Abstract

Renal cell carcinoma (RCC) accounts for 3% of all malignancies reported each year and is the sixth leading cause of cancer death in the US. Risk factors include smoking, obesity, high-fat diet and genetic and hereditary history. Early diagnosis of this disease is essential for intervention and cure due to the lack of effective treatments available for later stage and metastatic disease. Loss of responsiveness to TGF signaling has been proposed to play a prominent role in RCC carcinogenesis and progression. Loss of the type III Transforming Growth Factor-β (TGFβ) receptor (βIII) has been identified to cause a loss of TGFβ responsiveness.

TβRIII in a putative tumor suppressor and its expression has been identified to be lost or reduced in a number of cancers: prostate cancer 1, renal cell carcinoma (RCC) 2, ovarian cancer 3, breast cancer 4, and non-small cell lung cancer 5. Loss of TβRIII has been hypothesized to be an early event in renal cell cancer (RCC)

Identification of transcription factor response elements in the TβRIII 0.58KB distal promoter

Figure 3. Point mutations of putative binding sites in the proximal promoter of TβRIII lead to decreased expression and enhanced metastatic properties. TFβIII expression is decreased in UMRC2 cells treated with 5′AZA and DMSO compared to control. The proximal promoter is more responsive to TFβIII silencing putative transcription factors using lentiviral shRNA silencing putative transcription factors using lentiviral shRNA

Promoter regulation of endogenous TβRIII mRNA

Figure 4. Identification of enhancer regions in the proximal TβRIII promoter. 50 and UMRC2 cells were grown to 70% confluence on 10% FBS. Cells were treated with 5′AZA and DMSO (30 μM) for 2 days, then transfection with promoter luciferase. Luciferase activity was measured in Renilla as an internal control for transfection efficiency. Results are expressed as a ratio of Firefly activity normalized to the Tk promoter control vector.

Future Directions

- Identification of transcription factor family members and other proteins that are knocking out the 5′-50 bp region of the proximal promoter that are modulated in renal cancer cells.
- Creation of 5′AZA and DMSO deletion mutants of the 5′-50 bp region of the proximal promoter that are transfected with promoter luciferase. Luciferase activity is measured in Renilla as an internal control for transfection efficiency. Results are expressed as a ratio of Firefly activity normalized to the Tk promoter control vector.

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References