mcl-1 Is an Immediate-Early Gene Activated by the Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Signaling Pathway and Is One Component of the GM-CSF Viability Response

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Abstract

mcl-1, a bcl-2 family member, was originally identified as an early gene induced during differentiation of ML-1 myeloid leukemia cells. In the present study, we demonstrate that Mcl-1 is tightly regulated by the granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling pathway. Upon deprivation of survival factor from TF-1 myeloid progenitor cells, Mcl-1 levels quickly dropped prior to visible detection of apoptosis of these cells. Upon restimulation of these deprived cells with GM-CSF, the mcl-1 mRNA was immediately induced and its protein product was accordingly resynthesized. Analysis with Ba/F3 cells expressing various truncation mutants of the GM-CSF receptor revealed that the membrane distal region between amino acids 573 and 755 of the receptor beta chain was required for mcl-1 induction. Transient-transfection assays with luciferase reporter genes driven by various regions of the mcl-1 promoter demonstrated that the upstream sequence between -197 and -69 is responsible for cytokine activation of the mcl-1 gene. Overexpression of mcl-1 delayed but did not completely prevent apoptosis of cells triggered by cytokine withdrawal. Its down regulation by antisense constructs overcame, at least partially, the survival activity of GM-CSF and induced the apoptosis of TF-1 cells. Taken together, these results suggest that mcl-1 is an immediate-early gene activated by the cytokine receptor signaling pathway and is one component of the GM-CSF viability response.