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Cyclin D1 silencing suppresses tumorigenicity, impairs DNA double strand break repair and thus radiosensitizes androgen-independent prostate cancer cells to DNA damage

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Patients with hormone-resistant prostate cancer (PCa) have higher biochemical failure rates following radiation therapy (RT). Cyclin D1 deregulated expression in PCa is associated with a more aggressive disease: however its role in radioresistance has not been determined. Cyclin D1 levels in the androgen-independent PC3 and 22Rv1 PCa cells were stably inhibited by infecting with cyclin D1-shRNA. Tumorigenicity and radiosensitivity were investigated using in vitro and in vivo experimental assays. Cyclin D1 silencing interfered with PCa oncogenic phenotype by inducing growth arrest in the G1 phase of cell cycle and reducing soft agar colony formation, migration, invasion in vitro and tumor formation and neo-angiogenesis in vivo. Depletion of cyclin D1 significantly radiosensitizes PCa cells by increasing the RT-induced DNA damages by affecting the NHEJ and HR pathways responsible of the DNA double-strand break repair. Following treatment of cells with RT the abundance of a biomarker of DNA damage, γ-H2AX, was dramatically increased in sh-cyclin D1 treated cells compared to shRNA control. Concordant with these observations DNA-PKcs-activation and RAD51-accumulation, part of the DNA double-strand break repair machinery, were reduced in shRNA-cyclin D1 treated cells compared to shRNA control. We further demonstrate the physical interaction between CCND1 with activated-ATM, -DNA-PKcs and RAD51 is enhanced by RT. Finally, siRNA-mediated silencing experiments indicated DNA-PKcs and RAD51 are downstream targets of CCND1-mediated PCa cells radioresistance. In summary, these observations suggest that CCND1 is a key mediator of PCa radioresistance and could represent a potential target for radioresistant hormone-resistant PCa.

Keywords

Prostate cancer; cyclin D1; radioresistance.