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The tumor suppressor p16^{INK4a} expression bypasses 17AAG mediated cellular effects in human neuroblastoma, IMR-32

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The cancer chaperone, Hsp90 has been identified as a molecular target for cancer treatment interfering majorly with the proliferative potential of cells. Tumor cells can bypass the effects of tumor suppressors either through altered functions or deletions. We show that tumor cells that get adapted to tumor suppressor, p16INK4a circumvent growth suppressing functions and bypass Hsp90 inhibition mediated cell killing. The inability of cells to respond to Hsp90 inhibitor, 17AAG was found to be due to enhanced CDK6 dependent cell cycle regulation. Knocking down p16^{INK4a} enhanced CDK6 dependent cell cycle regulation in NRAS and CRAF dependent manner associating with enhanced migration and invasion. p16^{INK4a}KD cells then showed sensitivity to 17AAG by arresting at G1 phase of cell cycle and inhibiting cell migration and invasion. Further, p16^{INK4a}KD cells showed increased p14ARF, a negative regulator of MDM2 activating DNA damage response (DDR) through p53 stabilization and accumulation of p21$^{WAF1/CIP1}$. Although activated DDR in the functional compromise of Hsp90 induces cytotoxicity, we observed activation of cellular senescence, an alternative strategy to combat cancer. The in vitro findings are being evaluated *in vivo* using mice to affirm the anti-tumor effects of our treatment. Our results thus, have implications in anti-cancer therapeutics specifically against tumor cells that survive despite tumor suppressor expression.

Biography

Abhijnya KVV has major research interest in understanding the role of 'cancer chaperone, Hsp90' in tumor cell adaptations to stress. While several of oncogenic kinases are potential clients of Hsp90, how Hsp90 helps cells to adapt to single kinase mutations is an intriguing question. While addressing this question, I also intended to come out with inducing cellular senescence as a potential anticancer strategy. I have established tumor cells adapted to single mutation in Raf using primary human cells and uncovered how this mutated gene product activates Hsp90. Upon selective targeting of Hsp90 in these cells, they reverted from cancer progression back to senescence. Since the strategy I developed in the course of my study appears to be promising, I aim to bring about more such strategies either using a single Hsp90 inhibitor or in a combination against multiple types of cancers.

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