463

Chuang F[1], Shie J[2], Kuo H[2]

1. *Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hsopital, Kaohsiung, Taiwan,* ***2.*** *Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan*

INCREASED UROTHELIAL CELL APOPTOSIS AND CHRONIC INFLAMMATION MIGHT BE THE CAUSES OF RECURRENT URINARY TRACT INFECTION IN WOMEN

Hypothesis / aims of study

Recurrent urinary tract infection (UTI) is frequently occurred in women. Patients wit recurrent UTI might also have bladder irritative symptoms. Previous studies have revealed that patients with recurrent UTI have elevated urinary nerve growth factor, suggesting chronic inflammation is present in the bladder of these patients after resolution of UTI. We hypothesized that chronic inflammation might reside in the bladder wall, which might also cause urothelial dysfunction and defective barrier function. UTI might be easy to recur in these patients. This study was designed to investigate whether increased urothelial cell apoptosis and chronic inflammation were the causes of recurrent UTI in women.

Study design, materials and methods

The bladder biopsy specimens were collected from thirty women with recurrent UTI and ten controls. Recurrent UTI was defined as at least three symptomatic and medically diagnosed UTI in the previous 12 months. The bladder biopsies were performed during the period when UTI episode had been completely resolved and urine analysis and rine culture all showed negative. Immunofluorescence staining of the junction protein E-cadherin, mast cell and TUNEL (to assess urothelial apoptosis) were performed in all the bladder specimens. The expression of E-cadherin, mast cell and TUNEL were measured and quantified as positive cells (±SD) per 100 cells. In addition, western blots were also performed to analyze the inflammatory proteins (phospho-p38, tryptase) and apoptotic protein (Bax) in bladder mucosa specimens between two patients with recurrent UTI and one control.

Results

Immunofluorescence staining showed significantly lower E-cadherin in the recurrent UTI bladder tissue compared with the controls (25.4 ± 8.9 v 42.4 ± 16.7, P<0.0001). The mast cell expression was significantly stronger in the recurrent UTI bladder tissue compared with the controls (2.5 ± 1.8 v 1.3 ± 1.2, P=0.046). TUNEL staining revealed a significantly higher numbers of apoptotic cells in the recurrent UTI bladder tissue compared with the control bladder tissue (1.5 ± 1.8 v 0.08 ± 0.3, P<0.0001) (Fig. 1 and Table 1). Western blot analysis also showed that the expressions of phospho-p38, tryptase and Bax increased in two recurrent UTI specimens compared with one normal control specimen (relative intensity 3.6 ± 1.9, 2.0 ± 2.2 and 2.0 ± 0.,5 respectively) (Fig. 2).

Interpretation of results

The immunofluorescence staining and Western blot protein analysis of the bladder biopsy specimens of recurrent UTI women and controls revealed that the expressions of the inflammatory proteins and urothelial cell apoptosis were remarkable and the barrier function of urothelium was impaired in recurrent UTI cases.

Concluding message

Chronic inflammation, urothelial cell apoptosis and impairment of barrier function of urothelial cells could be the underlying pathophysiology of recurrent UTI in women. Chronic inflammation might reside in the bladder wall after resolution of UTI, which might also cause urothelial dysfunction and defective barrier function and UTI will be easy to recur in these patients.

Fig. 1. Immunofluorescence staining showed significantly lower E-cadherin, increased mast cell activity and increased apoptotic cells in the recurrent UTI bladder tissue compared with controls Control Recurrent UTI

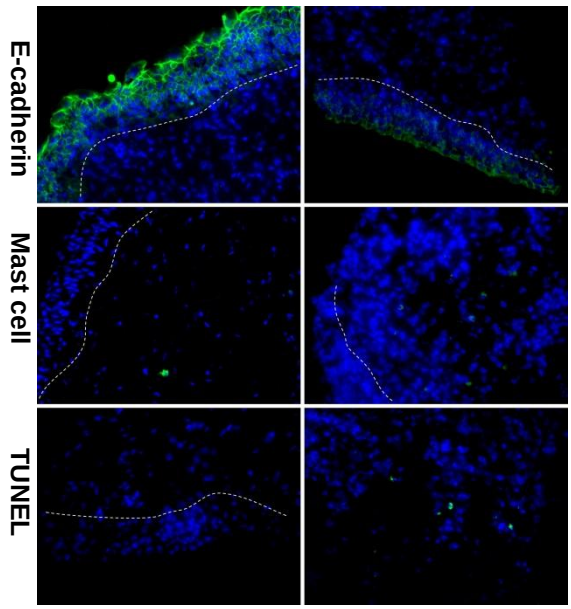
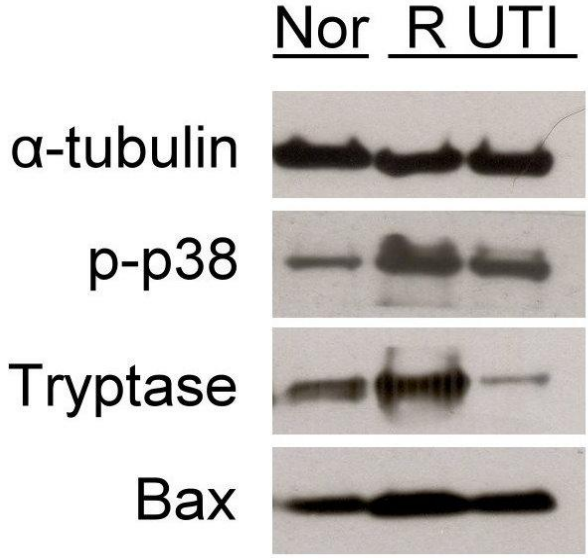


Table 1. Expression of E-cadherin, Mast cell and TUNEL in specimens of control and recurrent UTI patients

	Control (n=10)	Recurrent UTI (n=30)	P-value
E-cadherin	42.4 ± 16.7	25.4 ± 8.9	<0.0001
Mast cell	1.3 ± 1.2	2.5 ± 1.8	0.046
TUNEL	0.08 ± 0.3	1.5 ± 1.8	<0.0001

Data are expressed as mean ± SD numbers of positive cells per 100 cells, for E-cadherin data are expressed as mean ± SD pixel of image per area unit (μm^2)

Fig. 2. Western blot analysis of expression of phospho-p38, tryptase and Bax in 2 patients with recurrent UTI compared with one control. Relative intensity of phospho-p38, tryptase and Bax compared with α-tubulin.



Relative intensity

	Normal N=1	**Recurrent UTI N=2**
p-p38	**1.00**	**3.6±1.9**
Tryptase	**1.00**	**2.0±2.2**
Bax	**1.00**	**2.0±0.5**

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