Role of Prx4 in Prostate Cancer Development and Radiation Resistance

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Introduction & Objective

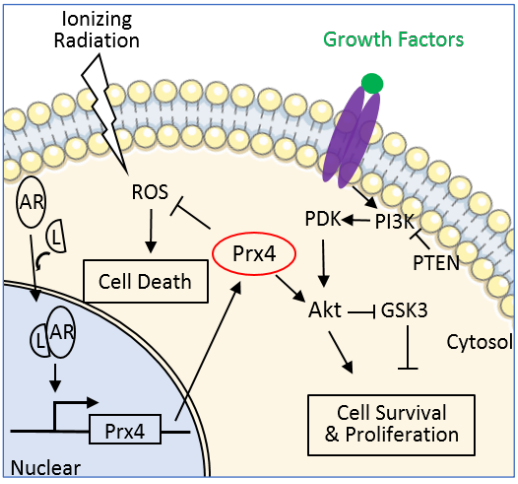
The peroxiredoxin (Prx) family of proteins functions as major cellular antioxidants that mediate oxidative signaling under physiological conditions as well as scavenge extra hydrogen peroxide in the context of oxidative stress. Among them, Prx4 is encoded by *PRDX4* gene on X chromosome and has been found to contribute to the development of male reproduction system. Previous studies indicate that Prxs are frequently upregulated in various types of human cancer. However, the role of Prx4 in prostate cancer has not been well defined. The purpose of this study is to examine the expression of Prx4 in prostate cancer and to explore its functional significance in cancer radiation resistance and recurrence.

Methods

Bioinformatic tools were used to evaluate genetic alterations of *PRDX4* gene as well as the levels of its transcripts in prostate normal and cancer populations. Kaplan-Meier survival analysis was used to explore the association of Prx4 levels with the prognosis of prostate cancer patients. Western blot and immunohistochemistry were used to evaluate the expression of Prx4 protein in cell lines and patient specimens. Loss of Prx4 in cells was achieved by knock down using lentiviral shRNA or knockout using CRISPR-Cas9 techniques. Cell proliferation, survival, and protein profiler kinase arrays were used to examine the differences between control and Prx4-depleted cells with or without ionizing radiation.

Results

We demonstrated that *PRDX4* gene is frequently amplified in prostate cancer and the level of its transcript is highly elevated. Patients with Prx4 at higher quartile have significantly reduced probability of survival compared with those in lower quartile. Prostate cancer cells express much higher levels of Prx4 than normal epithelial cells. Moreover, Prx4 is upregulated by the activation of AR-dependent signaling, and depletion of Prx4 sensitizes prostate cancer cells to radiation-induced cell death. Mechanistically, Prx4 contributes to prostate cancer radiation resistance through the activation of PI3K/AKT signaling pathway (Figure).



Conclusions

A combination of bioinformatic, histochemical, cellular, and molecular methods reveals that Prx4 plays a critical role in prostate cancer cell proliferation, radioresistance and reoccurrence.