BCL-2/BCL-X_L REGULATES CELL CYCLE THROUGH A NOVEL MECHANISM IN ADDITION TO CELL SURVIVAL

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Bcl-2 and Bcl-x_L are anti-apoptotic and inhibit proliferation. During cell cycle arrest, Bcl-2 or Bcl-x_L expression causes elevation of the CDK inhibitor p27, decrease in cell size and RNA content. This enhanced state of G_0 results in delay of G_0-G_1 transition and S phase entry upon cell cycle stimulation. We investigated the mechanism of the Bcl-2/Bcl-x_L cell cycle function and the relationship between apoptosis regulation and cell cycle control. To assess the role of mitochondrial functions in Bcl-2/Bcl-x_L-mediated cell cycle delay, we monitored ATP levels and found that cells expressing Bcl-2 or Bcl-x_L exhibit a delay in peak ATP during cell cycle entry; however, exogenous elevation of ATP did not reverse the delay in cell cycle entry. In mtDNA-free 143B ρ^0 cells defective in electron transport, Bcl-x_L is still able to delay cell cycle entry but not enhance G_0 arrest. To determine whether enhanced G_0 and subsequent delay in cell cycle are consequences of increased survival, we inhibited cell death by means other than Bcl-2/Bcl-x_L expression. Increasing survival by caspase inhibition partially recapitulated the cell cycle arrest phenotype of Bcl-2/Bcl-x_L, while cells expressing the survival kinase Akt exhibited none of the cell cycle phenotypes of Bcl-2/Bcl-x_L. These data indicate that the

cell cycle delay by Bcl-2/Bcl-x_L is not mediated through the regulation of ATP/ADP exchange, and does not require normal mitochondrial membrane potential. Bcl-2/Bcl-x_L may regulate quiescence partially through the inhibition of caspase-dependent apoptosis, but cell survival is not the sole mechanism of the cell cycle regulation by Bcl-2/Bcl-x_L. In addition to inhibition of mitochondrial apoptosis, mechanisms requiring an intact electron transport chain are necessary for the full cell cycle function of Bcl-2/Bcl-x_L.

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