Immune Evasion Strategies of *E. coli*

Saman[1], Raiha Qurban[2], Wishah Fatima[3], Muhammad Rauf Ahmad[4], Muhammad Irfan Malik[5], Hira Ahsan[6], Asma Baig[1], Mudasar Shabir[7], Maria Ayub[1] and Abu Baker Siddique[1,*]

[1]Institute of Microbiology, Government College University Faisalabad, 38000, Pakistan
[2]Institute of Microbiology and Molecular Genetics, University of Punjab, Lahore
[3]Department of Allied Health Professional, Government College University Faisalabad, Pakistan
[4]Department of Molecular Biology, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan
[5]Department of Parasitology, Faculty of Veterinary and Animal Science, The Islamia University of Bahawalpur, Pakistan
[6]Academy of Medical Sciences, College of Henan Medicine, Zhengzhou University, Zhengzhou, Henan, 450052, China.
[7]Institute of Advanced Materials and Flexible Electronics (IAMFE), School of Chemistry and Materials Science, Nanjing University of Information Science and Technology, Nanjing, China
*Corresponding author: absiddique@gcuf.edu.pk

Abstract

Escherichia coli, as intestinal flora exists in symbiotic relationship with host, contributes in gut health through vitamin K synthesis, role in digestion and competitively exclude colonization of pathogenic microbes. From commensal origin, *E. coli* turned into pathogenic one by acquiring genetic factors related to virulence or moving towards sterile sites to initiate infection. This transformation can be carried through horizontal gene transfer mediated by transposons, bacteriophage or plasmid. These additions into genetic island of *E. coli* augment many features that help them to survive in hostile conditions. These characteristics include how to evade immune surveillance (through antigenic variation in LPS, biofilm formation and intracellular bacterial communities), get adherence to host tissue, produce toxins and cause tissue damage. Upon getting entry in the lower urinary tract, uropathogenic *E. coli* manipulates host cells by invading bladder epithelial cells and create complex Intracellular Bacterial Communities. IBCs, formed through synchronous and asynchronous rounds of invasion and replication, establish quiescent intracellular reservoirs that promote persistent and chronic infections. Collectively all these mechanisms enable bacteria to resist immune clearance and cause infection that can be acute, recurrent or chronic. These immune evasion tactics causes hindrance in effective treatment eventually exacerbate illness and healthcare costs.

Keywords: *E. coli*, Immune evasion, Phagocytosis, Biofilm, Intracellular bacterial communities, Siderophore

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Introduction

Escherichia coli, first isolated by Theodor Escherich in 1885, initially named *Bacterium coli commune*, a versatile bacterium known for its dual role as harmless commensal in the gastrointestinal tract of warm-blooded animals and a significant pathogen capable of causing a wide spectrum of diseases. While over 90% of humans harbor *E. coli* as part of their gut flora, certain strains are implicated in infections ranging from diarrheal diseases to life-threatening conditions such as sepsis and meningitis (Riley, 2020). The transition from commensal to harmful pathogen can be triggered by ecological factors, changes in the host immune status or antibiotic pressure, leading to conditions such as gastrointestinal diseases, severe systemic infections and urinary tract infections.

Experimental evolution studies have demonstrated that commensal *E. coli* can acquire pathogenic traits under selective pressures, such as macrophage phagocytosis. These adaptations enhance survival mechanisms such as delayed phagosome maturation and escape hence enabling bacteria to evade macrophage killing. Similarly, other pathogens like *M. tuberculosis* and *S. flexneri* evolved under macrophage pressure employs mechanisms like hindering phagosome acidification and excessive colonic acid production, which facilitates immune evasion (Proença et al., 2017). For further impairment of immune function such adaptations not only protect the bacterium but also induce transcriptomic changes in host cells.

Additionally, due to the evolutionary closeness of Shigella to *E. coli*, which has over 98% of its genetic similarity to *E. coli*, *E. coli* pathogenicity becomes even more complicated. The pathogenic evolution of Shigella by acquiring pINV virulence plasmid is an example demonstrating how horizontal gene transfer drives pathogenic evolution. In fact, *E. coli* exhibits genetic plasticity (Geurtsen et al., 2022) by acquiring virulence and antimicrobial resistant genes from plasmids, transposons, bacteriophages and pathogenicity islands it can even form hybrid pathotypes with an enhanced virulent and resistance profile (Barrios-Villa et al., 2023).

Pathogenic *E. coli* is classified into intestinal pathogenic *E. coli* (IPEC) and extraintestinal pathogenic *E. coli* (ExPEC), each with distinct mechanisms of pathogenesis and disease manifestations (Govindarajan et al., 2020). IPEC strains, such as enteropathogenic *E. coli* (EPEC)

and Shiga toxin-producing *E. coli* (STEC) are major culprits in gastrointestinal diseases, whereas ExPEC strains, including uropathogenic *E. coli* (UPEC) are associated with infections beyond the gut (UTI and neonatal meningitis). These pathogenic strains are genetically adaptable, allowing them to survive in a broad range of host environments and escape immune reactions (Basavaraju & Gunashree, 2022).

A team of University of Virginia researchers has found how pathogenic *E. coli* avoids being detected by immune system in low oxygen environments, such as the large intestine and initiates infection. A small RNA fragment known as DicF is used by the bacteria to sense oxygen levels and, in response turn 'on' genes that promote infection such as those involved in making Shiga toxins that cause symptoms including cramps, diarrhea and vomiting. So it's a survival tactic from host immune mechanisms in which *E. coli* optimize metabolic processes to conserve energy resources and successfully colonize (Melson & Kendall, 2019).

E. coli, a virulent pathogen harness wide array of immune evasion approaches like biofilm formation, toxin secretion and siderophore production (Braz et al., 2020). Understanding of these mechanisms is crucial for new interventions and treatment strategies

Key Strategies of Immune Evasion

Like bacterial evasion tactics, host cell genome encodes multiple immune strategies to clear pathogens. Internalization and processing of antigens from food, external pathogens and indigenous bacteria lead to the activation of the gut mucosal immune system. Their association with gut microflora and immune cells as well as antimicrobial peptides (AMPs), such as human beta defensins, maintain homeostasis. IgA are also important in neutralization of toxin by occupying such active sites which disable toxin to bind with the host cell receptor specific to that toxin (Govindarajan et al., 2020).

In response, *Escherichia coli* have devised several means to subvert such immune attacks to ensure its own survival and persistence in the host. Strategies used by *E. coli* are antigenic variation, avoidance of phagocytosis, immune modulation, complement inhibition, biofilm formation and intracellular survival. However, success in causing acute infection, establishing chronic reservoirs and in resisting therapeutic interventions depends largely on the pathogen's ability to evade immunity.

Modulation of Host Signaling Pathways

Escherichia coli have developed a set of ways for modulating the host immune response to promote the bacterial persistence and survival in host tissues. Targeting innate and adaptive immunity, these mechanisms differ according to the pathogenic strain, such as EPEC, EHEC, UPEC and AIEC.

Secreted effectors and toxins modulate host processes and immune defenses, thus contributing to *E. coli* pathogenicity in both intestinal (e.g., EPEC, EHEC) and extraintestinal (e.g., UPEC, AIEC) (Christensen et al., 2021). These defenses are countered by the *E. coli* effectors that disrupt host cellular processes (i.e., signaling, cytoskeletal dynamics and apoptosis) to elude immune detection. EPEC and EHEC form attaching and effacing (A/E) lesions by effectors (e.g. Tir, EspF, EspG) in a locus of enterocyte effacement (LEE) encoded on a T3SS secreted effector platform. They disrupt tight junctions and induce inflammation, while also subverting cytoskeletal structures causing diarrhea (Halabitska et al., 2024).

The first line of defense against endogenous and exogenous antigens depends on pattern recognition receptors such as toll like receptors (TLRs). Besides, expression on immune cells like macrophages, dendritic cells and natural killer cells, they are also expressed on non-immune cells such as epithelial cells, therefore playing a vital part in detecting pathogen-associated molecular patterns (PAMPs), including lipopolysaccharides (LPS) from *E. coli* via TLR4 to activate NF-κB signaling to drive neutrophil recruitment by cytokines such as IL-6 and IL-8 (Govindarajan et al., 2020). Impairment of this pathway by mutation in TLR4, as in C3H/HeJ mice, increases susceptibility to *E. coli* infection. Instead, *E. coli* subverts TLR4 pathways to circumvent cytokine mediated neutrophil recruitment, allowing for persistent infections (Christensen et al., 2021).

The translocated intimin receptor (Tir) is the first effector protein introduced into host cells during infections caused by enteropathogenic and enterohemorrhagic *Escherichia coli* (EPEC and EHEC). It plays a role in pedestal formation and enhance attachment to host cells, working synergistically with intimin. Beyond these structural roles, Tir also involved in inhibiting or suppressing NF-κB activation through several mechanisms and interact with TNF receptor associated factor-2 (TRAF2) (Hunstad & Justice, 2010). They undergo degradation via a proteasome-independent pathway resulting in the inhibition of TNF-α-induced NF-κB activation. Rfa, rfb and waal genes involved in structural modification LPS which is important for suppression of NF-κB activation (Govindarajan et al., 2020).

The resistance of *E. coli* from antimicrobial peptides and oxidative stress management enhance their survival rate by using cytotoxic necrotizing factor 1 (CNF1) which deploys neutrophil activity (Heesterbeek et al., 2021). This strategy is important in delaying of immune response and undergoes immune evasion. (Carlini et al., 2021).

Production of intracellular bacterial communities and biofilm-like reservoirs located within epithelial cells by UPEC is the approach to evade from immune clearance. Confinement of UPEC in bladder is a strategy to avoid host defense, hence sustain itself for further infection by changing bacterial geometry and obstructing phagocytosis (Hogins et al., 2022).

Intracellular Survival and Reservoir Formation

The *E. coli* that causes food borne diseases survives in host cell and forms biofilm by deploying multiple sophisticated mechanisms that help its survival in the body, allowing it to escape host immune response, resist antimicrobial treatment and at the end achieve persistent infection (Govindarajan et al., 2024; Khasheii et al., 2021).

Intracellular Survival

E. coli strains can get invasion into various cell types, including epithelial cells, macrophages and even bladder epithelium by employing different adhesins or invasins. Upon entry, *E. coli* can form intracellular bacterial communities (IBCs) that serve as reservoirs and protect

bacteria from the host immune system, antibiotics and ultimately persist within the host. During this time period bacteria can reside inside target cell by vesicles formation in the cytoplasm or may undergo transition from motility to dormancy state (Liu et al., 2024). This transition allows the bacteria to evade immune recognition and to persist inside host for longer periods, contributing in the recurrence of infection (Day Christopher et al., 2021). For long term survival and recurrence of infection, UPEC have ability to establish quiescent intracellular reservoirs (QIR) within urinary epithelium. These QIR are dormant bacterial populations to protect itself from immune attack and killing by drugs.

Biofilm Formation

It's a survival strategy in which planktonic cells adhere to the host epithelium with the help of structural weapons (Fimbriae, Adhesins and Outer membrane proteins) then they colonize to form microcolony which lead to the formation of mature biofilm that can disperse or disseminate throughout the body. Biofilms are complex communities of bacteria which is covered with its self-produced extracellular matrix for protection from phagocytosis, killing by antibiotics and other environmental stresses like nutrient limitation. Ability to resist urine flow, immune cells attack and antibiotic treatments lead to the chronicity of infections (Akahoshi & Bevins, 2022).

Fimbriae and Surface Proteins in Biofilm Formation

Adherence of *E. coli*, to its host cell with the help of protein structure named as fimbriae or pili. Intestinal *E. coli* utilizes these surface proteins to attach with host epithelial cells of urinary tract and form biofilm to prolong its persistence in the gut as well as immune evasion. The most common are type 1 and P fimbriae assembled from a major structural protein FimH (binds to α-d-mannosylated glycoproteins) and PapG adhesin (binds to Galα (1-4) Gal containing glycolipids) respectively in *E. coli* through chaperone-usher (CU) system. The adhesins adhere to specific glycoproteins in the host surface, culminating in bacterial attachment and biofilm (Day Christopher et al., 2021).

Siderophores and Iron Acquisition

E. coli strains carry various siderophore systems including enterobactin (Ent), salmochelin, yersinia bactin and aerobactin, each contributing to distinct exo-metabolomes. These siderophores competitively chelate extracellular iron in iron-limited microenvironments and selectively import iron (III)–siderophore complexes through bacterial transporters (Zou et al., 2024). Iron is an essential element for virtually all organisms acting as a co-factor for some vital enzymes. The bladder is an iron-poor environment and so successful setting for UPEC strains with various siderophores proteins which scavenge this element as aerobactin (Walsh & Collyns, 2023). By enhancing iron uptake, *E. coli* can promote biofilm formation and resist immune-mediated killing (Khasheii et al., 2021).

Autotransporters and Adhesion to Host Tissue

Autotransporters are another group of surface proteins that play a key role in *E. coli* biofilm formation. Uropathogenic *E. coli* (UPEC), for instance, utilizes autotransporters like UpaB to adhere to the extracellular matrix (ECM) proteins, fibronectin (Fn), fibrinogen and laminin (Ln). UpaB's binding to Fn enhances bacterial attachment to host tissues (e.g. urinary tract) and aids in the formation of biofilms (Palmer et al., 2021).

Curli and Amyloid Fiber Formation

The formation of rough, wrinkled biofilm structures that provide enhanced protection against environmental stresses is mediated by Curli, thin amyloid like fibers. Host proteins including fibronectin and laminin present binding sites for curli fibers aiding bacterial internalization and promote biofilm mediated pathogenesis (Serra & Hengge, 2021).

Flagella and Motility in Biofilm Formation

Initial stages of biofilm formation rely on flagella allowing *E. coli* to move toward surfaces and to colonize tissues. *E. coli* can switch between motile and sessile state, once attached it is able to persist in biofilms and evade immune responses. Interactions of flagellin, a component of the flagella, with host extracellular matrix (ECM) proteins (collagen and fibronectin) therefore enhance bacterial adhesion and colonization. Additionally, *E. coli* can shut off flagellar expression to prevent installation of an unhealthy flagellar apparatus which ultimately trigger an immune response (Akahoshi & Bevins, 2022).

Avoidance of Phagocytosis and Complement System

Pathogenic *Escherichia coli* employs multiple strategies to evade host immune responses, specifically targeting phagocytosis and the complement system which are essential components of host defense.

For Enteropathogenic *E. coli* (EPEC), inhibition of phagocytosis involves dephosphorylation of host tyrosine-phosphorylated proteins in infected macrophages. This dephosphorylation is crucial for the observed antiphagocytic effect. PI 3-kinase, a protein essential for phagocytosis as a dephosphorylation target. EPEC inactivates PI 3-kinase in a Type III Secretion System (TTSS)-dependent but EspF-, Tir-, and intimin-independent manner. These results in inhibition of induced phagocytosis and also Fc receptor-mediated phagocytosis of bacteria with the help of type III secreted proteins (Esps) and depends on pedestal formation. Upon injection of secreted effectors into host cells, tyrosine phosphatases are either activated or injected directly, leading to dephosphorylation of host proteins necessary for phagocytosis (Zacharia et al., 2022).

Capsular polysaccharides within outermost layer involved in direct interaction with pericellular environment, hence play significant role in bacterial adaptation in new niche. E. coli produces about 80 types of capsule, important of which are K1, K2, K4, K5, colonic acid, K10 and K30 (Gao et al., 2024). K1 capsule, rich in polysialic acid, binds with host Factor H (FH), the primary regulator of alternative complement pathway. In the same way, K2 capsule augments serum resistance and bacterial survival in environments like urine and kidneys. These

interactions lead to downregulation of complement activation and ultimately protects encapsulated *E. coli* from complement-mediated lysis (Whitfield et al., 2020). Research suggests that mutant strains deficient with K2 capsule demonstrate higher susceptibility to serum bactericidal activity, that was restored after genetic complementation (Christensen et al., 2021).

Activated complement cascade (via classical, lectin and alternative pathways), leads to the formation of the membrane attack complex (MAC) to lyse pathogens, accompanied by inflammation and opsonization (Heesterbeek et al., 2021). One prominent mechanism includes recruitment and mimicry of host complement regulators. Pathogenic *E. coli* strains, such as neonatal meningitis *E. coli* (NMEC), use proteins like Omp A and NlpI to bind host complement inhibitors such as C4b-binding protein (C4BP), which inactivates the classical and lectin pathways. Similarly, OmpW recruits Factor H (FH), the main regulator of the alternative pathway, enhancing bacterial survival by reducing complement-mediated killing (Heesterbeek et al., 2021).

Two autotransporters with serine protease activity that inactivate complement components have been described in *E. coli*, extracellular serine protease P (EspP) and protein involved in colonization (Pic). The secreted proteases allow *E. coli* to attack complement mediated immunity and cleaves complement proteins C3/C3b and C5 but does not act on FH or FI (Tontanahal et al., 2022) prevents formation of the membrane attack complex (MAC). The secreted enterohemorrhagic *E. coli* SEFA, Pic, secreted by enteroaggregative *E. coli* (EAEC), uropathogenic *E. coli* (UPEC) and EPEC inactivates complement components from all three activation pathways, including C2, C3, C3b, C4 and C4b. The bacterial proteases, host FH and FI further degrade Pic-generated C3b-like molecules indicating the action of host complement regulators (Correa et al., 2024).

Shiga toxin 2 (Stx2) is also exploited by enterohemorrhagic *E. coli* (EHEC) to subvert complement regulators. Stx2 adhere with these regulators on host cell membranes and inhibits their function, leading to over activation of complement system which lead to tissue damage and causes severe conditions including HUS which is characterized by hemolytic anemia, thrombocytopenia and kidney failure (Menge, 2020).

E. coli shows unsurpassed abilities to evade complement mediated immune responses utilizing these adaptive tools which encompasses capsular defenses and protease activity as well as hijack host regulatory proteins (Alber et al., 2021).

Impact of Immune Evasion

Evasion of *E. coli* from human immune system is crucial for its toxicity which is facilitated by its assaultary weapons. Some strains like uropathogenic *E. coli* (UPEC) deploy both virulence factors and antimicrobial resistance (AMR) mechanisms to foster its evasion from immune attack. UPEC are gut commensal E. coli strains with acquired AMR and virulence traits become pathogenic in the cases of compromised immunity.

Low Antimicrobial Penetration

Production of biofilms, after colonization in urinary tract by bacterial strains produces a physical barrier which limits the penetration of antibiotics. Lipopolysaccharides and extracellular DNA (eDNA) together form the biofilm matrix, which provides a binding site for antibiotics in a way that they cannot penetrate into bacterial cell, and may cause hinderance in diffusion and antimicrobial effectiveness. (Garcez et al., 2020). In addition, this prevents immune system attacks by 'armoring' against penetration by antimicrobial agents and immune cells. Moreover, biofilm associated bacteria can degrade antibiotic through lyases, transferases and hydrolases, denying the antibiotics access to the target. These mechanisms synergistically increase antimicrobial tolerance, making it difficult for the immune system to clear the infection (Ridyard et al., 2023).

Reduced Growth Rates and Stress Responses

Within biofilms, bacterial cells in deeper layers exhibit reduced metabolic activity due to oxygen nutrient gradients and environment's lack of resources. Due to these stationary phase cells in biofilm, target availability for antibiotics decreases, as antibiotics are effective against actively growing cells (Sampaio et al., 2022). The bacteria growing with slow rates are less vulnerable to attack of complement system of host. Response against stressors like nutrient deficit, pH and temperature alteration are regulated by σ-factor (RpoS) that promote bacterial viability in unfavorable environment. Further they enable pathogen to escape from immunological identification and therapeutic strategies (Freire et al., 2022).

Persister Cells

Due to higher stress of antimicrobial agents (aminoglycosides, glycopeptides etc.) *E. coli* within biofilm undergoes dormant stage, variants of regular bacterial population(Niu et al., 2024). As in dormant phase, growth is negligible making them difficult targets for immune cells and antimicrobial agents. Persister cells can evade immune attacks and tolerate antimicrobial treatments by toxin-antitoxin systems, DNA repair mechanisms and upregulation of genes (OxyR, SoxRS and RpoS) as antioxidant response (Kaldalu, Hauryliuk, Turnbull, Mensa, et al., 2020). These cells can resuscitate to normal state when antibiotic pressure subsided, hence leading to persistent or recurrent infections. This is one major cause of treatment failure in patients with chronic infections like UTI and cystic fibrosis, in which extremely high levels of persister cells have been observed (Durrani et al., 2023).

Efflux Pump

Antibiotics or toxic substances like metal ions, surfactants or nanoparticles are actively expel out of *E. coli* cells through efflux pump (Wainwright et al., 2021). Efflux pumps are responsible for escaping bacterial cells from antimicrobial agents to promotes multidrug resistance. The over expression of these pumps inhibits the penetration of bactericidal agents. Efflux pumps are responsible for bacterial evasion from immune attacks like antimicrobial peptides and reactive oxygen species, in the same way prevent accumulation of

drugs inside bacterial cells (Kaldalu, Hauryliuk, Turnbull, La Mensa, et al., 2020). For example, it has been shown that the expression of genes encoding the AcrAB–TolC efflux pump in *E. coli* biofilm is induced as a result of antibiotic exposure. Reduced ability of *E. coli* to form biofilms is caused by mutations or deletions in efflux pump genes, and efflux pumps contribute to both biofilm formation and antibiotic resistance (Riley, 2020).

Horizontal Gene Transfer (HGT)

Horizontal gene transfer refers to the transfer of genetic material within bacterial cells that live in close proximity to each other. Because of the high cell density within the biofilm, antimicrobial resistance genes (ARGs) are exchanged in exponential rate (Tawfick et al., 2022). Such friendly contact in biofilms, HGT occurs more efficiently than in freely suspended bacteria (planktonic population) and promotes the dissemination of antimicrobial resistance. Additionally, these reservoirs of genetic diversity (including ARGs) can spread throughout the bacterial community producing hurdles in the treatment options (Ballén et al., 2022). Central resistance mechanisms such as extended-spectrum beta-lactamases and resistance-carrying plasmids (ColV) endorse survival and facilitate gene transfer (Mare et al., 2021).

Conclusion

As microbiota of human GI tract, certain *E. coli* strains can become pathogenic by acquiring virulence factors through mechanisms like plasmids, pathogenicity islands or DNA horizontal transfer. In *E. coli* biofilms, drug resistance poses challenges for in vivo eradication of pathogen due to increased minimum inhibitory concentration and limited drug accessibility. Biofilm formation significantly impacts immune evasion in *E. coli* by providing protection against both host immune responses as well as antimicrobial agents. *E. coli* deploys a combination of phenotypic adaptations, genetic factors to enhance antibiotic tolerance, particularly in biofilm-associated infections. Mechanisms involve modulation of host signaling pathways, making intracellular reservoirs, avoiding phagocytosis and complement system. These all mechanisms eventually make environment with low antimicrobial penetration, reduced growth rates and high persisted cells to ensure bacterial survival. Such factors contribute to the persistence of infection and the difficulty in treating biofilm-associated bacterial diseases, emphasizing need of more effective therapeutic interventions.

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