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INFECTION

Uropathogenic *Escherichia coli* get a return TRP

Expulsion of uropathogenic *Escherichia coli* (UPEC) encased in vesicles from bladder epithelial cells (BECs) is mediated by Ca^{2+} release from neutralized lysosomes via a transient receptor potential cation channel of the mucolipin subfamily (TRPML3), according to new data published in *Cell*.

> “...the bacterial defence mechanism ... seemed to trigger the cellular defence mechanism...”

The critical role of the cell-autonomous defence programme in protecting against pathogen infection is being increasingly appreciated. In UTIs, for example, UPEC that infect BECs have been shown to be expelled to the extracellular space. Now, Yuxuan Miao and co-workers from the University of Durham, NC, and the University of Michigan, MI, have described the cellular mechanisms underlying this defence process.

The researchers' investigation was based on findings that UPEC from urine of patients with UTIs were resistant to antibiotics that could not easily penetrate cellular membranes. However, treatment with a surfactant restored antibiotic sensitivity. The team demonstrated that the extracellular UPEC were encased in exosomes and that, upstream, the bacteria were intracellularly sequestered in multivesicular bodies. Notably, further experiments showed that autophagy pathways were involved in this export mechanism, raising the question why UPEC were not being degraded in lysosomes, as would be expected during autophagic processes.

The researchers identified that, although the bacteria-containing autophagosomes did fuse with lysosomes, acidification of the resulting autolysosomes was repressed in cells infected with UPEC, but not when cells had been infected with a nonpathogenic *E. coli* strain. When the team mimicked blockade of lysosome acidification using a drug under autophagic conditions in the absence of bacterial infection, they found a strong increase in expelled exosomes. Overall, the bacterial defence mechanism of repressing lysosome acidification seemed to trigger the cellular defence mechanism of lysosome exocytosis.

Investigation of the intracellular trafficking pathway of UPEC in BECs confirmed that the bacteria passed through several intracellular compartments,

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but that expulsion only occurred at the stage of UPEC-mediated neutralization of the lysosome. Finally, the researchers discovered that lysosomal TRPML3 is the key sensor of the expulsion process in BECs. TRPML3 was activated upon lysosome neutralization and the resulting Ca^{2+} release into the cytosol prompted the ensuing vesicle expulsion from the cell. These findings point toward TRPML agonists as a potential new drug class for the treatment of UTIs.

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Original article Miao, Y. *et al.* A TRP channel senses lysosome neutralization by pathogens to trigger their expulsion. *Cell* doi:10.1016/j.cell.2015.05.009