Opposing roles of PIK3CA gene alterations to EZH2 signaling in Non-Muscle Invasive Bladder Cancer

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Abstract

Bladder cancer (BC) is a current challenging problem in the clinics. At diagnose, it can appear in two different pathological forms. The non-muscle invasive bladder cancer (NMIBC) represents 70% of BC cases and is treated by transurethral resection. However, they also show one of the highest rates of recurrence, which in some cases can progress into aggressive muscle-invasive tumors (MIBC). This requires a regular surveillance making NMIBC one of the most costly malignancies to health care systems in developed countries [1]. Moreover, there are not effective therapies for MIBC, besides cystectomy followed by conventional chemotherapy, which is still ineffective. Therefore is required the identification of biomarkers that may help to determine recurrence and possible progression in NMIBC. We previously demonstrated that PIK3CA gene alterations are extremely frequent in NMIBC, being present in non-affected bladder tissue, and predicted low recurrence and progression [2]. On the other hand, genomic profiling indicated that gene expression mediated by increased EZH2 expression, were associated with increased recurrence and progression [3]. The different clinical evolution of tumors characterized by either PIK3CA gene alterations, or increased expression and activity of EZH2, led us to hypothesize that these two pathways may exert opposite roles in NMIBC. Here, we report that molecular evidences using clinical samples and BC cell lines, that PI3K-dependent signaling negatively regulates EZH2-dependent processes. We demonstrate that *PIK3CA* alterations mediate increased expression of two miRNAs, miR-101 and miR-138, which post-transcriptionally downregulate EZH2 expression. In addition, the PIK3-dependent signaling activates Akt, which in turn phosphorylatesEZH2 on Ser21, which produces decreased H3K27 methyl transferase activity. These observations could help to define better clinical intervention protocols for NMIBC management.

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