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Suppression of ribosomal protein RPS6KB1 by Nexrutine increases sensitivity of prostate tumors to radiation

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Radiation therapy (XRT) is a standard treatment for prostate cancer (PCa). Although dose escalation increases local control, toxicity hampers further escalation. Broader improvement will be possible by the addition of adjuvant therapies, which can synergize with radiation and thus improve efficacy. We have identified a natural compound (Nexrutine, Nx) that inhibits the survival and growth of PCa cells in combination with radiation. Combination studies demonstrated strong interaction between Nx and radiation both *in vitro* in multiple PCa cell lines and in the Transgenic adenocarcinoma of mouse prostate (TRAMP) model. Nx potentiated growth inhibitory effects of IR by down regulating ribosomal protein S6K (RPS6KB1), CyclinD1, Chk1 and HIF-1 α and prolonging G2/M checkpoint block. RPS6KB1 is upregulated in prostate cancers and its expression is correlated with tumor grade. Knockdown of RPS6KB1 in PCa cells increased their sensitivity toward radiation-induced survival inhibition. Overall, we provide scientific evidence (i) in support of Nx as an adjuvant in PCa patients receiving XRT (ii) suggesting that RPS6KB1 is an important player in Nx-mediated combinatorial benefits and emphasizes that RPS6KB1 is a novel target for PCa treatment. These data underscore the need to test the agent in additional preclinical models to validate these observations.