WHAT MAKES AN ORGANISM PATHOGENIC?

**Uropathogenic Escherichia coli – an opportunistic pathogen and model system**

*UPEC as a clinically important pathogen*

Approximately 50% of women will suffer a urinary tract infection (UTI) at some point in their life, and 20-30% of these women will suffer a recurrent UTI within three to four months. The rates of UTI increase in the immunosuppressed, including the elderly and children, and may result in significant complications, including renal scarring, septicemia, and pyelonephritis. Approximately 80% of community acquired UTIs are caused by uropathogenic *E. coli* (UPEC), a Gram-negative gammaproteobacteria. UPEC has been linked to several outbreaks in recent years, and, of particular concern, antibiotic resistance within UPEC has begun to spread intercontinentally, resulting in increased morbidity and mortality. This spread of multi-drug resistant, highly virulent strains of UPEC, as well as the rate of infection in the U.S. necessitate an understanding of the underlying population dynamics of this pathogen.

*UPEC as a model system*

In addition to being clinically important, UPEC is also an excellent model system to study the evolution of virulence in opportunistic pathogens. UPEC have been used to study biofilm formation, pili expression, epithelial cell invasion, toxin production, and population bottlenecks, in addition to its obvious use as a model for uropathogenicity. UPEC offer a number of unique advantages as a model system, including the range of laboratory tools available specific to *E. coli*, the tractability of genetic modification, and the wealth of genomic data available for the pathogen. Despite these benefits, and in contrast to other forms of pathogenic *E. coli*, the genome dynamics and population structure of UPEC remain largely unexplored. Additionally, although there has been attention paid to the global phylogenetic structure of UPEC, relatively few investigations have sought to describe the within-host distribution of the UPEC populations or elucidate the changes in population structure that occur within patients with recurrent UTIs. However, new technologies and bioinformatic tools now enable high-resolution descriptions of bacterial population structures using genomic analyses, enabling research into these unexplored areas.

**The population structure of UPEC – a tale of two homes**

*UPEC phylogenetics*

*Intra-host habitats and niches*

*Population dynamics during UTI*

The population structure of UPEC is dynamic during the course of a UTI, as has been described previously{Schwartz:2011cy, Walters:2012hq}. UPEC that invade the bladder are thought to originate in the gastrointestinal tract56–58, although direct evidence for this phenomenon has not been provided10. Once UPEC are in the lumen of the bladder, Type 1 pili tipped with a FimH adhesin bind to mono-mannosylated ligands present on the bladder epithelium known as uroplakins59. Following adherence, UPEC subsequently invade the epithelial cell and establish a clonal community called an intracellular bacterial community (IBC) in a FimH dependent manner60,61. After maturation of the IBC, the clonal UPEC flux out of the urothelium, killing the host cell and invading new epithelial cells. Continuation of this cycle results in chronic cystitis and occurs if bacterial titers are high enough in the initial acute phase of the UTI54. Alternatively, quiescent intracellular reservoirs (QIRs) may develop if the UPEC gain entry into the underlying epithelium below the superficial facet cells lining the bladder35. In such cases, UPEC may exist in a dormant state and emerge at a later time to cause a recurrent UTI35. During infection progression, a combination of population bottlenecks during invasion and IBC formation, founder effects during recurrent UTIs, and migration patterns between the gut and bladder habitats have significant effects on the population structure of UPEC54,62.

*Transmission and recurrence*

**UPEC virulence factors – a tool for every occasion**

*Distribution of virulence factors*

A number of UPEC strains have been sequenced, including the standard model strains CFT07311 and UTI8912, in addition to a very wide array of sequence data available regarding the prevalence of different virulence factors involved in uropathogenicity. The majority of differences between strains of *E. coli* are found in the accessory genome, which is comprised of all genes that exist in at least one, but not all, of the genomes that species 7,11,12,32. The accessory genome of *E. coli*, which is still growing with each new genome sequenced,consists of over 10,000 genes and is nearly five times larger than the core genome, which is the collection of genes shared between all strains, indicating a highly reticulated population structure9,33,34. In the last decade a number of comparative genomics investigations identified a suite of virulence factors and molecular mechanisms involved in uropathogenicity, pathoadaptation, and niche adaptation in UPEC strains8,20,35–41.

*Function of common UPEC virulence factors*

**Urovirulence factors: swords or plowshares?**

**Future plans directions and unanswered questions**