BAX Inhibitor-1 Is a Negative Regulator of the ER Stress Sensor IRE1?

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Adaptation to endoplasmic reticulum (ER) stress depends on the activation of an integrated signal transduction pathway known as the unfolded protein response (UPR). Bax inhibitor-1 (BI-1) is an evolutionarily conserved ER-resident protein that suppresses cell death. Here we have investigated the role of BI-1 in the UPR. BI-1 expression suppressed IRE1? activity in fly and mouse models of ER stress. BI-1-deficient cells displayed hyperactivation of the ER stress sensor IRE1?, leading to increased levels of its downstream target X-box-binding protein-1 (XBP-1) and upregulation of UPR target genes. This phenotype was associated with the formation of a stable protein complex between BI-1 and IRE1?, decreasing its ribonuclease activity. Finally, BI-1 deficiency increased the secretory activity of primary B cells, a phenomenon regulated by XBP-1. Our results suggest a role for BI-1 in early adaptive responses against ER stress that contrasts with its known downstream function in apoptosis. ©