Gene 33/Mig6 Regulates Apoptosis and the DNA Damage Response through Independent Mechanisms

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Gene 33/Mig6 Regulates Apoptosis and the DNA Damage Response through Independent Mechanisms

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ABSTRACT

Gene 33 (Mig6, ERRFI1) is an inducible adaptor/scaffold protein whose expression can be induced by both stress and mitogenic signals. It contains multiple domains for protein-protein interaction and is involved in a broad spectrum of cellular functions. Gene 33 promotes apoptosis in a cell type-dependent manner. A recent study has linked Gene 33 to the DNA damage response (DDR) induced by hexavalent chromium [Cr(VI)]. Here we show that Gene 33 induces apoptosis via both c-Abl/p73 and EGFR/AKT-dependent pathways in lung epithelial and lung carcinoma cells. Ectopic expression of Gene 33 also triggers DDR in an ATM-dependent fashion and through pathways with or without association with apoptosis. We observed significant presence of Gene 33 in the nucleus and chromatin. We show that the nuclear localization of Gene 33 is dependent on its 14-3-3 binding domain. We find that the chromatin localization of Gene 33 is, at least in part, dependent on its EBD motif. Our data also show that Gene 33 may regulate chromatin targeting of c-Abl and EGFR. Moreover, we observed strong association of Gene 33 with histone H2AX and that Gene 33 promotes interaction between ATM and histone H2AX without triggering DNA damage. Our study reveals novel nuclear functions of Gene 33, which mediate DDR and apoptosis through independent mechanisms. Given our previous finding that Gene 33 depletion promotes Cr(VI)-induced DNA damage, our data suggest that Gene 33 may foster DNA repair by activating DDR.

BACKGROUND

Gene 33 protein

Protein, which inhibits Cr(VI)-induced DNA damage that lead to genomic instability, cell transformation and carcinogenesis.

RESULTS

Gene 33/Mig6 is an inducible adaptor/scaffold protein whose expression can be induced by both stress and mitogenic signals. It contains multiple domains for protein-protein interaction and is involved in a broad spectrum of cellular functions. Gene 33 promotes apoptosis in a cell type-dependent manner. A recent study has linked Gene 33 to the DNA damage response (DDR) induced by hexavalent chromium [Cr(VI)]. Here we show that Gene 33 induces apoptosis via both c-Abl/p73 and EGFR/AKT-dependent pathways in lung epithelial and lung carcinoma cells. Ectopic expression of Gene 33 also triggers DDR in an ATM-dependent fashion and through pathways with or without association with apoptosis. We observed significant presence of Gene 33 in the nucleus and chromatin. We show that the nuclear localization of Gene 33 is dependent on its 14-3-3 binding domain. We find that the chromatin localization of Gene 33 is, at least in part, dependent on its EBD motif. Our data also show that Gene 33 may regulate chromatin targeting of c-Abl and EGFR. Moreover, we observed strong association of Gene 33 with histone H2AX and that Gene 33 promotes interaction between ATM and histone H2AX without triggering DNA damage. Our study reveals novel nuclear functions of Gene 33, which mediate DDR and apoptosis through independent mechanisms. Given our previous finding that Gene 33 depletion promotes Cr(VI)-induced DNA damage, our data suggest that Gene 33 may foster DNA repair by activating DDR.

CONCLUSIONS

Gene 33 binds to histone H2AX and promotes interaction between ATM and histone H2AX. BEAS-2B cells were infected with the indicated adenoviruses followed by IP and IB as indicated. Far right: 293T cells were transfected with expression plasmids encoding FLAG-tagged wild type or 1-350AA of Gene33. Green: FLAG, blue: DAPI. 200x.