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An Investigation of Tetraspanin Proteins' Role in UPEC Infection

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Abstract : Urinary tract infections (UTIs) are the most prevalent of infectious diseases and > 80% are caused by uropathogenic E. coli (UPEC). Infection occurs following adhesion to urothelial plaques on bladder epithelial cells, whose major protein constituent are the uroplakins (UPs). Two of the four uroplakins (UPIa and UPIb) are members of the tetraspanin superfamily. The UPEC adhesin FimH is known to interact directly with UPIa. Tetraspanins are a diverse family of transmembrane proteins that generally act as "molecular organizers" by binding different proteins and lipids to form tetraspanin enriched microdomains (TEMs). Previous work by our group has shown that TEMs are involved in the adhesion of many pathogenic bacteria to human cells. Adhesion can be blocked by tetraspanin-derived synthetic peptides, suggesting that tetraspanins may be valuable drug targets. In this study, we investigate the role of tetraspanins in UPEC adherence to bladder epithelial cells. Human bladder cancer cell lines (T24, 5637, RT4), commonly used as in-vitro models to investigate UPEC infection, along with primary human bladder cells, were used in this project. The aim was to establish a model for UPEC adhesion/infection with the objective of evaluating the impact of tetraspanin-derived reagents on this process. Such reagents could reduce the progression of UTI, particularly in patients with indwelling catheters. Tetraspanin expression on the bladder cells was investigated by q-PCR and flow cytometry, with CD9 and CD81 generally highly expressed. Interestingly, despite these cell lines being used by other groups to investigate FimH antagonists, uroplakin proteins (UPIa, UPIb and UPIII) were poorly expressed at the cell surface, although some were present intracellularly. Attempts were made to differentiate the cell lines, to induce cell surface expression of these UPs, but these were largely unsuccessful. Pre-treatment of bladder epithelial cells with anti-CD9 monoclonal antibody significantly decreased UPEC infection, whilst anti-CD81 had no effects. A short (15aa) synthetic peptide corresponding to the large extracellular region (EC2) of CD9 also significantly reduced UPEC adherence. Furthermore, we demonstrated specific binding of that fluorescently tagged peptide to the cells. CD9 is known to associate with a number of heparan sulphate proteoglycans (HSPGs) that have also been implicated in bacterial adhesion. Here, we demonstrated that unfractionated heparin (UFH)and heparin analogs significantly inhibited UPEC adhesion to RT4 cells, as did pre-treatment of the cells with heparinases. Pre-treatment with chondroitin sulphate (CS) and chondroitinase also significantly decreased UPEC adherence to RT4 cells. This study may shed light on a common pathogenicity mechanism involving the organisation of HSPGs by tetraspanins. In summary, although we determined that the bladder cell lines were not suitable to investigate the role of uroplakins in UPEC adhesion, we demonstrated roles for CD9 and cell surface proteoglycans in this interaction. Agents that target these may be useful in treating/preventing UTIs.

Keywords : UTIs, tspan, uroplakins, CD9
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