53 Spliceosome components and splicing factors as novel therapeutic targets for prostate cancer

Eur Urol Suppl 2019; 18(1);e71

Jiménez-Vacas J.M. [1], Herrero-Aguayo V. [1], Gómez-Gómez E. [1], León-González A.J. [1], Sáez-Martínez P. [1], Montero-Hidalgo A.J. [1], González-Serrano T. [2], Requena-Tapia M.J. [3], Castaño J.P. [1], Gahete M.D. [1], Luque R.M. [1]

[1]Maimonides Institute of Biomedical Research of Cordoba, Dept. of Cell Biology, Physiology and Immunology, Córdoba, Spain, [2]Maimonides Institute of Biomedical Research of Cordoba, Dept. of Anatomical Pathology, Córdoba, Spain, [3]Maimonides Institute of Biomedical Research of Cordoba, Dept. of Urology, Córdoba, Spain

Introduction & Objectives: Dysregulation of splicing variants expression has recently emerged as a novel cancer hallmark. Splicing process is accurately controlled by the tight interplay between the spliceosome and the splicing factors (SFs). Although the generation of some splicing variants (e.g. ARv7, sst5TMD4, In1-ghrelin) has been associated to prostate cancer (PCa) aggressiveness and/or castration resistant PCa (CRPC) development, the role of most of the spliceosome components (SCs) and SFs in PCa remain still unknown. For that reason, we aimed to investigate the possible dysregulation of SCs and SFs expression in PCa, and their potential as novel therapeutic targets for this pathology.

Materials & Methods: Expression levels of 14 SCs and 28 SFs were measured by a microfluidic-based qPCR array in PCa samples (n=126) and non-tumoral samples (n=84) from two independent cohorts. In addition, functional (cell proliferation, migration, apoptosis and tumorspheres formation) and mechanistic assays (gene expression by qPCR and protein levels by Western Blot) were performed in normal prostate cells (RWPE-1 cell-line and primary cell-cultures from cystoprostatectomies) and PCa cells (LNCaP, 22Rv1, PC-3 and DU145 cell-lines and primary cell cultures from PCa biopsies) in response to SFs silencing with siRNAs or treatment with the spliceosome-inhibitor Pladienolide-B.

Results: The expression levels of 7 SCs and 19 SFs were significantly altered in PCa compared to their adjacent non-tumoral regions. Specifically, higher expression levels of SRSF3, snRNP200 and SRRM1 were associated with elevated Gleason Score and T stage levels, as well as with metastatic stage and higher probability to develop recurrence, perineural- and lymphovascular-invasion. The expression levels of SRSF3, snRNP200 and SRRM1 were also positively correlated with ARv7 (but not AR) expression. In addition, silencing of SRSF3, snRNP200 and SRRM1 expression by siRNAs as well as spliceosome inhibition by Pladienolide-B exerted antitumoral effects by reducing proliferation, migration and tumorsphere formation as well as by increasing the apoptotic rate, likely through the reduction of oncogenic transcripts (AR-v7, PCA3, In1-ghrelin, MKI67, PTTG, VIM and CDKs) expression, as well as through the decrease of p-AKT and p-JNK protein levels in PCa cell lines. Additionally, primary PCa-derived cells were significantly more sensitive to the anti-viability effect exerted by Pladienolide-B, as compared to primary non-tumoral cells. Finally, Pladienolide-B was able to markedly alter the expression of numerous SCs and SFs, some of them previously related to higher PCa aggressiveness and/or ARv7 generation (e.g. SFPQ, U2AF2, KHDRSB1).

Conclusions: The spliceosome machinery and specially SRSF3, snRP200 and SRRM1 could represent attractive novel therapeutic targets for PCa and CRPC.