**Abstract**

BK5.COX2 MODEL: Bladder cancer is a common malignancy. Numerous studies have demonstrated that increased expression of cyclooxygenase-2 (COX-2) plays a critical role in the development and progression of bladder cancer. COX-2 overexpression is associated with bladder tumor development, progression, and metastasis. However, the exact role and mechanisms of COX-2 overexpression during bladder carcinogenesis have not been well defined. In this study, we aimed to elucidate the role of COX-2 overexpression in bladder carcinogenesis using BK5.COX2 transgenic mice.

**Objectives**

- To determine the effect of COX-2 overexpression on the gene expression profile in bladder epithelium.
- To explore potential mechanisms by which COX-2 can influence urinary bladder carcinogenesis.

**Introduction**

Bladder cancer represents an important health concern. The identification of new therapeutic strategies for bladder cancer prevention and therapy is a potential means to reduce the development and progression of this disease. Numerous studies have demonstrated that COX-2 is upregulated in TCC of human urinary bladder. The degree of COX-2 expression is significantly correlated with the tumor grade and depth of invasion (3,4). In addition, COX-2 overexpression is an independent prognostic factor for muscle-invasive bladder cancer (5). The current study involved BK5.COX2 mice, which allows us to study gene expression changes that were due solely to the overexpression of COX-2 in the bladder tissue of a novel transgenic mouse model. This model may serve as a powerful tool to study the etiology and prevention of human urinary bladder cancer.

**Methods**

BK5.COX2 transgenic mice were crossed with mice expressing the transgene under the control of a tissue-specific promoter to generate BK5.COX2 transgenic mice. Urinary bladders were excised and RNA was isolated. Microarray analysis was performed to compare gene expression in wild-type and BK5.COX2 transgenic mice. Immunochemical staining and Western blotting were used to validate gene expression changes.

**Results**

COX-2 overexpression induces the regulation of genes involved in immune stress. The downstream signaling molecules in bladder epithelium were significantly upregulated in BK5.COX2 transgenic mice compared to wild-type controls.

**Conclusions**

COX-2 overexpression regulates the expression of genes involved in immune-stress, angiogenesis, proliferation, cell cycle, and extracellular matrix remodeling events as initiating responses.

The growth factor, epiregulin, is the most significantly upregulated gene as validated by qRT-PCR.

The expression of epiregulin and the TGF-beta family was consistently deregulated with the progression of urinary bladder mucosa carcinogenesis.

*Bladder tissues were excised from 10 wk old wild-type and BK5.COX2 transgenic mice. Ten Mouse 430 GeneChips (Affymetrix Inc., Santa Clara, CA) were used; one chip per experimental group. Gene expression was assessed using the Affymetrix microarray platform. Gene expression levels were normalized against the housekeeping gene GAPDH and evaluated using the Affymetrix GeneChip Operating Software (GCOS) (Affymetrix, Santa Clara, CA). Results were validated using qRT-PCR.

**Future Directions**

- Determine the presence and level of all the prostaglandins and their respective receptors.
- Examine the role of epiregulin and the downstream signaling pathways in bladder carcinogenesis.
- Explore the role of the immune response in regulating the hyperplastic response of the bladder transitional epithelium.

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