Downregulation of ERK2 is Essential for the HSP25-Mediated Radioresistance in L929 cells: Effects on Cell Cycle Regulation and Apoptosis

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We previously reported that overexpression of HSP25 delayed cell growth (increased p21waf and reduced levels of cyclin D1, cyclin A and cdc2) that partially related to the HSP25-induced radioresistance (Radiat Res 154: 421-428, 2000). In this study, we further investigated the modification of cellular signaling pathways in hsp25-transfected cells. HSP25 overexpression induced radioresistance and co-transfection of antisense plasmid for hsp25 gene abolished this phenomenon. Extra cellular regulated kinase (ERK) and MAP/ERK (MEK) expressions as well as their phospho-forms were inhibited by hsp25-overexpression that was mediated by neither protein kinase C (PKC) nor epidermal growth factor receptor (EGF-R) signaling. Moreover, when PD98059, MEK inhibitor was treated, radioresistance of control vector cells was acquired, suggesting that inhibited ERK1/2 activities were essential for radioresistance in L929 cells. To know the relationship between ERK1/2 and hsp25-mediated radioresistance, ERK1 or ERK2 was co-transfected to the hsp25 overexpressed cells and radioresistance was examined. HSP25-mediated radioresistance was abolished by ERK2-cotransfected cells, but not by ERK1-cotransfection. Alteration of cell cycle distribution and cell cycle protein expression (cyclin D, cyclin A and cdc2) by hsp25 transfection was also recovered by ERK2-cotransfection. Overexpressed bcl-2 protein by hsp25 transfection also inhibited by ERK2-cotransfection. In addition, increased radiation-induced G2 phase arrest by hsp25 transfection was attenuated by ERK2-cotransfection. From these results, downregulation of ERK2 is essential for the HSP25-mediated radioresistance.