

## INVESTIGATION OF THE FUNCTION OF INTEGRIN-MEDIATED BACTERIAL ADHERENCE PROTEINS AND THEIR RECEPTORS IN WOMEN WITH RECURRENT BACTERIAL CYSTITIS AND INTERSTITIAL CYSTITIS

### Hypothesis / aims of study

Urinary tract infection (UTI), in particular cystitis, is very common in women of all ages and can drastically compromise the quality of life of sufferers. A characteristic feature of UTI is its marked tendency to reoccur. Interstitial cystitis is a chronic inflammatory disorder of the bladder that is notoriously difficult to manage and can result in considerable morbidity. The causes of interstitial cystitis remain obscure but infection has been commonly postulated.

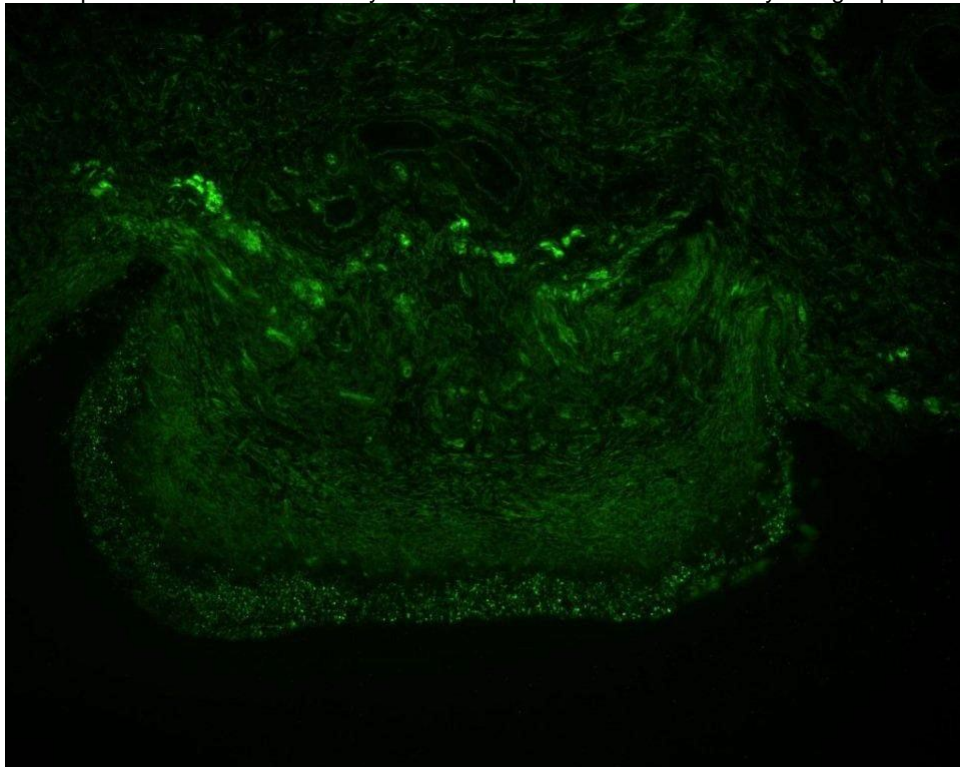
An ascending route of infection is the most common pathogenic mechanism and *Escherichia Coli* (*E. Coli*) is the predominant aetiologic agent. Previous research has shown that adhesion of uropathogenic *E. Coli* to the epithelial lining, and subsequent invasion and colonisation of the cells, are mediated by the Afa family of bacterial surface proteins. The integrin family of cell surface receptors expressed by the urothelium have been implicated in the bacterial adhesion process using a model experimental system<sup>1</sup>. Integrins are large membrane glycoproteins consisting of two subunits  $\alpha$  and  $\beta$ . The  $\alpha$  and  $\beta$  subunits in various combinations are known to form at least 19 integrins. This diversity of integrins provides cells with the ability to recognise a variety of adhesive substrates<sup>2</sup>. The results from previous studies suggest that the  $\beta 1$  integrin in particular is a common receptor for Afa bacteria proteins<sup>3</sup>.

The aim of our research has been to investigate integrin expression and spatial distribution in the urinary tract epithelium in women with recurrent bacterial cystitis and interstitial cystitis, and to compare these integrins with those expressed in the urinary tract epithelium of healthy asymptomatic women. If "pathogenic" subtypes of integrins could be identified, it should in principle be possible to suppress these. This suppression could then be used in the prevention and treatment of recurrent bacterial cystitis and interstitial cystitis.

### Study design, materials and methods

Bladder biopsies were collected from patients with interstitial cystitis, recurrent bacterial cystitis and controls, from women undergoing surgery for stress incontinence. Cryosections were taken from each biopsy and fixed in cold acetone prior to staining. Immuno-histochemistry was performed using primary monoclonal antibodies to cytokeratin 18, integrins  $\alpha\beta 3$ ,  $\alpha 5\beta 1$  and the subunit  $\alpha 5$ , followed by a FITC-conjugated secondary antibody.

Figure 1. Microscopic fluorescent immunohistochemistry of bladder tissue showing strongly positive staining for  $\alpha 5\beta 1$  integrin in the epithelial and submucosal layers in a sample from the interstitial cystitis group.



### Results

Integrins  $\alpha 5\beta 1$  and  $\alpha\nu\beta 3$  were identified within the epithelium, lamina propria and submucosa of bladder specimens. Expression of the integrin subtypes and their spatial distribution were different in the interstitial cystitis, recurrent bacterial cystitis and control groups. A persistent, strongly positive expression of  $\alpha 5\beta 1$  integrin was observed in both the epithelium and the submucosal layers in bladder biopsies from the interstitial cystitis group. The same integrin was present in the submucosal layer, but not in the epithelium, in 12 out of 13 specimens from the recurrent bacterial cystitis group.

### Interpretation of results

Our results show that the expression and spatial distribution of integrins  $\alpha 5$ ,  $\alpha 5\beta 1$  and  $\alpha v\beta 3$  in bladder mucosa differ in women with recurrent bacterial cystitis, interstitial cystitis and healthy controls. However, integrin  $\alpha 5\beta 1$  is commonly expressed in both the epithelial and the submucosal layers of the bladder in the interstitial cystitis group, and is also generally present in the submucosal layer of the bladder in the recurrent bacterial cystitis group.

### Concluding message

This study suggests that the  $\alpha 5\beta 1$  integrin is commonly expressed in the bladder mucosa of women with recurrent bacterial cystitis, and also of those with interstitial cystitis. Suppression of this "pathogenic" subtype of integrin could potentially be used in the prevention and/or treatment of both recurrent bacterial cystitis and interstitial cystitis.

### References

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<b><i>Was this study approved by an ethics committee?</i></b>	<b>Yes</b>
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