Exosomal matrix metalloproteinases 2 and 9 in Prostate Cancer.

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VI Congreso de Señalización Celular, SECUAH 2021.
29 de marzo a 30 de abril, 2021. Universidad de Alcalá. Alcalá de Henares, Madrid. España.

Keywords: Prostate cancer; Exosomes; Matrix metalloproteinases; Liquid biopsy

Abstract

Prostate Cancer (PCa) is the second most frequent type of cancer in men around the globe, with an incidence of 1,3 million cases in 2018 and it's expected to be increased by 79,8% in 2040. Most of the cases are multifocal adenocarcinomas and their differentiation and progression shows an important heterogeneity: while some will stay asymptomatic and localized, some others will spread and cause metastasis, event related to most cases of death due to PCa.

The diagnosis is based on the histological characteristics observed in needle biopsies or radical prostatectomy, using the Gleason Score. Furthermore, the current biomarker, the prostate-specific antigen (PSA), shows poor specificity, which leads to frequent false positive and unnecessary medical interventions. It urges to find a method to distinguish PCa patients from not PCa ones, but it is also essential a parameter that discriminates aggressive tumours from latent ones.

Exosomes are one type of extracellular vesicles, characterized by a diameter of 30-150 nm produced by all types of human cells and they can be found in human fluids, such as blood or urine. In PCa, exosomes contribute to cell transformation, angiogenesis and tumour progression, due to the molecular mediators they carry. Matrix metalloproteinases 2 and 9 (MMPs 2 and 9) are zinc and calcium-dependent endopeptidases that break down extracellular matrix proteins. They are related to aggressive PCa phenotype and they are carried by exosomes.

We suggest that MMP2 and 9 can be used as biomarkers of PCa in liquid biopsy, such as urine. This biochemical analysis of urine samples will be complemented by the immunohistochemistry analysis of needle prostate biopsies. Finally, we will study the effect of isolated exosomes on the neurodifferentiation of androgen-dependent prostate cancer cell line (LNCaP).

Urine and needle biopsies samples were provided by Urology Service of University Hospital Principe de Asturias . Urine samples were processed in order to isolate exosomes. Biochemical analysis, such as Zymography or Western blotting, were performed with non-cancer and cancer samples. Alongside, immunohistochemistry (IHC) study of the expression of several molecules, such as prostatic specific membrane antigen (PSMA) or MMPs, in needle biopsies was conducted. Eventually, LNCaP cells were treated with isolated exosomes from urine of non-cancer and cancer patients.

Preliminary results showed: 1) a higher expression of PSMA in apical cytoplasm of Gleason 6 epithelial cells as compared to non-cancer samples; 2) LNCaP cells treated with exosomes from patients with cancer showed an increment in the percentage of the neuroendocrine differentiation.

In order to complete this research, we will continue examining more urine samples, complete more IHC with different Gleason score and replicate cell culture experiments in the following weeks.

Citation: Huertas, Raquel; Muñoz, Laura; Arenas, María Isabel; Román, Irene de los Dolores; Sanchís, Ángeles; Bajo, Ana María (2021) Exosomal matrix metalloproteinases 2 and 9 in Prostate Cancer. Proceedings of the VI Congreso de Señalización Celular, SECUAH 2021. 29 de marzo a 30 de abril, 2021. Universidad de Alcalá. Alcalá de Henares, Madrid. España. dianas 10 (1): e202103a07. ISSN 1886-8746 (electronic) journal.dianas.e202103a07 http://www3.uah.es/dianas?e202103a07.
URI http://hdl.handle.net/10017/15181