Protein arginine methyltransferase 5 (PRMT5): An emerging epigenetic regulator and novel therapeutic target for prostate cancer radiosensitization

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Radiation therapy (RT) is a potentially curative treatment used for the majority of prostate cancer patients. In general, RT utilizes ionizing radiation (IR) to kill cancer cells by generating double strand breaks (DSBs) in DNA. As resistance to RT can occur due to enhanced repair of DSBs, targeting proteins critical to the DNA damage response (DDR) is a promising radiosensitization approach for prostate cancer treatment. Upon recognition of extensive DSBs, ‘core repair proteins’ are upregulated and recruited to the sites of damage to facilitate repair either through homologous recombination (HR) or non-homologous end joining (NHEJ). Although the highly regulated recruitment and action of core repair proteins is well characterized, little is known about the selective induction of their expression upon DNA damage to ensure successful repair. Gene expression profiling using RNA-seq suggest that protein arginine methyltransferase 5 (PRMT5) acts as a master epigenetic activator of DNA damage response (DDR) genes including several well characterized core repair proteins. Knockdown or pharmacological inhibition of PRMT5 hinders repair of IR-induced DSBs in multiple normal and cancer cell lines. Among 121 genes that are differentially regulated by PRMT5 in response to IR, approximately 80% of which are DDR genes including those required for HR, NHEJ, and G₂ arrest. Further, PRMT5 is quickly upregulated and recruited to promoters to activate gene expression upon IR treatment. Lastly, PRMT5 levels also correlate positively with the expression of these target genes in multiple human cancer tissues. Additionally, targeting PRMT5 sensitizes both AR-expressing and AR-null prostate cancer cell lines to radiation. Given that PRMT5 is overexpressed in several cancers, including prostate cancer, and that targeting DSB repair is a valid therapeutic approach for cancer treatment, PRMT5 targeting may be explored as a monotherapy or combination therapy with radiation therapy (RT) and chemotherapy for prostate cancer and across various cancer types.