00281 The Concerted Action of Small Rabgtpase and Exocyst Vesicular Trafficking Mediates Bacterial Expulsion From Bladder Epithelium

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Aims: Urinary Tract Infections (UTIs) caused by uropathogenic E.coli (UPEC) are common community-acquired infections with significant morbidity and impact upon the health care system. UPEC continues to grow rapidly particularly affecting women, with no promising therapeutic options. Much of the difficulty in the treatment of UTIs lies in the ability of UPEC to invade and persist within bladder epithelial cells (BECs). In their intracellular niche, UPEC are able to subvert both host immune defenses and antibiotic treatment. Previous studies have demonstrated that these intracellular UPEC are believed to be a major reservoir for recurrent UTIs. However, the mechanisms governed by UPEC to survive within BECs are partly understood. We aimed to understand such mechanisms at the molecular level that may lead to the identification of a novel target for the development of new preventive measures against infections caused by UPEC.

Methodology: Using siRNA tools, we identified and characterized the vesicular trafficking signaling molecules/substrates involved in successful UPEC expulsion. Mouse model approach was subsequently used to validate in vitro results. UPEC infection was quantitated using colony forming units (CFU).

Result: Subcellular vesicular trafficking typically involves multiple small Rabs GTPases, with each specific step mediated by a distinct Rab GTPases. We demonstrate that the concerted actions of both RAB11a and RAB27b in BECs, along with their respective effectors (Rab11a-FIP3/Rab27b-MyosinVII), are mobilized by innate immune signaling, resulting in the prompt expulsion of intracellular UPEC from their intracellular niche. Notably, this collaboration is further coordinated by deposition of the Exocyst complex on bacteria-containing vesicles (BCVs), an event triggered by the innate receptor TLR4. Both RAB11a and RAB27b are recruited and activated by the Exocyst complex components SEC6/SEC15 on BCVs to promote expulsion of bacteria.

Conclusion: Altogether, the cell autonomous defense system can mobilize and coalesce multiple subcellular trafficking circuitries to combat bacterial infections.