Cytokine Receptor Common β Chain as a Potential Activator of Cytokine Withdrawal-Induced Apoptosis

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Abstract

Growth factors and cytokines play an important role in supporting cellular viability of various tissues during development due to their ability to suppress the default cell death program in each cell type. To date, neither the triggering molecule nor the transduction pathway of these default apoptosis programs is understood. In this study, we explored the possibility that cytokine receptors are involved in modulating cytokine withdrawal-induced apoptosis (CWIA) in hematopoietic cells. Expression of the exogenous cytokine receptor common beta chain (betac), but not the alpha chains, accelerated CWIA in multiple cytokine-dependent cell lines. Reduction of the expression level of endogenous betac by antisense transcripts resulted in prolonged survival during cytokine deprivation, suggesting a critical role of betac in modulating CWIA. Fine mapping of the betac subunit revealed that a membrane-proximal cytoplasmic sequence, designated the death enhancement region (DER), was critical to the death acceleration effect of betac. Furthermore, DER accelerated cell death either as a chimeric membrane protein or as a cytosolic protein, suggesting that DER functions independently of the cytokine receptor and membrane anchorage. Cross-linking of the chimeric membrane-bound DER molecules by antibody or of the FK506-binding protein-DER fusion protein by a synthetic dimerizing agent, AP1510, did not abrogate the death acceleration effect. Transient transfection assays further indicated that DER promoted cell death in the absence of serum in the nonhematopoietic 293 cell line. In summary, our data suggest that betac plays an important role in modulating CWIA via an anchorage-independent and aggregation-insensitive mechanism. These findings may facilitate further studies on the signaling pathways of CWIA.