Abstract

Title: CHARACTERIZATION OF THE CLINICAL UROPATHOGENIC *Escherichia coli* ISOLATES AND THEIR HOST PATHOGEN INTERACTION: A MOLECULAR PERSPECTIVE

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In clinical practice, one of the most frequent bacterial infections is urinary tract infection (UTI), accounting for significant morbidity rates and high healthcare expenses. Pregnancy-related UTIs pose a major risk to the fetus and are frequently associated with premature birth, early membrane rupture, maternal chorioamnionitis, low birth weight, developmental retardation, or fetal necrosis. UTIs in non-pregnant population, especially in older women, can develop a number of consequences and if untreated can be fatal. 80%-90% of UTIs in both populations are caused by uropathogenic *Escherichia coli* (UPEC).

Urine culture is the gold standard for detection of UTI in human, and this time-consuming method leads to the empirical antibiotic prescription resulting in emergence of multi-drug resistance (MDR) and pose difficulty in its clinical management. Hence identification and in-depth characterization of UPEC from pregnant and non-pregnant population, with respect to their antibiotic resistance pattern, pathogenicity, colonization potential and the ability to elicit host-cytokine response is required to develop effective clinical measures against UTI.

In this study, statistically significant incidence of MDR with ESBL and carbapenemase production was observed among UPEC isolates from pregnant and non-pregnant groups. The distribution of major resistant genes (oxacillinase, cephalosporinase, carbapenemase), mobile genetic elements, plasmid replicon types, virulence factor genes were significantly prevalent among both groups. Phylogroup E, followed by novel phylotype property (NPP) were also prevalent in these two groups. Clonal heterogenicity and predominance of ST405 and CC131 were evident among isolates from both groups, with implication of zoonotic transmission. HTB-4 uroepithelial cells upon infection with UPEC isolates from pregnant population (UPECp) displayed a correlation between expression of *fimH* and *IFNγ*, *fimH* and *IL17A*, and *fimH* and *IL1β* whereas a correlation was observed between expression of *papC* and *GCSF*, *hlyA* and *TGFβ* upon infection with UPEC from non-pregnant population (UPECnp). The severity of infection was further tested *in vivo* in murine model with two different UPEC isolates from these two different groups, with different virulence scores and phylogenetic background. Upon infection in mice, they revealed highest bacterial colonization on different post-infection (p.i.) days, and displayed varying levels of cytokines; IL1β, IL17A, GCSF and TGF-β in bladder and kidney tissues, and in serum. The IL1β levels were significantly different amongst the two batches of mice infected with UPECp and UPECnp isolates. Hence IL-1β might be a potent non-invasive marker to stratify the severity of UTI.

Therefore, this study revealed the necessity of cytokine profiling which is much less time-consuming in addition to urine culture and AMR analysis, to help clinicians to cease empiric treatment and formulate effective prescription policy in UTI.

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