The role of caspase-1, caspase-4, NLRP3 and IL-1RA in bladder epithelial cells infected by uropathogenic Escherichia coli

av

Anna Lindblad

Akademisk avhandling

Avhandling för medicine doktorsexamen i Medicinsk vetenskap, inriktning biomedicin,
som kommer att försvaras offentligt
fredag den 8 december 2023 kl. 09:00,
Hörsal X1, Campus USÖ, Örebro universitet

Opponent: Professor Manisha Yadav
Dr. B.R. Ambedkar Center for Biomedical Research (ACBR)
University of Delhi,
Delhi, India

Örebro universitet
Institutionen för medicinska vetenskaper
701 82 ÖREBRO

Abstract

Anna Lindblad (2023): The role of caspase-1, caspase-4, NLRP3 and IL-1RA in bladder epithelial cells infected by uropathogenic Escherichia coli. Örebro Studies in Medicine 284.

Urinary tract infection is one of the most common infections and is mostly caused by uropathogenic *Escherichia coli* (UPEC). The inflammasome-associated proteins caspase-1, caspase-4 and NLRP3 are essential in the host cell response during urinary tract infection by regulating IL-1β release. The pro-inflammatory effects of IL-1β can be inhibited by binding of the IL-1 receptor antagonist (IL-1RA) to the IL-1 receptor. The aim of this thesis is to investigate what role caspase-1, caspase-4, NLRP3 and IL-1RA have on the pro-inflammatory host response evoked by UPEC and their role in recurrent UTI.

The results showed that the inflammasome-associated proteins caspase-1, caspase-4 and NLRP3 are involved in cytokine and chemokine release and in antimicrobial activities of neutrophils during UTI. We conclude that IL-1RA influences the release of various inflammatory proteins during a UPEC infection from bladder epithelial cells. In addition, deficiency in IL-1RA led to decreased UPEC colonization and invasion of bladder epithelial cells. Our results also show that NLRP3 has a regulative function on estrogen signalling and the expression of antimicrobial peptides. Additionally, we found that capsase-1 and caspase-4 can regulate the gene expression of important immune regulators, including TLR4, antimicrobial peptides, cytokines and chemokines.

Together, our results show that that the inflammasome-associated proteins caspase-1, caspase-4, NLRP3 and IL-IRA are important immune-regulators during UPEC infection in bladder epithelial cells. They regulate UPEC colonization, cytokines and chemokines release, antimicrobial activities of neutrophils and estrogen signalling.

Keywords: Urinary tract infection, inflammasome, uropathogenic *Escherichia coli*, NLRP3, caspase-1, caspase-4, IL-1RA, antimicrobial peptides, estrogen

Anna Lindblad, School of Medical Sciences, Örebro University, SE-701 82 Örebro, Sweden, e-mail: Anna.lindblad@oru.se