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***Escherichia coli* Physiology and Metabolism Dictates Adaptation to Diverse Host Microenvironments**

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Summary

Bacterial growth in the host is required for pathogenesis. To successfully grow *in vivo*, pathogens have adapted their metabolism to replicate in specific host microenvironments. These adaptations reflect the nutritional composition of their host niches, inter-bacterial competition for carbon and energy sources, and survival in the face of bactericidal defense mechanisms. A sub-group of *Escherichia coli*, which cause urinary tract infection, bacteremia, sepsis, and meningitis, have adapted to grow as a harmless commensal in the nutrient-replete, carbon-rich human intestine but rapidly transition to pathogenic lifestyle in the nutritionally poorer, nitrogen-rich urinary tract. We discuss bacterial adaptations that allow extraintestinal pathogenic *E. coli* to establish both commensal associations and virulence as the bacterium transits between disparate microenvironments within the same individual.

Keywords

uropathogenic; extraintestinal; ExPEC; UTI; UPEC

Introduction

Escherichia coli, one of the most important model organisms in the laboratory, is the best studied microorganism. The primary niche occupied by *E. coli* is the lower intestinal tract of mammals, where it resides as a beneficial component of the commensal microbiota. Although it is well-known that *E. coli* resides in the human intestine as a harmless commensal, specific strains or pathotypes have the potential to cause a wide spectrum of intestinal and diarrheal diseases. For example, at least six pathotypes have been described: enterohemorrhagic, enteropathogenic, enterotoxigenic, enteroaggregative, diffusely-adherent, and enteroinvasive *E. coli* (respectively, EHEC, EPEC, ETEC, EAEC, DAEC, and EIEC). On the other hand, extra-intestinal diseases that include urinary tract infection (UTI), bacteremia, septicemia, and meningitis can be caused by additional pathotypes known as extraintestinal pathogenic *E. coli* (ExPEC) [1]. The loss or gain of mobile genetic elements is responsible for the ability of *E. coli* to cause a broad range of human diseases. The core genome shared by all *E. coli* strains represents approximately 2,000 genes, while the pan genome that represents the collective gene content for all sequenced *E. coli* strains exceeds

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10,000 genes [2*]. Thus, for each *E. coli* strain, which contains 4,800 genes on average, it is the specific composition of horizontally acquired genetic material that determines its ability to cause a certain disease and be defined as a specific pathotype [3].

Intestinal *E. coli* pathotypes, like the infamous EHEC O157:H7 serotype, resides in the bovine intestine as a commensal bacterium and cause severe diarrheal disease only when accidentally introduced into the human intestinal tract. In contrast, extraintestinal *E. coli* pathotypes reside harmlessly in the human intestinal microenvironment but, upon access to sites outside of the intestine, become a major cause of human morbidity and mortality as a consequence of invasive UTI (pyelonephritis, bacteremia, or septicemia) [4,5]. Thus, extraintestinal pathotypes like uropathogenic *E. coli* (UPEC) possess an enhanced ability to cause infection outside of the intestinal tract and colonize the urinary tract, the bloodstream, or cerebrospinal fluid of human hosts [5,6]. It follows that extraintestinal pathogenic *E. coli* possess the unique ability to shift its behavior between harmless colonizer of the nutrient-rich human intestine and virulent pathogen of the nutritionally limited bladder (Fig. 1) [7–9]. Here, we discuss the current understanding of the role for uropathogenic *E. coli* metabolism and physiology in adapting to these diverse host microenvironments.

Traditional extraintestinal *E. coli* virulence factors

Traditional studies of bacterial pathogenesis have focused on pathogen-specific virulence properties including toxins, adhesins, secretion, and iron acquisition systems, and mechanisms to avoid the innate and adaptive immune response. Epidemiological studies have identified a number of specific virulence factors or genetic determinants associated with extraintestinal pathogenic *E. coli* (ExPEC) isolates. Extraintestinal virulence genes like those encoding P-fimbriae or hemolysin are frequently clustered in genomic islands known as pathogenicity-associated islands (PAIs) [10] and encode a variety of fimbrial and non-fimbrial adhesins, toxins, and iron acquisition systems [4,11]. Of *E. coli* pathotypes, ExPEC isolates generally have the largest number of PAIs and horizontally acquired genes; specifically, the prototype pyelonephritis UPEC strain CFT073 has 13 PAIs and is the largest genome (5,388 predicted genes) of sequenced *E. coli* strains [2*]. One outstanding question, however, is whether these horizontally acquired determinants are maintained in UPEC because they confer an advantage during intestinal colonization or are selected for increased extraintestinal fitness [12,13**].

An intriguing aspect of the pathogenesis of *E. coli* UTI is the lack of a dominant virulence factor or common set of virulence determinants shared by all UPEC strains but absent from commensal *E. coli* or intestinal pathogens. Bacterial metabolism during infection has only been recently appreciated to contribute to persistence as much as their virulence properties. Due to the requirement for these *E. coli* to replicate in and colonize both the intestine and extraintestinal environments, we posit that physiology and metabolism of ExPEC strains is paramount. Indeed, we propose that the ability to survive in the urinary tract depends as much on bacterial physiology and metabolism as it does on the well-considered virulence determinants [14].

Life as an intestinal commensal: nutrient-rich with diverse bacterial competitors

E. coli strains reside and grow in the nutrient-rich mucus lining of the mammalian intestine [15]. Important early colonization studies show the Entner Duodoroff pathway, and gluconate or other sugar acids, are required for intestinal growth of commensal *E. coli* [16]. *E. coli* acquires nutrients from the intestinal mucus, a complex mixture of glycoconjugates, and up-regulates genes that encode enzymes involved in the catabolism of N-

acetylglucosamine, sialic acid, glucosamine, gluconate, arabinose and fucose [16,17]. EHEC O157:H7 requires the same central carbon pathways as do commensal strains, and mutations in pathways that utilize galactose, hexuronates, mannose, and ribose resulted in colonization defects [17]. Further, multiple mutations in a single strain had an additive effect on colonization levels suggesting that some *E. coli* strains depend on the simultaneous metabolism of up to six sugars to support colonization of the intestine [17]. These findings suggest that *E. coli* uses multiple limiting sugars for growth in the intestine and supports the assertion that *E. coli* grows in the intestine using simple sugars released upon breakdown of complex polysaccharides by anaerobic gut residents [18,19].

Synthesis and degradation of glycogen, an endogenous glucose polymer, plays an important role for *E. coli* and *Salmonella* during colonization of the mouse intestine by functioning as an internal carbon source for the bacterium during nutrient limitation [20,21]. When faced with limiting sugars due to consumption by other colonizing bacteria, *E. coli* can also switch from glycolytic to gluconeogenic substrates to sustain growth in the intestine [22]. For example, EHEC utilizes glycolytic substrates and switches to gluconeogenic substrates when present in the intestine with commensal *E. coli* that are utilizing glycolytic pathways for *in vivo* growth [22]. This finding, that competition *in vivo* can alter preferred routes of carbon flux through the central pathways, introduces the notion that metabolic flexibility and an increased capacity to utilize diverse carbon sources are likely important for successful long-term intestinal colonization by extraintestinal *E. coli*.

Commensal *E. coli* that are resident in the intestine are three times more likely to belong to the phylogenetic group B2 (ExPEC primarily belong in B2) than transient intestinal colonizers [23,24]. If ExPEC strains are superior colonizers of the human intestine then it is expected that horizontally acquired genomic islands and PAIs must be contributing to enhanced persistence in the intestine. Recent studies have shown that acquisition and regulation of genes that encode proteins to transport and catabolize prebiotic fructooligosaccharides provides a fitness advantage in the intestine for ExPEC strains [25,26]. The gene cluster required for ExPEC growth on fructooligosaccharides encodes two glycoside hydrolases that belong to family 32 in the carbohydrate active enzyme database (CAZY) and a predicted cytoplasmic fructokinase [25]. The latter is important because fructose must be phosphorylated to be catabolized by *E. coli*. Another horizontally acquired gene cluster proposed to provide a fitness advantage in the intestine has been discovered in ExPEC, the *frz* operon, which also encodes a sugar kinase in addition to two aldolases, and IIA, IIB, and IIC fructose family PTS transporter subunits [27]. These findings suggest that ExPEC genomic islands and PAIs may indeed provide added metabolic flexibility and promote persistence in the competitive intestinal microenvironment.

Rapid in-host transition from intestinal colonizer to extraintestinal pathogenic lifestyle

Many studies, primarily from the Conway and Cohen laboratories, have contributed much to the understanding of the *in vivo* metabolic requirements of *E. coli* gastrointestinal colonization [16,17,21,22,28]. These groups have also found that mutants that accumulate L-fucose-1-phosphate stimulate catabolism of ribose *in vivo* and thus fucose metabolites play a role in regulating *E. coli* carbon utilization in the intestine [29]. This finding that intracellular levels of one metabolite control the expression of genes encoding enzymes for utilization of an unrelated metabolite implies that nutritional sensing may be important for competing with other bacteria for limiting nutrients in the intestine [18] or could represent a mechanism signaling the arrival into a different host microenvironment such as the urinary tract. Signal transduction using two component regulatory systems, which contain a transmembrane sensor kinase and a cognate response regulator transcription factor, are the

best described mechanism used by bacteria to coordinate gene expression in response to specific external stimuli. In UPEC, disruption of the QseBC two component regulatory system attenuates virulence in *E. coli* within the urinary tract by altering carbon flux through central pathways, which negatively affects the expression of multiple adhesins that are involved in bladder colonization [30]. The horizontally acquired *frz* operon has also been shown to link the metabolic capacity of ExPEC with expression of genes required for adherence to the bladder epithelium; the presence of the *frz* operon favors the ON orientation of the invertible type 1 fimbriae promoter [27]. UPEC catabolism of D-serine in the urinary tract is also an important signaling mechanism to trigger virulence gene expression [31–33]. These studies suggest that movement of ExPEC from a commensal-like lifestyle in the nutrient- and carbon-rich intestine to the nutritionally poor, nitrogen-rich lower urinary tract would be quickly sensed by changes in metabolism, which would trigger expression of genes required for pathogen colonization of an extraintestinal microenvironment (Fig. 1).

Life as an uropathogen: nutrient-poor with decreased competition and increased host defense

In contrast to the nutritionally diverse intestine, urine in the bladder is a high-osmolality, moderately oxygenated, iron-limited environment that contains mostly amino acids and small peptides [34–37]. It is therefore not surprising that defects in the both branches of the pentose phosphate pathway, the Entner-Doudoroff pathway, and glycolysis have limited or no impact on *E. coli* fitness in the bladder and kidney microenvironments [14]. Studies on UPEC metabolism during UTI have revealed that the ability to catabolize the amino acid D-serine in urine, which is both a nutrient and a signaling mechanism to trigger virulence, supports UPEC growth in the nitrogen-rich urinary tract [33]. The utilization of short peptides and amino acids as a carbon source during bacterial infection of the bladder and kidneys is also supported by the observation that UPEC mutants defective in peptide import have reduced fitness during UTI while auxotrophic strains do not [14]. Metabolism of nucleobases is also required for *E. coli* colonization of the bladder. Signature-tagged mutagenesis screening identified a mutant in the dihydroorotate dehydrogenase gene *pyrD* [38] and in a separate transposon screen, a gene involved in guanine biosynthesis, *guaA*, was also identified; a *guaA* mutant was found to be attenuated *in vivo* during UTI [39]. Both are supported by the recent finding that *E. coli* are rapidly replicating in the bladder [40*].

UPEC growing in human urine induces expression of multiple isoforms of both dipeptide- and oligopeptide-binding proteins, both of which were found to be required for UPEC to effectively colonize the bladder and kidneys [14]. Since the nutrient content in the kidney is expected to be very different from urine in the bladder, it is surprising that mutants lacking the ability to produce peptide-transport proteins were attenuated in both the kidneys and bladder because growth in urine mainly mimics only the bladder microenvironment. The host renal physiology might be expected to provide UPEC with several metabolizable carbon sources during reabsorption of the kidney glomerular filtrate in the tubules; however the ischemic damage caused by UPEC during pyelonephritis could alter nutrient availability [41]. Lack of a fitness defect for UPEC amino acid auxotrophs during bladder and kidney colonization and impaired colonization of bladder and kidneys for peptide-transport deficient mutants indicates that these bacteria actively import short peptides found in urine and suggests that peptides or amino acids represent the primary carbon source for *E. coli* during UTI [14]. In fact, dissimilatory acetate metabolism coupled to the degradation of amino acids during *E. coli* colonization of the bladder and kidneys shows that ExPEC are adapted to acetogenic growth rather than acetate assimilation [42].

Further, prolonged asymptomatic carriage of *E. coli* in the bladder selects for mutations that increase expression of D-serine deaminase and peptide/amino acid transport in *E. coli* [43**]. Gluconeogenic amino acids, like D- and L-serine, can be degraded to oxaloacetate or to pyruvate that can enter the TCA cycle, which is necessary to provide substrates for gluconeogenesis when *E. coli* use amino acids as a carbon source. Consistent with peptides and amino acids being important carbon sources during UTI, only bacteria with defects in peptide transport, gluconeogenesis, or the TCA cycle demonstrate a fitness defect during colonization of the host urinary tract [14].

Energy metabolism and surviving bactericidal activities of the host

The TCA cycle, in *E. coli* and in nearly all living cells, is an amphibolic pathway because TCA intermediates are important for anabolic processes in addition to catabolism of acetogenic and gluconeogenic carbon sources like amino acids. Both the complete aerobic TCA cycle and the incomplete reductive pathway are intimately linked to energy metabolism and respiration; pyruvate from glycolysis is oxidized to CO₂ concomitant with production of NADH and FADH₂, both of which must be reoxidized because all pathways would cease in that absence of NAD⁺. During respiration, the reoxidation of NADH is coupled to the generation of a proton gradient (ΔpH) that is used, among many processes, to drive ATP production via proton influx through the F₁F₀ ATPase stator. Much like the flexibility of *E. coli* carbon metabolism in the intestine, the modular respiratory chains of *E. coli* can be assembled in a variety of configurations depending on the available terminal electron acceptor and the energy needs of the bacterium [44]. In the intestine, the ability to respire aerobically and anaerobically provides a substantial fitness advantage for *E. coli* [28]. In the extraintestinal environment, loss of the TCA cycle enzyme succinate dehydrogenase, SdhB, results in a UPEC strain that has reduced fitness *in vivo* [14], suggesting that a complete TCA cycle and aerobic respiration are important in the urinary tract. At first approximation, aerobic respiration and acetogenic growth (fermentation) during UTI appear contradictory; however, during rapid growth in the host urinary tract it is likely that acetate metabolism reflects a certain degree of reductive overflow, or an electron sink, to relieve carbon flux through the TCA cycle when the respiratory capacity has been reached [40*].

The flexibility of energy metabolism and the modular respiratory chains for *E. coli* is also critical for adapting to respiratory stress [45*]. Utilization of alternative respiratory chains not only confers flexibility dependent upon the available energy source or terminal electron acceptor [44] but also allows for modulation of the proton motive force (μH^+), the gradient of charge and protons across the cytoplasmic membrane [46**]. By reducing membrane potential ($\Delta\psi$), *E. coli* can limit or prevent uptake of antibiotics and exist as a bacterial “persister” that can only be eradicated by antibiotics when specific metabolites are present to stimulate respiratory generation of μH^+ [47*]. This strategy is also utilized by *E. coli* to prevent killing by the bactericidal activities of mammalian phagocytes. In the urinary tract, extraintestinal *E. coli* infection elicits a massive inflammatory response characterized by neutrophil influx [48,49] and host production of the antimicrobial peptide LL-37 cathelicidin [50]. In response to antimicrobial peptides and acidic pH generated by neutrophils, the PhoPQ regulatory system becomes activated and up-regulates genes that encode electroneutral respiratory chain components, cation import systems, and anion efflux channels to limit respiratory generation of μH^+ and reverse membrane polarity from inside-negative to inside-positive, respectively [51**]. This control of membrane potential promotes *E. coli* resistance to cationic antimicrobial peptides and acidic pH, which potentiates bacterial survival against bactericidal activities of neutrophils during UTI. Indeed, UPEC lacking PhoP are exquisitely sensitive to polymyxin and acidic pH, and are severely attenuated during acute infection of the bladder [51**].

Conclusions

In the future, studies using deep sequencing and expression technologies, like RNAseq will provide a clearer understanding of how the transcriptional architecture of *E. coli* changes between intestinal and extraintestinal environment. This will be important because it is not only the presence or absence of genes that confers virulence, but rather how pathogenic *E. coli* coordinate expression of genes and regulons, shared by all *E. coli*, to silently enhance commensal associations in the intestine and rapidly respond to environmental cues and unveil pathogenicity in the urinary tract. It will also be important to understand how the presence or acquisition of genomic islands and PAIs affects the metabolome and metabolic capacity of *E. coli*. Investigating changes in carbon flux through central metabolism caused by transcriptional regulators, nutrient-uptake systems, and carbohydrate utilization systems encoded on PAIs will help to identify traits that confer a fitness advantage for UPEC when faced with bacterial competition for nutrients in the human intestine. For *E. coli* transitioning from the carbon-rich intestine to the nitrogen-rich urinary tract, it is likely that the ratio of carbon:nitrogen, or fluctuations in the intracellular C:N levels plays an important role controlling pathogenicity. Nitrogen metabolism and ammonia generated by catabolism of amino acids can act as a form of long-range interbacterial communication to induce oxidative stress responses and increase resistance to antibiotics [52**].

Basic principles of physiology, shared by nearly all living cells, are beginning to be appreciated as playing a key role in processes that are essential for pathogenesis. Bacterial respiration coordinates type three secretion system (TTSS) assembly with movement of *Shigella* from the intestinal lumen to the mucosa [53]. *E. coli* modulate their respiratory activity and limit or reverse membrane potential as a protective counter-measure against mammalian host defenses during UTI [51**]. These studies demonstrate the important link between fundamental bioenergetics and pathogenesis and suggest that energy metabolism might be an important signal used by bacterial pathogens to identify specific host microenvironments. By studying carbon metabolism, key differences between *E. coli* growing in the intestine and colonizing the urinary tract have been identified. Commensal *E. coli* require the Entner-Doudoroff pathway and glycolysis for intestinal colonization; while the TCA cycle, pentose phosphate pathway, and gluconeogenesis are dispensable [16]. In contrast, for *E. coli* infecting the urinary tract, the pathways required for commensal colonization are dispensable while the TCA cycle and gluconeogenesis are required [14]. Other aspects of UPEC physiology such as determining if the numerous well-considered or presently uncharacterized fimbriae that predominate in ExPEC strains [54] function as adhesive organelles to promote bacterial adherence in the intestine or in the urinary tract will be beneficial to understand the selective pressures that actively shape and maintain the UPEC pan-genome. Once we better understand how ExPEC are able to transition and adapt to both the intestinal and extraintestinal host microenvironments within the same individual it will be feasible to develop antimicrobials that target pathogenic strains and avoid eradicating beneficial commensal bacteria.

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Glossary

Pathotype	sub-groups of <i>E. coli</i> defined by type of disease caused in humans
Pan genome	the total gene pool derived from all <i>E. coli</i> genomic sequences

Virulence factor	usually a gene or collection of related genes that confer a pathogenic trait, e.g. invasion or iron acquisition
TCA cycle	tricarboxylic acid cycle; also known as the citric acid cycle, or Krebs cycle
Membrane potential ($\Delta\psi$)	the electrochemical gradient of charge across the cytoplasmic membrane one component of proton motive force (μH^+)
Persister	dormant bacteria that are refractory to treatment with antibiotics

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Recommended papers, published within the past 2 years, have been annotated as being of special interest (*) or outstanding interest (**).

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Highlights

- Uropathogenic *E. coli* are uniquely adapted to colonize disparate host niches in humans.
- Flexible carbon and energy metabolism give UPEC a fitness advantage in the intestine and urinary tract.
- The ability to survive in the urinary tract depends as much on bacterial physiology as it does on the well-considered virulence determinants.

Figure 1. Adaptation of metabolism and basic physiology allows *E. coli* to replicate in diverse host microenvironments

Extraintestinal pathogenic *E. coli* that cause urinary tract infection, bacteremia, sepsis, and meningitis, have adapted to grow as a harmless commensal in the nutrient-replete, carbon-rich human intestine but rapidly transition to pathogenic lifestyle in the nutritionally poor, nitrogen-rich urinary tract. In order to establish a commensal association within the human intestine, adaptive factors such as metabolic flexibility allow *E. coli* to successfully compete for carbon and energy sources with a large and diverse bacterial population. *E. coli* acquires nutrients from the intestinal mucus, including N-acetylglucosamine, sialic acid, glucosamine, gluconate, arabinose, fucose and simple sugars released upon breakdown of complex polysaccharides by anaerobic gut residents. When UPEC transition to the urinary tract, the bacteria encounter a drastic reduction in the abundance of nutrients and bacterial competition. Consequently, to replicate in a new host microenvironment, UPEC utilization of metabolic pathways required for growth in the dilute mixture of amino acids and peptides in the bladder signals the bacterium to elaborate virulence properties to successfully cause invasive disease and survive the onslaught of bactericidal host defenses. These adaptations are a unique and essential characteristic of ExPEC that enable a successful transition between disparate microenvironments within the same individual.