Uropathogenic *Escherichia coli*, multidrug-resistance and induction of host defense mechanisms

av

Isak Demirel

Akademisk avhandling

Avhandling för medicine doktorsexamen i Medicinsk vetenskap, inriktning biomedicin, som kommer att försvaras offentligt fredagen den 23 maj 2014 kl. 09:00

Hörsal C1, Campus USÖ, Örebro universitet

Opponent: Docent Gabriela Godaly
Institutionen för laboratoriemedicin Malmö, Medicinsk Mikrobiologi, Lunds universitet

Örebro universitet
Institutionen för hälsovetenskap och medicin
70182 ÖREBRO
Abstract


Uropathogenic Escherichia coli (UPEC) is the primary cause of urinary tract infection (UTI), which is one of the most common infections in humans. UPEC strains have acquired successful strategies to subvert the host defense and antibiotics to persist in the urinary tract. The main aim of this thesis was to investigate the host defense mechanisms during a UPEC infection in vitro.

The results showed that SOCS3, a key regulator of the immune system, was increased in bladder epithelial cells in response to a UPEC infection. In addition, UPEC decreased the phosphorylation of the SOCS3 regulated transcription factor STAT3. Nitric oxide (NO), a host-derived antimicrobial factor was shown to increase the release of IL-6 from renal epithelial cells alone or in combination with UPEC. The induction of IL-6 was mediated by ERK1/2 and p38 MAPK signaling and NO was also shown to attenuate UPEC-induced IL-6 mRNA degradation. Furthermore, extended-spectrum beta-lactamase (ESBL)-producing UPEC isolates were shown to induce higher PMN migration and ROS-production, but lower cytokine secretion from renal epithelial cells than susceptible isolates. Ineffective ceftibuten treatment of ESBL isolates induced bacterial filamentation associated with an increased release of ATP and LPS, with a subsequent enhancement of the ESBL-evoked host response.

Taken together, the findings show that UPEC can induce SOCS3, a suppressor of host responses and that NO can regulate pro-inflammatory mediators. In addition, the data suggest that there are differences between ESBL- and non-ESBL-producing isolates ability to evoke a host response. Exposing resistant isolates to ineffective antibiotics was shown to alter the evoked host response.

Keywords: Urinary tract infection, uropathogenic Escherichia coli, suppressor of cytokine signalling 3, nitric oxide, cytokines, extended-spectrum beta-lactamases, filamentation, IL-6

Isak Demirel, School of Health and Medical Sciences, Örebro University, SE-701 82 Örebro, Sweden, Isak.Demirel@oru.se