Influence of the survivin inhibitor shepherdin on proliferation, migration and apoptosis of Rhabdomyosarcoma tumor cells

Autor: Li Niu
Institut / Klinik: Pathologisches Institut
Doktorvater: Prof. Dr. A. Marx

Rhabdomyosarcomas are the most frequent soft tissue malignancies of children. Despite improved 5-year overall survival rates in patients with localized tumors in recent years, the outcome with advanced RMS is still poor. Therefore, new therapeutic treatments are urgently needed. The survivin inhibitor Shepherdin (shp) is such a promising new therapeutic option. It acts through interference with the stabilizing effect of the heat shock protein 90 (Hsp90) on its ‘client’ protein, survivin. Survivin is an anti-apoptotic protein that belongs to the inhibitor of apoptosis family. Because survivin is expressed in many tumors but not in normal adult tissue, inhibition of survivin is assumed to have a selective effect on tumors. Indeed, preclinical studies showed a strong influence of shp on tumor cell viability, proliferation and migration in vitro and in vivo. In the present study the influence of shp on RMS tumor cells in terms of morphology, proliferation, migration as well as cytoskeleton changes was studied. To ensure that the observed effects were survivin specific, cellular and molecular consequences of shp treatment in vitro were compared with the effects of specific survivin knock down through shRNA technology.

Both treatments elicited reduced proliferation and migration of RMS tumor cells in vitro, however, due to different effects on tumor cells. While survivin knock down cells exhibited strong signs of cell division malfunctions that resulted in enlarged cell size with polynucleated cells and reduced growth rate, shp treated cells started dying after 12 h of treatment. Furthermore, the cytoskeleton of shp treated cells showed i) filopodia-like outgrowths with condensed networks of actin fibers and ii) redistribution of CDC42 from a perinuclear to a more diffuse distribution throughout the cytoplasm. These latter changes were not observed in RMS cells following shRNA-mediated survivin knock down. The shp effects on RMS were potentially mediated through down regulation of Focal Adhesion Kinase (FAK).

Taken together, this study revealed that shp has strong effects on proliferation, survival and migration of RMS cells in vitro. The observed effects were not exclusively caused by shp induced survivin down-regulation, but likely by the impact of shp on a broader spectrum of Hsp90 client proteins, including FAK. It is assumed that shp induced down regulation of FAK caused the observed cytoskeleton changes and effects on cell proliferation and migration. Therefore, further investigation of the effect of shp on FAK and other Hsp90 client proteins in RMS tumor cells is warranted to eventually reveal new therapeutic targets.