**STAT5A/B BLOCKADE SENSITIZES PROSTATE CANCER TO RADIATION THROUGH INHIBITION OF RAD51 AND DNA REPAIR**

Maranto C[#1,2], Udhane V[#1,2], Hoang DT[3], Gu L[3], Alexeev V[4], Malas K[1,2], Cardenas K[1,2], Brody JR[5], Rodeck U[4], Bergom C[6], Iczkowski KA[1], Jacobsohn K[7], See W[7], Schmitt SM[1,2], **Nevalainen MT[8,2].**

[1]Department of Pathology, Prostate Cancer Center of Excellence at Medical College of Wisconsin Cancer Center, Medical College of Wisconsin, Milwaukee, Wisconsin.
[2]Department of Pharmacology & Toxicology, Prostate Cancer Center of Excellence at Medical College of Wisconsin Cancer Center, Medical College of Wisconsin, Milwaukee, Wisconsin.
[3]Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania.
[4]Department of Dermatology, Thomas Jefferson University Medical College, Philadelphia, Pennsylvania.
[5]Department of Surgery, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania.
[6]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin.
[7]Department of Urology, Prostate Cancer Center of Excellence at Medical College of Wisconsin, Milwaukee, Wisconsin.
[8]Department of Pathology, Prostate Cancer Center of Excellence at Medical College of Wisconsin Cancer Center, Medical College of Wisconsin, Milwaukee, Wisconsin. mnevalainen@mcw.edu.
[#]Contributed equally

**Background**: The standard treatment for organ-confined prostate cancer is surgery or radiation, and locally advanced prostate cancer is typically treated with radiotherapy alone or in combination with androgen deprivation therapy. Here, we investigated whether Stat5a/b participates in regulation of doublestrand DNA break repair in prostate cancer, and whether Stat5 inhibition may provide a novel strategy to sensitize prostate cancer to radiotherapy.
**Methods**: Stat5a/b regulation of DNA repair in prostate cancer was evaluated by comet and clonogenic survival assays, followed by assays specific to homologous recombination (HR) DNA repair and nonhomologous end joining (NHEJ) DNA repair. For HR DNA repair, Stat5a/b regulation of Rad51 and the mechanisms underlying the regulation were investigated in prostate cancer cells, xenograft tumors, and patient-derived prostate cancers ex vivo in 3D explant cultures. Stat5a/b induction of Rad51 and HR DNA repair and responsiveness to radiation were evaluated in vivo in mice bearing prostate cancer xenograft tumors.
**Results**: Stat5a/b is critical for Rad51 expression in prostate cancer via Jak2-dependent mechanisms by inducing Rad51 mRNA levels. Consistent with this, genetic knockdown of Stat5a/b suppressed HR DNA repair while not affecting NHEJ DNA repair. Pharmacologic Stat5a/b inhibition potently sensitized prostate cancer cell lines and prostate cancer tumors to radiation, while not inducing radiation sensitivity in the neighboring tissues.
**Conclusions**: This work introduces a novel concept of a pivotal role of Jak2–Stat5a/b signaling for Rad51 expression and HR DNA repair in prostate cancer. Inhibition of Jak2–Stat5a/b signaling sensitizes prostate cancer to radiation and, therefore, may provide an adjuvant therapy for radiation to reduce radiation-induced damage to the neighboring tissues.

**Conflict of Interest:** U. Rodeck reports receiving commercial research grants from REATA Pharmaceuticals. K.A. Iczkowski is a consultant/advisory board member for 3D Biopsy, LLC and MicroGen DX. No potential conflicts of interest were disclosed by the other authors.

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