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Synergetic effect of PI3K inhibition and Bcl2/STAT5 knockdown in breast cancer cell lines

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PI3K signaling cascade is often hyperactivated in human cancer and is involved in both vertical and horizontal resistance to different targeted therapies. Inhibition of PI3K often show limited efficacy due to the reactivation of PI3K/AKT signaling. Kinases of the Janus family (JAKs) and their effector molecules (STATs) also play an important role in cancer since they are capable of stimulating cell proliferation, differentiation, migration, and survival. This pathway is activated upon binding of hormones and cytokines which are secreted by cancer cells and by cells from the tumor microenvironment. JAK2 is a known activator of PI3K and it is possible that JAK2 activation induced by PI3K inhibition contributes to AKT reactivation. Analyses of cytokine profiles after PI3K inhibition resulted in expression changes of several cytokines, IL-8 upregulation. Secreted IL-8 activates JAK2/STAT5 in breast cancer cells with a higher expression of CXCR receptors. It has been previously reported that activation of BIM and downregulation MCL1 are required for induction of cell death. The PI3K and JAK2 pathways activate the pro-survival protein MCL1 and suppress the pro-apoptotic protein BIM. Combined inhibition of PI3K/mTOR and JAK2 activates BIM and concomitantly downregulates MCL1, causing an increase in apoptosis, reduced tumor seeding and metastasis. Bcl-2 may serve as a target in the treatment of breast cancer as it is a known anti-apoptotic protein. Previous reports suggest that NF-kB and PI3K may contribute to Bcl-2 up-regulation in resistant cancers. Thus, IKK and PI3K inhibitors may potentially be used therapeutically in resistant breast cancers that have increased expression of Bcl-2. We propose that the knockdown of resistance molecules STAT5 and Bcl2 along with the chemical inhibition of PI3K will have a synergetic effect promoting an increased apoptotic rate of the treated breast cancer cells than by inhibiting only PI3K and JAK2.

Biography

Daniel Díaz obtained his Biology BSc at the Universidad Juárez del Estado de Durango (México), he then obtained his PhD diploma at the Universidad Autónoma de Nuevo León where he was awarded with an Academic Excellence fellowship from the National Board for Science and Technology (CONACyT) and a fellowship granted by the Science and Technology Research Support Program (PAICyT). He had the opportunity of undergoing extensive training in the Medical Center (Houston, TX) under the tutelage of several researchers in the University of Texas and M.D. Anderson Cancer Center and in the Institute of Biotechnology in Madrid, Spain. Currently, he is a Post-Doctoral Fellow in the Faculty of Medicine of the Charles University at Prague, Czech Republic.