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ROCK Signaling and Radio Resistance: The Association and the Effect

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Abstract : Irradiation plays a pivotal role in cervical cancer treatment, however some tumors exhibit resistance to therapy while some exhibit relapse, due to better repair and enhanced resistance mechanisms operational in their cells. The present study aims to understand the signaling mechanism operational in resistance phenotype and in the present study we report the role of Rho GTPase associated protein kinase (ROCK) signaling in cervical carcinoma radio-resistance. ROCK signaling has been implicated in several tumor progressions and is important for DNA repair. Irradiation of spheroid cultures of SiHa cervical carcinoma derived cell line at 6Gy resulted in generation of resistant cells in vitro which had better clonogenic abilities and formed larger and more colonies, in soft agar colony formation assay, as compared to the non-irradiated cells. These cells also exhibited an enhanced motility phenotype. Cell cycle profiling showed the cells to be blocked in G2M phase with enhanced pCDC2 levels indicating onset of possible DNA repair mechanism. Notably, 3 days post-irradiation, irradiated cells showed increased ROCK2 translocation to the nucleus with enhanced protein expression as compared to the non-irradiated cells. Radio-sensitization of the resistant cells was enhanced using Y27632, an inhibitor to ROCK signaling. The treatment of resistant cells with Y27632 resulted in increased cell death upon further irradiation. This observation has been confirmed using inhibitory antibodies to ROCK1/2. Result show that both ROCK1/2 have a functional contribution in radiation resistance of cervical cancer cells derived from cell lines. Interestingly enrichment of stem like cells (Hoechst negative cells) was also observed upon irradiation and these cells were markedly sensitive to Y27632 treatment. Our results thus suggest the role of ROCK signaling in radio-resistance in cervical carcinoma. Further studies with human biopsies, mice models and mechanistic of ROCK signaling in the context of radio-resistance will clarify the role of this molecule further and allow for therapeutics development.

Keywords : cervical carcinoma, radio-resistance, ROCK signaling, cancer treatment
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