimulation. It was recently shown that Daxx, in unstressed cells, seems to destabilize p53 by stabilizing Mdm2 which, as an E3 ligase, promotes p53 ubiquitination and degradation [9]. The apparent paradox may explain at least in part the perplexity on the functions of Daxx as to whether Daxx is a pro- or anti-apoptotic protein. The key evidence for a potential anti-apoptotic function of Daxx came from Daxx knockout mouse embryos which display increased global apoptosis [10]. In contrast, pro-apoptotic functions of Daxx have been obtained with tumor cells or transformed cells treated with diverse stimuli, such as UV, TGF-β, hydrogen peroxide, interferon-γ and arsenite trioxide. It is therefore reasonable to suggest that Daxx exerts an anti-apoptotic function in unstressed primary cells, and acts as a proapoptotic factor in tumor cells or transformed cells treated with various stresses.

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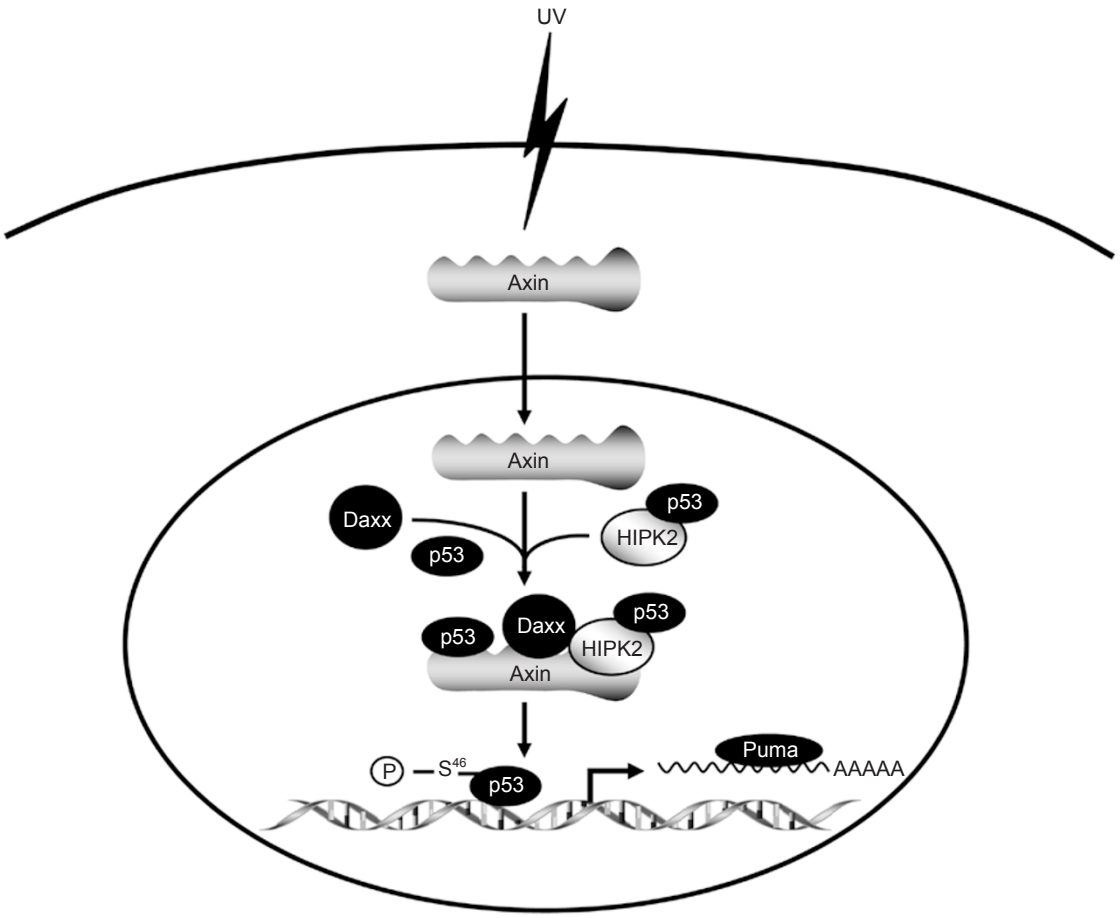

Figure 1 Axin serves as a tethering factor for Daxx to associate with p53. Upon UV irradiation, Axin is translocated into the nucleus whereby it forms a large complex with Daxx and two pools of p53 (one directly bound to Axin, and the other occupied by HIPK2). HIPK2 in the Axin complex is activated upon complex formation, resulting in phosphorylation of p53 at Ser^{46}. Of note, Daxx and Axin cooperate with each other to elevate HIPK2 kinase activity towards p53. Axin-mediated p53 activation seems to selectively regulate certain target genes such as PUMA.

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