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Presentation Abstract

Abstract Number: C149

Presentation Title: STAT3 is a critical mediator of the pro-survival effect of Bcl-2-Rac1 interaction in human cancer cells

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Abstract Body: The small GTPase Rac1 is involved in the activation of the reduced NAD phosphate oxidase complex resulting in superoxide production. We recently showed that Bcl-2 overexpression inhibited apoptosis by creating a pro-oxidant intracellular milieu, and that inhibiting intracellular superoxide production sensitized Bcl-2-overexpressing cells to apoptotic stimuli. Gene silencing and functional inhibition of Rac1 blocked Bcl-2-mediated increase in intracellular superoxide levels in tumor cells. We provide evidence for a co-localization and physical interaction between the 2 proteins, which could be blocked in vitro and in vivo by the BH3 mimetics as well as by synthetic Bcl-2 BH3 domain peptides. That this interaction is functionally relevant is supported by the ability of the Bcl-2 BH3 peptide as well as the silencing and functional inhibition of Rac1 to inhibit intracellular superoxide production as well as overcome Bcl-2-mediated drug resistance in human leukemia and cervical cancer cells. Notably, the interaction was observed in primary cells derived from patients with B-cell lymphoma overexpressing Bcl-2 but not in noncancerous tissue. In an attempt to study the functional implication of this interaction, we carried out a computer simulation driven virtual predictive experiments based on the protein pathway dynamic network created by Cellworks Group Inc. The base line used for the study was a KRAS over-activated, PI3K overexpressed, CDKN2A deleted, β -catenin overexpressed and Bcl-2 overexpressed system aligned to HCT116 human

colorectal cancer cell line. When a variant of the above base line was created with Rac1 overexpression, phenotypic indices of angiogenesis, proliferation, viability, metastasis as well as tumor volume were all upregulated. Strikingly, the expression levels of STAT3 and β -catenin were significantly amplified in the computer modeled variant cell line; however upon Rac1 or Bcl-2 knockdown in both the base and the variant cell lines, apoptotic markers such as Bax, caspase 3 and cleaved PARP1 were increased while STAT3, β -catenin, NF- κ B and AGER were significantly down-regulated. Intrigued by these predictions, we set out to verify the link between STAT3 signaling and Bcl-2-Rac1 interaction. Interestingly, the activation status of STAT3 (pY705) strongly correlated with Bcl-2 expression as well as Rac1 activation status. Furthermore, STAT3 was found localized to mitochondria and preliminary results suggest an interaction with Bcl-2.

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