pRb/E2F-1-mediated caspase-dependent induction of Noxa amplifies the apoptotic effects of the Bcl-2/Bcl-xL inhibitor ABT-737

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Résumé en anglais	Although Bcl-2 family members control caspase activity by regulating mitochondrial permeability, caspases can, in turn, amplify the apoptotic process upstream of mitochondria by ill-characterized mechanisms. We herein show that treatment with a potent inhibitor of Bcl-2 and Bcl-xL, ABT-737, triggers caspase-dependent induction of the BH3-only protein, Mcl-1 inhibitor, Noxa. RNA interference experiments reveal that induction of Noxa, and subsequent cell death, rely not only on the transcription factor E2F-1 but also on its regulator pRb. In response to ABT-737, pRb is cleaved by caspases into a p68Rb form that still interacts with E2F-1. Moreover, pRb occupies the noxa promoter together with E2F-1, in a caspase-dependent manner upon ABT-737 treatment. Thus, caspases contribute to trigger the mitochondrial apoptotic pathway by coupling Bcl-2/Bcl-xL inhibition to that of Mcl-1, via the pRb/E2F-1-dependent induction of Noxa.
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