Human bladder microtissue model to study chronic and recurrent UTIs

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Urinary tract infections (UTIs) rank as the second most frequent reason for prescribing antibiotics and have a high rate of recurrence [1]. The survival and growth tactics of Uropathogenic E. coli (UPEC) are complex, especially in the challenging environments of urine and bladder epithelium. Most insights into UPEC's behaviour are derived from in-vivo research, involving mouse models or studies on human bladder tissue explants. Here we introduce an in-vitro model designed to examine the dynamic interaction between urine and epithelial micro-environments in real-time. The human mini-bladder model mimics the physiology of in-vivo bladder tissue, with flowing urine, stretching tissue and ability to study complex and chronic infection conditions.

We develop this microtissue model by culturing primary human bladder epithelial cells in a collagen scaffold, with nutritive media and urine. This stimulates multi-layer stratification, directional differentiation, with an apical layer of bi-nucleated cytokeratine-20 expressing umbrella cells and a tight tissue barrier. Micturition effects are established through induced urine flow and pressure-controlled tissue stretching. We can distinctively simulate chronic untreated UPEC infections of over 10 hours without loss of microtissue integrity. We also observe the bacteria invade the tissue, grow in intracellular bacterial colonies and filament. When the infected tissue is treated with Fosfomycin in an osmoprotected urine, we observe rod-shaped UPEC convert into cell-wall deficient L-forms in the lumen [2]. The lumenal L-forms, upon cessation of Fosfomycin treatment, can reconvert into rod shaped UPEC and reseed into the tissue. We also find an increased bacterial load in the tissue and higher recurrence rate in the case of high osmolarity in urine. In summary, the human mini-bladder provides an ideal in-vitro tissue model for studying the nature of intracellular niches of UPEC and identifying their survival and growth mechanisms.

References:
[1] Flores-Mireles et al., *Nature Reviews Microbiology* (2015)
[2] Errington J. *Biochem Soc Trans* (2017)