**Uropathogenic *Escherichia coli* subverts mitochondrial metabolism to enable intracellular bacterial pathogenesis in urinary tract infection.**

Beebout, C.J., Robertson, G.L., Reinfeld, B.I. *et al.*  *Nat Microbiol* **7**, 1348–1360

**Presenter:** Wu Zhen Yee                        **Date/Time:** 2024/10/31, 15:10 -16:00

**Commentator:** Ching-Hao Teng Ph.D.             **Location:** Room 601, Med College Building

**Background:**

Urinary tract infections (UTIs) are highly prevalent, affecting around 150 million people annually, with uropathogenic *Escherichia coli* (UPEC) responsible for approximately 80% of these cases. UPEC enters a transient intracellular lifecycle during bladder infections, replicating within the cytosol of urothelial cells to form multicellular communities in a nutrient-rich environment. During the pathogenesis of UPEC, oxygen is crucial for UPEC to colonize the bladder and form resilient biofilms. Among its three respiratory oxidases, only the loss of cytochrome *bd* significantly affects UPEC's fitness in the bladder. Cytochrome *bd* has a high affinity for oxygen, enabling it to function under low-oxygen conditions and providing additional biochemical activities that help the bacteria tolerate toxic substances and immune responses. The study demonstrates that cytochrome *bd* facilitates intracellular bacterial pathogenesis by scavenging oxygen, which supports bacterial replication and alters the metabolism of urothelial cells. This process stabilizes the hypoxia-inducible transcription factor HIF-1, shifts cellular metabolism, and prevents apoptosis. These findings highlight the metabolic strategies employed by UPEC to survive and thrive during UTIs.

**Objective:**

To investigate how UPEC utilize aerobic respiration to undergoes intracellular replication in urothelial cells to colonize the bladder and form resilient biofilm.

**Results:**

While previous study has confirmed the loss of cytochrome *bd* affects the fitness of UPEC, the author proved further by infecting cytochrome *bd* defecting UPEC into animal mice model and the results show cytochrome *bd* defecting UPEC failed to replicate within urothelial cell. By further characterizing the cytochrome *bd*, the author found the respiratory function is essential for intracellular survival and replication of UPEC rather than the non-respiratory function. At the meantime, by conducting oxygen consumption rate assay (OCR), the author validified that the UPEC not only utilizes cytochrome *bd* to undergoes reparatory function during formation of the intracellular bacteria communities. On the other hand, the author found that during UPEC infection, the level of hypoxia induced factor (HIF-1) have been elevated and urothelial cell metabolism has been rewired throughout the infection, these results suggest that UPEC compete the oxygen level in urothelial cell during pathogenesis. The author sums up the study by investigating the role of UPEC in urothelial survival. During normal infection, the urothelial cell will undergo apoptosis and exfoliate to prevent further replication of the bacteria to infect other cells. However, the author found out that during UPEC infection, the HIF-1 upregulation by UPEC competing for oxygen will impede the apoptosis process, this result will then increase the replication rate of UPEC and further invading more urothelial cells.

**Conclusion:**

This study demonstrates that UPEC utilizes cytochrome *bd* to compete the oxygen in urothelial cell while reduce the cell apoptosis rate and further replicates under aerobic respiration to form intracellular bacteria communities.