

P57 Role of toll-like receptor 3 in prostate cancer therapy-resistance

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Introduction & Objectives: Prostate cancer (PCa) is the most frequent non-skin cancer affecting men in developed countries. One common curative strategy aimed to maintain disease under control is the androgen-deprivation therapy, which consists of lowering testosterone circulating levels by the use of anti-androgen molecules, such as Enzalutamide and Abiraterone. Despite initial effectivity, patients might eventually develop resistance, progressing into a condition of castration-resistant PCa (CRPC) associated with further development of the tumor. Thus, curative strategy shifts to the use of chemotherapeutic agents, like Docetaxel, which ultimately may also lead to chemoresistance, with disease progress into metastatic condition. Toll-like receptors (TLRs) are key proteins in immune response and have been reported to be expressed also in epithelial cells. Moreover, studies showed that TLRs may affect prognosis in patients affected by PCa, by the activation or inhibition of pathways involved in carcinogenesis. The aim of our study was to evaluate the expression of TLRs in PCa and to assess a possible connection between TLRs and therapy-resistant PCa.

Results: For this purpose, we screened 38 TLR- and oncogene-associated molecules in control and tumor patient sample, in clinically relevant patient-derived xenografts (PDX) and in four PCa cell lines with different resistance status. Regardless the heterogeneous expression of the assayed markers in our models, we found that TLR3 and TLR4 genes were up-regulated in all resistant models, but only TLR3 modulation was observed also at a protein level, assayed by methods including flow cytometry. Given that TLR3 was reported to induce apoptosis in PCa through the activation of IRF3-dependent pathway, we evaluated the phosphorylation of this transcription factor. Although no striking difference was observed in the baseline expression, we detected a defect in TLR3 activation ability in therapy-resistant models.

Conclusions: Taken together, our results show a potential implication of TLR3 in PCa and therapy-resistance.

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