Immunogenetics of prostate cancer: first clinical insights

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Immune system acts as a double-edged sword in different stages of cancer battle, exerting a direct activity both in the microenvironment and in the global response to cancer. The deeply definition of such mechanism is essential to develop new strategies to harness the power of immunity to defeat cancer. A possible way to go in deepening this matter is to understand the potential role of polymorphisms (SNPs) in factors involved in immune system activity. One clinical setting of interest is represented by clinically localized prostate cancer (PCa), that represents 90% of all diagnosed prostate cancers. Despite the improvement obtained with the introduction of different treatment strategies, a large number of patients relapse. One parameter commonly used in the clinical practice to evaluate recurrence is represented by an increase of plasma prostate-specific antigen (PSA) levels, that determines the biochemical PSA recurrence (BCR). It is estimated that BCR is detected in 15% to 46% of PCa patients treated with RT. The prompt identification of this subgroup of patients can play a pivotal clinical role because it can be translated in a more frequent patients' follow-up and a more appropriate maintenance therapy. The need of more specific and accurate prognostic biomarkers has not been overcome yet. In this scenario, immunogenetics could be the key to find an answer to this compelling necessity.

This study aimed to identify new immunogenetic prognostic biomarkers in PCa patients treated with RT as primary therapy. The first clinical end-point was the identification of genetic biomarkers associated with BCR and overall survival (OS). The secondary end-point was the definition of an immunogenetic score.

For this purpose, we analyzed 447 SNPs localized in genes involved in immune system activity in a group of 418 Caucasian PCa patients treated with RT. The genetic analyses were performed in a Veracode (Illumina) platform. Multivariate COX regression was applied to identify the prognostic role of the SNPs. Five different genetic models were considered for each polymorphism, the most significant one was selected according to p-value (<0.05) and q-value (<0.15) defined according to the False discovery rate (FDR) method. Eighteen SNPs were significantly associated with BCR, no one with OS. Interestingly, these SNPs, not in linkage, addressed in an independent way the key role of PDL1, VEGFR, FOXO3, SMAD3, SMAD2, and IL4R, genes involved in angiogenesis and TGFβ pathway, that play a pivotal role in PCa and in RT response.

Through an automatic selection, the most robust biomarkers were identified: SMAD3-rs7162912, SMAD3-rs9302242, PDL1-rs4143815, PDL1-rs1411262, SMAD2-rs4940086, STAT1-rs16824035, VEGFR-rs12498529, IL2RB-rs84460. Applying the genetic recessive models to these SNPs, a genetic score was defined. It significantly discriminated the risk of BCR among 4 groups of patients according to their genotypes (p=5.4*10-4). This represents the most relevant result of this study

considering the improved capability of the score to define patients' prognosis comparing to the prognostic role of the individual SNPs.

In the next months, we plan to test the prognostic role of the 18 SNPs and of the identified genetic score in a validation set of 131 PCa patients. These analyses are needed to hopefully offer to clinicians new biomarkers to optimize PCa patients' management.