mcl-1 Is a Common Target of Stem Cell Factor and Interleukin 5 for the Apoptosis Prevention Activity via MEK/MAPK and PI-3K/Akt Pathways

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Abstract

Stem cell factor (SCF) has been suggested as essential for optimal production of various hematopoietic lineages mainly because of its apoptosis prevention function when it costimulates with other cytokines. However, the underlying mechanism of this synergism of apoptosis prevention is largely unknown. The present study examined the expression of some Bcl-2 family members, including Bcl-2, Bcl-XL, Mcl-1, and Bax, in response to cytokine stimulation in TF-1 and JYTF-1 cells in which SCF costimulation is differentially required for optimal proliferation. The results revealed that only the expression of Mcl-1 highly correlated with the antlapoptotic activity of interleukin-5 (IL-5) and the synergistic effect of SCF. In TF-1 cells, the defect of IL-5 in apoptosis suppression and Mcl-1 induction was associated with the incapability to highly phosphorylate Janus kinases (JAK1, JAK2), signal transducer and activator of transcription-5 (STAT5), mitogen-activated protein kinase (MAPK), and Akt/PKB, whereas SCF costimulation restored the potent phosphorylation of MAPK and Akt/ PKB, but not STAT5. The importance of MAPK and Akt/PKB signaling pathways in regulating the expression of Mcl-1 and cell survival was further supported by the observation that inhibition of MEK by PD98059 or phosphatidylinositol-3 kinase (PI-3K) by LY294002 independently resulted in the reduction of Mcl-1 expression and loss of cell viability. Therefore, the data suggest that Mcl-1 is a common antiapoptotic target of both early-stage cytokine SCF and late-stage cytokine IL-5. Both MEK/MAPK and PI-3K/Akt signaling pathways are essential in the regulation of Mcl-1 expression and apoptosis prevention.