beta1-integrin-mediated signaling essentially contributes to cell survival after radiation-induced genotoxic injury.

Abstract:
Integrin-mediated adhesion to extracellular matrix proteins confers resistance to radiation- or drug-induced genotoxic injury. To analyse the underlying mechanisms specific for beta1-integrins, wild-type beta1A-integrin-expressing GD25beta1A cells were compared to GD25beta1B cells, which express signaling-incompetent beta1B variants. Cells grown on fibronectin, collagen-III, beta1-integrin-IgG or poly-l-lysine were exposed to 0-6 Gy X-rays in presence or depletion of growth factors and phosphatidylinositol-3 kinase (PI3K) inhibitors (LY294002, wortmannin). In order to test the relevance of these findings in tumor cells, human A-172 glioma cells were examined under the same conditions after siRNA-mediated silencing of beta1-integrins. We found that beta1A-integrin-mediated adhesion to fibronectin, collagen-III or beta1-IgG was essential for cell survival after radiation-induced genotoxic injury. Mediated by PI3K, pro-survival beta1A-integrin/Akt signaling was critically involved in this process. Additionally, the beta1-integrin downstream targets p130Cas and paxillin-impaired survival-regulating PI3K-dependent JNK. In A-172 glioma cells, beta1-integrin knockdown and PI3K inhibition confirmed the central role of beta1-integrins in Akt- and p130Cas/paxillin-mediated prosurvival signaling. These findings suggest beta1-integrins as critical regulators of...
cell survival after radiation-induced genotoxic injury. Elucidation of the molecular circuitry of prosurvival beta1-integrin-mediated signaling in tumor cells may promote the development of innovative molecular-targeted therapeutic antitumor strategies.