OMICS International
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J Cancer Sci Ther 2015, 7:8
http://dx.doi.org/10.4172/1948-5956.C1.052

7th Global Summit on

Cancer Therapy

October 05-07, 2015 Dubai, UAE

RIP2 enhances survival through NF-κB in triple negative breast cancer

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Background: RIP2 is receptor interacting protein kinase well known for its function in immunity and inflammation by activation of the NF-κB pathway. It was also reported to be involved in cell proliferation and cancer development and metastasis. Here we show role of RIP2 in triple negative breast cancer. RIP2 increased cell count and resistance to death induced by cytotoxic drugs in MDA-MB-231 cells through NF-κB activation in these cells.

Introduction: ER-negative and basal breast cancers (BC) are known to have high NF-κB activity. McCarthy et al showed that receptor-interacting protein kinase 2, RIP2, activates NF-κB signaling and according to Singel et al RIP2 is significantly over-expressed in triple-negative BC. Here we show the relevance ofRIP2 in BC cells and its impact on NFκB signaling and survival.

Methods: Online BC databases were analyzed for RIP2 impact on patient survival and correlation with NFκB. MDA-MB-231 BC cells were transfected with plasmids encoding RIP2, various RIP2 mutants and shRNA against RIP2. The cells were then treated with cytotoxic and genotoxic drugs. Cell death and apoptosis was measured by various assays. MDA-MB-231 luciferase-reporter cells were used to measure NF-κB activity. Targeting NF-κB by peptide inhibition (SN50) or NF-κB super-repressor plasmid reversed the RIP2 cell survival effect.

Results: Kaplan-Meier survival plots showed that RIP2 over-expression in BC patients significantly decreases overall patient survival and progression-free survival. In addition, RIP2 expression is positively correlated with NF-κB expression in patients with basal BC ($P<0.001$). In MDA-MB-231 cells we observed that RIP2 over expression increased NF-κB activity and enhanced cell resistance to ceramide and taxol-induced cell death. In addition, RIP2 mutants and knockdown decreased NF-κB activity, increased sensitivity of these cells to cytotoxins, increased caspase-3 activity and altered the cell cycle profile such that more cells were observed in the subG1 phase which is indicative of apoptosis.

Conclusion: RIP2 enhances survival and proliferation in BC and protects it from apoptotic death induced by cytotoxic drugs. By targeting RIP2, it might be possible to interfere with the NF-κB pro-survival signaling pathway and sensitize BC cells to induction of apoptosis by cyto/genotoxic drugs and may improve outcomes in advanced BC patients.

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