DEVELOPMENT OF URINARY BLADDER AUTOIMMUNE CYSTITIS MODEL

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INTRODUCTION AND OBJECTIVE: The etiology of interstitial cystitis (IC) remains unclear, but evidence suggests that an immune/autoimmune inflammatory process is involved in the pathogenesis. We created a transgenic (Tg) autoimmune cystitis model to determine the role of T helper (Th) polarization in the development of bladder autoimmune disease.
METHODS: A plasmid DNA (pUPII-OVA) containing the urothelium-specific uroplakin II gene promoter and a chimeric transgene consisting of human transferrin receptor transmembrane domain and chicken ovalbumin (OVA) was constructed. The 6.1 Kb KpnI-DraIII fragment of pUPII-OVA was microinjected for the development of proposed Tg mice (termed as URO-OVA Tg mice). Tail genotyping was performed for Tg screening and Tg founders were backcrossed with C57BL/6 mice. Various tissues were prepared from F1 mice and processed for RT-PCR and ELISA. The effectiveness of CD4+ T cells as effectors in the induction of OVA-mediated cystitis was tested using OVA CD4 T cell receptor (TCR) Tg mice (OT-II mice).
RESULTS: The constructed plasmid pUPII-OVA (~8.9 Kb) resulted in a cell-type specific OVA expression in transient expression assay in vitro. Among the 82 pups produced, 6 Tg founders were obtained. Four Tg founders produced a total of 23 F1 offspring with 16 pups being positive by tail DNA genotyping. To determine the specificity of OVA expression, 1 mouse (F1 generation) from each of 3 positive lines was processed for tissue RNA extraction and RT-PCR analysis. Among various tissues tested, the bladder was found to be the predominant organ for OVA expression while skin also showed weak OVA expression. Densitometry analysis indicated that OVA mRNA expression was 3-27 fold higher in the bladder than in the skin. Interestingly, although 2 Tg lines tested showed comparable expression of OVA in the bladder by ELISA, 1 Tg line showed no detectable OVA expression in skin whereas the other showed clear OVA expression in skin. Naïve OT-II Tg mice developed bladder inflammation after 5 doses of intravesical OVA administration (10 mg/dose; once a week). OT-II CD4+ T cells also demonstrated to be effective on induction of cystitis after adoptive transfer into wild-type C57BL/6 mice followed by 1 dose of intravesical OVA administration (10 mg).
CONCLUSIONS: Three URO-OVA Tg lines have been developed. All exhibit high OVA expression in the bladder and low OVA expression in skin. OT-II CD4+ T cells have shown to be potent effectors in the development of OVA-mediated cystitis and will facilitate determination of the role of Th polarization in the development of autoimmune cystitis.

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