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Cytoplasmic expression of HSPB11 correlates with the clinical grade of brain tumors

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AlphaB-crystallin homology, heat stress induction and chaperone activity suggested that a previously encloned gene product is a novel small heat shock protein (HSPB11). Suppression of HSPB11 by siRNA sensitized cells to hydrogen peroxide or taxol induced cell-death, while its over-expression protected cells against stress stimuli by inhibiting cytochrome c release from the mitochondria, nuclear translocation of AIF and endonuclease G, and caspase 3 activation. Recombinant HSPB11 protected mitochondrial membrane potential against calcium induced collapse *in vitro* indicating that it stabilizes mitochondrial membrane systems. HSPB11 formed self-aggregates and bound to Hsp90. Inhibition of Hsp90 by geldanamycin diminished the cytoprotective effect of HSPB11 indicating that this effect was Hsp90-mediated. HSPB11 over-expression increased lipid rafts formation as demonstrated by increased cell surface labeling with fluorescent cholera toxin B, and increased Akt phosphorylation. The inhibition of PI-3-kinase-Akt pathway by LY-294002 or wortmannin significantly decreased the protective effect of HSPB11. Progressive cytoplasmic expression of HSPB11 also correlated with brain tumor malignancy based upon the findings on 91 diagnosed brain tumor cases. To study how cytoplasmic abundance of HSPB11 augments tumor malignancy, we overexpressed HSPB11 in NIH3T3 fibroblasts and silenced its expression in HeLa cervix carcinoma cells. Endogenous HSPB11 expression is low in NIH3T3 and high in HeLa cells. Both cell lines and their untransfected control counterparts were exposed to 150 nM paclitaxel, a known inducer of apoptotic and necrotic death. We determined type of cell death, association of HSPB11 with mitochondria, mitochondrial fission and deactivation of dynamin-like protein-1 (DRP-1). We found that HSPB11 increased inhibitory phosphorylation of DRP-1, attenuated mitochondrial fission and cell death, which was exclusively apoptotic in NIH3T3 and predominantly apoptotic in HeLa cells. Furthermore, paclitaxel did not increase mitochondrial association of HSPB11. All these data suggests that DRP-1 dependent mitochondrial network stabilization could contribute to elevated apoptosis resistance and increased malignancy in HSPB11 over expressing tumors.

Biography

Ferenc Gallyas Jr., Ph.D., DSc, full Professor at the Department of Biochemistry and Medical Chemistry, University of Pecs Medical School (Pecs, Hungary) is working on the mechanisms of cell death with special focus on the nuclear enzyme poly (ADP-ribose) polymerase (PARP) and mitochondrial integrity. He was involved in the characterization of novel proteins affecting the cell death process (HspB11, SOUL, Galectin-13, TIP-47), elucidation of mechanisms of mitochondrial permeability transition and extra-nuclear effects of PARP activation as well as development of novel mitochondria-targeted and PARP inhibitory substances that could have potentiality in cancer diagnostics and therapy.

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