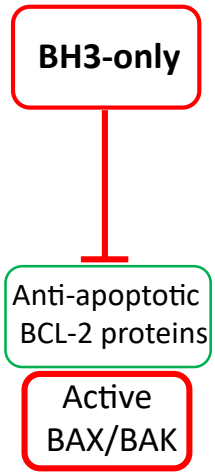
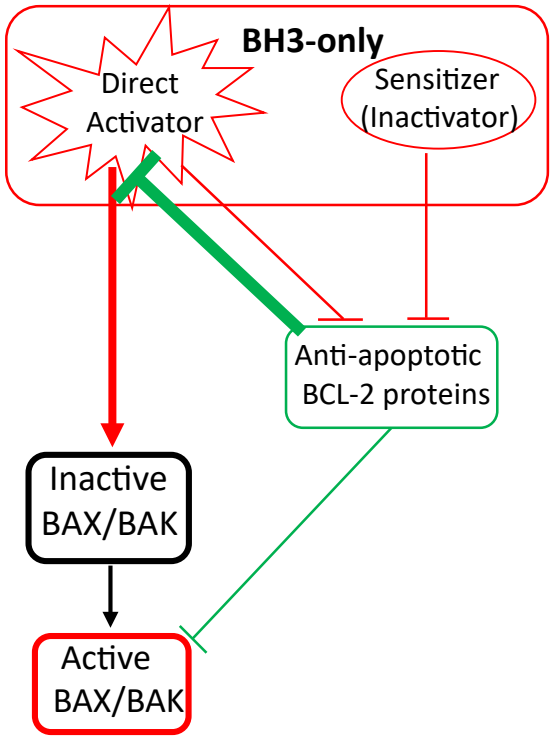
a



Indirect Activation
(Displacement model)

b



Direct Activation

Fig. S8 The Indirect (Displacement) and Direct Models of BAX/BAK activation through the BH3-only proteins.

(a) The Indirect Activation (Displacement) Model of BAX/BAK activation by BH3-only proteins. BAX/BAK proteins are constitutively active but are normally sequestered by the anti-apoptotic BCL-2 proteins. During apoptosis, the BH3-only proteins bind to the anti-apoptotic BCL-2 family proteins, and release the active BAX/BAK molecules. (b) The Direct Activation Model of BAX/BAK activation by BH3-only proteins. The BH3-only proteins are classified into the "direct activators" and "sensitizers". Sensitizers only bind to and neutralize the anti-apoptotic BCL-2 family proteins, but not BAX/BAK. The direct activators, on the other hand, not only binds to and neutralize the anti-apoptotic BCL-2 proteins, but also directly bind to and allosterically activate BAX/BAK. The anti-apoptotic proteins not only bind to and sequester the active effector proteins BAX/BAK, but also bind to and block the direct activators from activating BAX/BAK. The direct activator BH3-only proteins and the anti-apoptotic BCL-2 proteins are therefore mutual inhibitors. During apoptosis, both groups of BH3-only proteins neutralize the anti-apoptotic BCL-2 proteins, allowing the direct activators (i.e., BID, BIM, PUMA) to bind to BAX/BAK and trigger their conformational transformation into active molecules capable of inducing pores on the mitochondrial outer membrane.