AMERICAN SOCIETY FOR MICROBIOLOGY | Infection and Immunity®

MINIREVIEW

Beyond Homeostasis: Potassium and Pathogenesis during Bacterial Infections

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ABSTRACT Potassium is an essential mineral nutrient required by all living cells for normal physiological function. Therefore, maintaining intracellular potassium homeostasis during bacterial infection is a requirement for the survival of both host and pathogen. However, pathogenic bacteria require potassium transport to fulfill nutritional and chemiosmotic requirements, and potassium has been shown to directly modulate virulence gene expression, antimicrobial resistance, and biofilm formation. Host cells also require potassium to maintain fundamental biological processes, such as renal function, muscle contraction, and neuronal transmission; however, potassium flux also contributes to critical immunological and antimicrobial processes, such as cytokine production and inflammasome activation. Here, we review the role and regulation of potassium transport and signaling during infection in both mammalian and bacterial cells and highlight the importance of potassium to the success and survival of each organism.

KEYWORDS potassium, host-pathogen interactions

Potassium is the most abundant intracellular cation in all living organisms, where it is required for numerous basic cellular functions, including regulating intracellular pH, governing the magnitude of the transmembrane electrical potential, and balancing turgor/osmotic pressure (1). However, a large asymmetric distribution between intracellular and extracellular potassium concentrations nearly always exists. Therefore, eukaryotic and prokaryotic cells alike must acquire potassium across steep membrane concentration gradients, utilizing both active and passive mechanisms, including dedicated channels and specialized transport systems. These mechanisms of potassium homeostasis have been well characterized, and they vary greatly in their regulation, energization, and utilization. Until recently, however, considerably less was known about the role and regulation of potassium acquisition during infection and its function at the host-pathogen interface.

In mammalian systems, potassium has fundamental roles in processes as diverse as kidney function, muscle contraction, and neuronal transmission. Potassium transport in nonexcitable immune and epithelial cells has also been shown to contribute to effective antimicrobial functions (2). For example, potassium flux in monocytes and macrophages during bacterial infection is required for the activation of the NLRP3 and NLRC4 inflammasomes (3, 4). Furthermore, potassium availability acts as a key signal in host-microbiome dysbiosis, directly affecting cytokine and antimicrobial peptide production (5).

While potassium availability in animal systems is tightly controlled through diet and renal release, bacterial pathogens must survive or grow under conditions containing a wide range of potassium concentrations, from low ($\leq$4 mM)-potassium environments, such as water, soil, blood, and extracellular spaces, to those containing high ($\geq$100 mM) potassium concentrations, such as within the host cytoplasm. Environmental potassium concentrations have also been shown to affect virulence gene expression, host cell invasion, antimicrobial

Citation Do EA, Gries CM. 2021. Beyond homeostasis: potassium and pathogenesis during bacterial infections. Infect Immun 89: e00766-20. https://doi.org/10.1128/IAI.00766-20.

Editor Anthony R. Richardson, University of Pittsburgh

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Accepted manuscript posted online 19 April 2021

Published 16 June 2021

resistance, biofilm formation, and host colonization in a variety of bacterial pathogens. Together, these findings have established potassium transport as a conserved mediator of bacterial infection outcome.

Here, we review significant reports that have identified and characterized the crucial role of potassium at the host-pathogen interface. We discuss the effects of potassium transport on antibacterial immune function and describe the contribution of potassium transport to pathogenesis in various bacterial species. Finally, we review recent findings on the role of potassium in bacterial intercellular and interspecies electrical communication. To date, this subject has not been reviewed and, therefore, will shed much-needed light on this important element of host-pathogen interaction.

POTASSIUM AND IMMUNE FUNCTION

In mammalian systems, potassium homeostasis involves the regulation of both intracellular potassium concentrations and extracellular potassium availability (6). Serum potassium levels are maintained at nearly constant levels in healthy individuals (3.5 to 5.0 mM), as potassium excretion from the kidney is balanced by the flux of intracellular potassium in the liver and muscles. Potassium retention from dietary intake replaces any deficits, and postprandial insulin stimulates cellular potassium uptake. As discussed further below, catecholamines also regulate potassium distribution, as β-adrenergic receptors promote and α-adrenergic receptors impair cellular potassium uptake (7). Changes in plasma osmolality and acid-base balance also influence potassium balance (8). Finally, nutritional increases in plasma potassium stimulate adrenal aldosterone secretion, which subsequently stimulates renal potassium excretion until plasma potassium levels return to homeostasis (9).

In most cells, potassium accumulation is largely mediated by the sodium-potassium ATPase, which extrudes intracellular sodium while importing extracellular potassium, leading to a potassium gradient across the membrane. However, multiple voltage-gated (e.g., $K_V1.3$), "leak" (e.g., K_{2P}), and calcium-linked (e.g., $K_{Ca}3.1$) potassium channels play important roles in immune cell function (2, 10, 11). In general, immune cells require mechanisms of potassium flux to maintain a hyperpolarized membrane potential critical for sustaining a calcium gradient. Immune cell activation (e.g., antigen recognition) induces calcium influx, which promotes nuclear factor (NF)-κB activity and inflammatory gene transcription (12). Furthermore, differentiation and activation of mononuclear cells modulates inward-rectifying potassium channel expression and activity (13). Dendritic cells have also been shown to upregulate and utilize K_V channel activity for cytokine production, major histocompatibility complex (MHC) class II expression, chemotaxis, and phagocytosis in response to lipopolysaccharide (LPS) (14, 15). Potassium channel activity is required for antimicrobial nitric oxide (NO) production in macrophages (13, 16). Neutrophil phagosomes have also been shown to rapidly accumulate potassium during maturation, which is required for activation of neutrophil elastase and cathepsin G, leading to bacterial killing (17); however, this is not due to large-conductance calcium-activated potassium (BK) channel activity (18). Finally, $K_V1.3$ and $K_{Ca}3.1$ localize to the immunological synapse between a T cell and antigen-presenting cell following T cell receptor (TCR) activation; however, the function of this localization is still unclear (19, 20).

HYPERKALEMIA AND HYPOKALEMIA

Substantial deviations from a normal serum potassium range, termed hyperkalemia and hypokalemia, are often associated with life-threatening health complications, including cardiovascular and neuromuscular dysfunction, which can lead to increased mortality, especially in critically ill patients (21, 22). Potassium intake is considered inadequate in many countries, which may increase the risk for hypertension and cardiovascular disease (23). Changes in potassium distribution can also be affected by disturbances in the acid-base balance due to transcellular exchange of hydrogen and potassium ions, resulting in metabolic acidosis or alkalosis (24). Further, the stimulation of β2-adrenergic receptors modulates the movement of potassium into the intracellular space, while nonselective β2 blockage can induce hyperkalemia (25). Recent studies

have demonstrated that hyperkalemia is commonly associated with ventricular arrhythmia, bradycardia, and cardiac arrest (26) as well as a higher incidence of hepatic encephalopathy, bacterial infections, gastrointestinal bleeding, and acute kidney injury (27, 28). Of note, infection was found to be a leading cause of mortality in patients hospitalized with hyperkalemia (28). Transient hyperkalemia can result from either a significant dietary intake or infusion of potassium, while sustained hyperkalemia can result from a combination of decreased renal potassium excretion and excessive potassium intake (29). Hyperkalemia also induces metabolic acidosis by impairing ammonia excretion (30). As a result, potassium is released into the extracellular space to maintain electroneutrality and compensate for hydrogen uptake.

On the other hand, hypokalemia enhances ammonia excretion and affects proteins involved in ammonia metabolism in the kidney (30), thereby resulting in metabolic alkalosis, where extracellular potassium is exchanged for intracellular hydrogen. In animal models, low potassium, even when within the conventional range of serum potassium, may impair myocardial contractile and relaxation responses to epinephrine (31). Hypokalemia is also significantly associated with higher risk of cardiovascular disease, infection, and all-cause mortality by contributing to the hemodynamic hyporesponsiveness that occurs in some patients with septic shock (32, 33). Similarly, clinical reports have implicated hypokalemia with an enhanced generalized susceptibility to bacterial infection (34), as a substantial serum potassium deficiency may be detrimental to the innate immune system by impairing the cellular mechanisms necessary for inflammasome activation and activity (35).

CATECHOLAMINES

In addition to their roles in vascular resistance and neuromodulation, catecholamines act as neurotransmitters and hormones vital to the homeostatic regulation of potassium distribution by the sympathetic nervous system (36). Under normal physiologic conditions, catecholamines target alpha- and beta-adrenergic receptors, which utilize either cyclic AMP (cAMP) or phosphoinositol second messenger systems to impair or promote the cellular entry of potassium, respectively (37–39). Catecholamine signaling is also heavily involved in the regulation of inflammatory responses, including cell activation, proliferation, and cytokine (e.g., tumor necrosis factor [TNF], interleukin-10 [IL-10], and IL-6) production (40, 41). The stimulation of catecholamine signaling through α-adrenergic receptors promotes proinflammatory responses, whereas stimulation of catecholamine signaling through β-adrenergic receptors exerts significant immunoregulatory mechanisms involved in anti-inflammatory responses, specifically through its effect on macrophages (42). In general, myeloid cells typically produce α- and β-adrenergic receptors, whereas lymphocytes mainly express β-adrenergic receptors. The endogenous release of catecholamines, specifically dopamine and norephinephrine, has also been found to increase bacterial proliferation and pathogenesis, including motility, toxin production, iron acquisition, and host cell adherence (43, 44).

POTASSIUM AND INFLAMMASOME ACTIVATION

Potassium flux plays a significant role in NLRP3 (3, 45) and NLRC4 (4) inflammasome activation in response to various microbial products, including from a wide variety of Gram-positive and Gram-negative commensals and pathogens (46, 47) (Fig. 1). Canonical NLRP3 inflammasome activation is regulated by two distinct signals. First, toll-like receptor and NF-κB activation by various pathogen-associated molecular patterns (PAMPs) upregulates NLRP3 expression, and then damage-associated molecular patterns (DAMPs) initiate assembly of the NLRP3 inflammasome, including the adaptor protein ASC and procaspase-1 complex (48). Potassium efflux is a well-established DAMP trigger required in canonical NLRP3 activation (45, 49) as well as caspase-11-mediated (noncanonical) activation (50), and high extracellular potassium

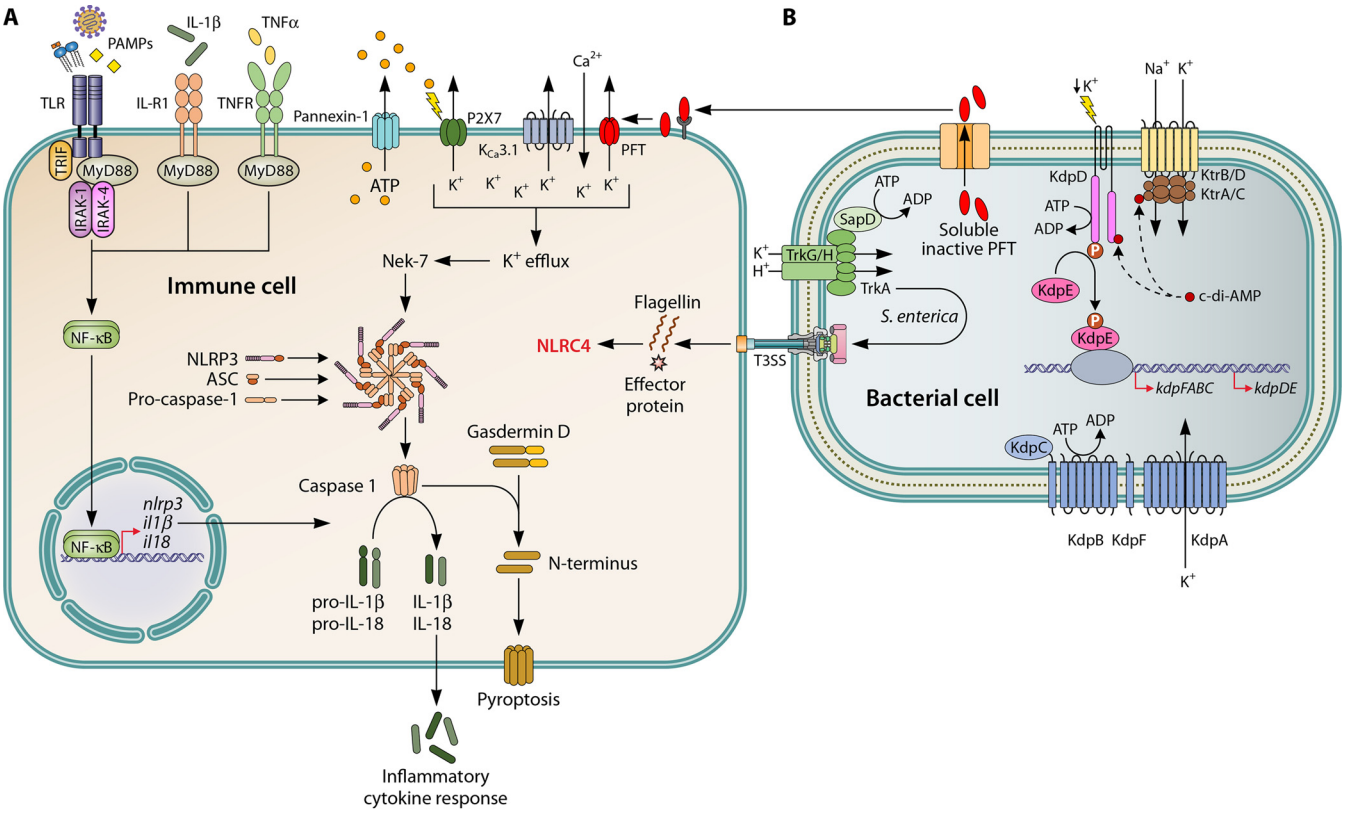

FIG 1 Role of potassium during bacterial infection. (A) Activation of the NLRP3 inflammasome is dependent on two distinct signals. The priming signal is provided by recognition of pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (e.g., toll-like receptors; TLRs) and inflammatory cytokines (e.g., TNF-α and IL-1β). These signals induce MyD88-dependent activation of NF-κB, which promotes the transcription of NLRP3, pro-IL-1β, and pro-IL-18. The activation signal is commonly provided by potassium (K^+) efflux via P2X7, an ATP-gated cation channel, and the calcium (Ca^{2+})-linked potassium channel $K_{Ca}3.1$. Similarly, the insertion and oligomerization of bacterial pore-forming toxins (PFT; e.g., alpha-toxin and listeriolysin O) promotes the efflux of potassium and other small molecules (e.g., ATP) that trigger inflammatory responses. The activation signal promotes the assembly of NLRP3, ASC, and procaspase-1 to form an active NLRP3 inflammasome, leading to the maturation and release of caspase-1, which, in turn, cleaves pro-IL-1β and pro-IL-18 into their mature forms prior to release. Gasdermin D is also cleaved and inserts into the cellular membrane to form a transmembrane pore and induce pyroptosis. Additionally, bacterial flagellin and components of the Gram-negative type three secretion system (T3SS) induce host NLRC4 inflammasome activation (not fully depicted). (B) The Trk, Ktr, and Kdp systems are three of the most common, multicomponent potassium transport systems in bacteria. The Trk system is composed of a transmembrane component (e.g., TrkG/H), cytoplasmic regulatory proteins (e.g., TrkA) that function to cotransport potassium and protons (H^+), and, in some cases, an ATPase (e.g., SapD). The Ktr system is also multimeric and consists of dimeric transmembrane components (e.g., KtrB/D) and respective octameric cytoplasmic regulatory components (e.g., KtrA/C). The Ktr system is thought to energize potassium uptake via sodium (Na^+) cotransport. Activity of the Ktr system is often promoted by ATP and inhibited by c-di-AMP binding to the cytoplasmic regulatory component. The inducible Kdp system is transcriptionally regulated by the two-component KdpDE system, where the histidine kinase sensor, KdpD, senses environmental potassium concentration and phosphorylates the transcription factor, KdpE, to activate the expression of *kdpFABC*. This high-affinity transporter component is composed of a potassium channel (KdpA), ATPase (KdpB), a secondary membrane component thought to mediate affinity (KdpC), and a hydrophobic protein implicated in stabilizing the Kdp complex (KdpF).

blocks NLRP3 inflammasome activation (3, 45). This occurs following extracellular ATP binding to the cation-selective P2X7 channel, which opens a pore that triggers potassium efflux down its electrochemical gradient (51). Interestingly, *Mycobacterium tuberculosis* infection susceptibility has been linked to genetic polymorphisms in the P2RX7 gene (52, 53). Numerous ionophores and bacterial pore-forming toxins, including *Listeria monocytogenes* listeriolysin O (54) and *Staphylococcus aureus* α-hemolysin (55, 56), directly facilitate potassium release and promote NLRP3 activation (57). Thus, the NLRP3 inflammasome can be activated in response to signaling pathways triggered by bacterial infections involving PAMPs and pore-forming toxins that deplete intracellular potassium.

Both NLRP3 and NLRC4 combine with active caspase-1 to cleave several proinflammatory IL-1 family cytokines to their mature form, including IL-1β and IL-18, and induce pyroptosis, a distinctive and highly inflammatory form of programmed cell death (58). The activation of caspase-1 and the subsequent secretion of mature IL-1β

and IL-18 play fundamental roles in innate immunity and the inflammatory response. Unlike NLRP3, the NLRC4 inflammasome is activated in response to a restricted set of stimuli, the intracellular bacterial flagellin and type III secretion system (T3SS) machinery (59, 60) (Fig. 1). While not described in detail here, it has also been shown that NLRC4 inflammasome activation is dependent on potassium efflux, albeit to a lesser degree than NLRP3 inflammasome activation (4).

POTASSIUM AND BACTERIAL PATHOGENESIS

Not only do bacterial pathogens need to produce virulence factors and/or immune modulators to enable invasion, survival, and proliferation within their host but they must also carry out processes necessary for all living organisms, including nutrient acquisition and metabolism. Additionally, maintenance of chemiosmotic homeostasis during infection dictates overall cellular health by regulating membrane turgor and components of the proton motive force, including ΔpH and transmembrane electrical potential. Ion flux is central to establishing electrochemical energy, and, as mentioned above, the most abundant bacterial intracellular cation is potassium. Bacteria use a variety of potassium transport systems that differ in their structure, affinity, kinetics, transcriptional and posttranslational regulation, and energy coupling. These systems have been compared elsewhere (61, 62) and, thus, will not be discussed in great detail. Rather, this section will focus on general mechanisms of potassium transport used by various bacterial pathogens and how potassium sensing and uptake contributes to their pathogenesis.

The conserved structure and function of bacterial potassium channels have been appreciated for decades (63, 64), and high-resolution crystal structures of numerous channel proteins have been resolved, thereby permitting the detailed assessment of ion conductance mechanisms (65, 66). Essentially, a central selectivity pore permits the passage of potassium across the membrane while simultaneously excluding other ions. The gating of ion conductance through the pore is an essential component of potassium transport, as evidenced by the numerous transport systems that are comprised of a channel protein and cognate cytoplasmic regulatory protein(s). For example, the multimeric Trk and Ktr transport systems, which satisfy the general potassium requirements of various bacteria, consist of an ion-conducting transmembrane subunit and a separate regulatory subunit (67) (Fig. 1B). Furthermore, as opposed to stand-alone potassium channels, most bacterial transport systems are "active," utilizing either ATP hydrolysis (e.g., Kdp), the proton motive force, or cotransport of another ion to energize potassium uptake (61). High-affinity Kdp systems often rely on the KdpDE two-component system to sense low extracellular potassium and induce the expression of the KdpABC ATPase and channel proteins (68); however, some *Bacillus* species lack KdpDE and instead regulate the expression of *kdpFABC* using a riboswitch (69). The presence of and variation among potassium transport systems likely reflects evolutionary adaptations made to enhance survival in specific environmental niches. Interestingly, many intracellular pathogens lack major potassium uptake systems (64, 67).

The role of potassium in bacterial pathogenesis ranges from its function as a compatible solute under times of hyperosmotic shock, adaptation to pH stress, modulating resistance to antimicrobials, to mediating virulence factor expression. As described below, mechanisms of potassium transport have also been shown to play crucial roles during infection and colonization in a variety of animal models (Table 1). Bacterial potassium transporters may also serve as potential drug targets, as they have no close homologues in animals (67). This review highlights the evolving appreciation for the role of potassium beyond mediating chemiosmotic homeostasis and demonstrates how potassium is a well-conserved mediator of bacterial pathogenesis.

GRAM-POSITIVE PATHOGENS

***Staphylococcus aureus*.** *S. aureus* is a leading cause of both health care- and community-associated infections, often manifesting as skin and soft-tissue infections,

TABLE 1 Bacterial potassium transporters and their roles in pathogenesis

Bacterial pathogen	Characterized transport system(s)	Role in pathogenesis	Reference(s)
Staphylococcus aureus	Ktr, Kdp	Hyperosmotic tolerance, virulence factor production, antimicrobial resistance, murine abscess formation	73–77, 79
Listeria monocytogenes	Ktr, Kdp, Kim	ND[a]	82, 83
Streptococcus pneumoniae	Trk	Possibly linked to c-di-AMP levels	87, 88
Streptococcus mutans	Trk	Acidic stress, hyperosmotic tolerance, biofilm formation	101, 102
Mycobacterium tuberculosis	Trk, Kdp	Acidic stress, macrophage intracellular survival, murine intranasal infection	105–109
Salmonella enterica	Trk, Kdp, Kup	Acidic stress, virulence factor production, epithelial cell invasion, replication within macrophages, protamine resistance, murine intragastric and intraperitoneal infection	115–122
Acinetobacter baumannii	Trk, Kdp	Virulence factor production, murine pneumonia infection	124
Helicobacter pylori	Kch (channel)	Murine orogastric infection	127
Francisella tularensis	Trk, Kdp	Virulence factor production, hyperosmotic tolerance, survival in blood, murine intraperitoneal infection	131–134
Pseudomonas aeruginosa	Trk	Antimicrobial resistance, biofilm formation	137–139
Vibrio vulnificus	Trk	Protamine and polymyxin B resistance, growth in serum, murine subcutaneous and intraperitoneal infection	141, 142
Haemophilus influenzae	Trk	Antimicrobial resistance, murine nasopharynx and middle ear colonization	145

[a]ND, not determined.

sepsis, endocarditis, and osteomyelitis. Also characterized as a halotolerant organism, *S. aureus* is well known for its ability to grow in salt concentrations ranging from trace amounts to greater than 2 mol/liter. In fact, mannitol salt agar, which contains 7.5% (1.3 M) NaCl, is recommended as a selective and differential medium for the clinical isolation of staphylococci based on their well-established high salt tolerance (70). *S. aureus* is also capable of withstanding considerable changes in environmental osmolarity, salt concentration, pH, and mechanical stress, which mediates colonization and survival on human skin (71). In addition, high osmotic tolerance is thought to enable colonization of host epithelial and mucosal surfaces and contamination of cured foods (72). Elevated salinity also induces broad alteration of *S. aureus* gene expression, including genes involved in capsule polysaccharide synthesis, virulence, central metabolism, and amino acid utilization (73). Consistent with many other bacteria, the growth and survival of *S. aureus* in high-salinity environments requires mechanisms of potassium transport that have only come to light within the last decade (73–76). These studies identified and characterized two distinct potassium transporters: a multicomponent Ktr system and a Kdp transporter.

The role of KdpDE in responding to extracellular potassium and regulating the transcription of *kdpFABC* in *S. aureus* remains unclear, as shown by several conflicting reports (73, 76, 77). Initial findings suggested that the KdpE response regulator directly suppresses *kdpFABC* expression, even under potassium-limiting conditions (76, 77); however, subsequent findings from another group indicate that KdpE indeed activates *kdpFABC* expression (73), consistent with that of other bacteria. Moreover, the overall contribution of the *S. aureus* Kdp system to potassium uptake is contradictory, with two reports describing little to no role for KdpFABC in low-potassium growth (75, 76) and another identifying Kdp as the primary potassium transporter (73). The *S. aureus* KdpDE two-component system has also been shown to regulate the expression ofseveral virulence-associated genes, including protein A, capsular polysaccharide, alpha-toxin, aureolysin, lipase, and gamma-hemolysin (73, 76; reviewed in reference 78). Together, these studies have begun to illuminate the role of KdpDE in *S. aureus* pathogenesis, but several key aspects of the system, including the contribution of the KdpFABC transporter itself, require additional examination.

The *S. aureus* Ktr system is unique compared to other bacterial Ktr systems; it harbors two ion-conducting membrane proteins, KtrB and KtrD, but only one cytoplasmic gating protein, KtrC (also termed KtrA) (73, 75). Interestingly, only one channel protein is necessary and sufficient for full *S. aureus* Ktr function (75). This type of Ktr system was the first to be described, and its existence appears to be conserved among most staphylococcal species (75). The Ktr system is required for normal growth in medium containing less than 10 mM potassium (73–75), while the role for the Kdp system, as described above, ranges from primary to functioning as a potassium scavenger in the absence of a functional Ktr system. The Ktr system has also been shown to play a significant role in *S. aureus* antimicrobial resistance; mutation of KtrC substantially increased susceptibility to aminoglycoside antibiotics, host cationic antimicrobial peptides, polymyxin B, and gramicidin (75). The Ktr system is also required for pathogenesis in a mouse sepsis model of kidney abscess infection (75), likely owing to the combination of its role in osmotolerance, antimicrobial resistance, and central metabolism (79).

Finally, the essential bacterial nucleotide second messenger cyclic di-AMP (c-di-AMP) binds and inhibits KtrC activity in *S. aureus* (74, 80). C-di-AMP also binds the sensor kinase KdpD and inhibits the upregulation of *kdpFABC* under salt stress (74, 81). Recent studies have shown that c-di-AMP also binds a putative *S. aureus* KimA transporter (82), similar to that in *B. subtilis* (83), which permits growth in low potassium when expressed in *Listeria monocytogenes*. As described for other bacterial species below, the conserved interaction of c-di-AMP with potassium transporters has identified novel mechanisms of regulating channel activity, and the implications are only just being revealed.

***Listeria monocytogenes*.** *L. monocytogenes* is an opportunistic foodborne pathogen commonly found in diverse environments such as soil, water, food products, and the gastrointestinal tract of animals (84). Ingestion of *L. monocytogenes* is often associated with self-limited acute febrile gastroenteritis in healthy individuals but can present as bacteremia, meningitis, and meningoencephalitis in immunocompromised, pregnant, and elderly individuals. As a facultative intracellular pathogen, transition of *L. monocytogenes* from the environment to the cytosol requires efficient adjustment to ionic conditions. Early studies showed that *L. monocytogenes* superoxide dismutase, catalase, and listeriolysin O activity are increased in high-potassium environments akin to intracellular conditions (85). *L. monocytogenes* encodes both Kdp and Ktr systems and a newly identified KimA potassium transporter (82, 83). Interestingly, the *L. monocytogenes* Kdp system was not able to support growth of *E. coli* strain LB650, which lacks all potassium uptake systems, suggesting that it is not functional (82). Similar to *S. aureus*, c-di-AMP binds and inhibits *L. monocytogenes* KtrC to prevent overaccumulation and osmotic swelling. Furthermore, c-di-AMP binds *L. monocytogenes* KdpD and KimA from both *L. monocytogenes* and *S. aureus* (82). While c-di-AMP contributes to *L. monocytogenes* virulence, to date, no studies have investigated the role of the Ktr, Kdp, or KimA potassium transporter in *L. monocytogenes* pathogenesis.

***Streptococcus pneumoniae*.** *S. pneumoniae* is an opportunistic pathogen that commonly colonizes the mucosal surfaces of the human upper respiratory tract. When aspirated or locally spread, *S. pneumoniae* can cause invasive infections, including pneumonia, septicemia, meningitis, and otitis media (86). *S. pneumoniae* encodes two potassium uptake systems, a TrkH-CabP (c-di-AMP binding protein) system and another putative Trk-like system; however, only TrkH-CabP appears to play the central role in potassium uptake (87, 88). Bai et al. examined the role of c-di-AMP in TrkH-CabP function and found that c-di-AMP inhibits potassium uptake by preventing interaction between TrkH and CabP (87). This mechanism of inhibition may also be present in the putative Trk and Ktr systems of group B *Streptococcus* (89), although functional analyses of these transporters have yet to be performed. Interestingly, deletion of *S. pneumoniae* CabP, but not TrkH, markedly reduced intracellular c-di-AMP levels (88), which influences pneumococcal growth and virulence (90, 91), indicating that CabP has additional roles besides potassium uptake. This may be attributed to CabP interacting with another Trk/Ktr channel protein (SPD_0429) that was not assessed in these studies (92). Finally, it was also found that

pneumococcal diadenylate cyclase expression was affected by environmental potassium concentration (88), as shown in other organisms (83).

***Streptococcus mutans*.** *S. mutans* is an opportunistic human oral pathogen notable for its association with dental caries and the formation of dental plaque. Following adherence to the tooth surface, *S. mutans* proliferates and forms biofilms, which metabolize dietary sugars to produce acidic end products leading to tooth demineralization and decay (93, 94). Numerous studies have demonstrated that *S. mutans* requires potassium to survive and metabolize under acidic (pH $\leq$5) conditions (95–97). Furthermore, several putative Trk genes were found to be significantly upregulated when *S. mutans* was placed under acid stress, further suggesting their involvement in acid tolerance (98). Glutamate transport, which plays a major role in bacterial acid tolerance, also utilizes potassium ions for function in *S. mutans* (99, 100).

S. mutans requires relatively high concentrations of available potassium (25 mM) for optimal growth, and growth is limited in $\leq$5 mM potassium (101). *S. mutans* encodes four putative potassium transporters, annotated Trk1 (*trkB*, *trk*, and *pacL*), Trk2 (*trkA* and *trkH*), Kch, and the glutamate transporter GlnQHMP. Of the four transport systems, Trk2 was found to be critical for growth under low potassium conditions, membrane potential, survival during acidic and osmotic stress, and biofilm formation, while Trk1 played a minor role, particularly in the absence of Trk2 (101). The defect in biofilm formation of the *trk2* mutant was attributed to decreased glucan production as a result of impaired glucosyltransferase activity. Because potassium acquisition is necessary for bacterial growth under adverse environmental conditions, efficient potassium transport systems, including Trk2, would be crucial for bacterial cell survival and persistence of *S. mutans* and phylogenetically related bacteria. Finally, a report published at the same time as Binepal et al. found two *S. mutants* Trk proteins that bind c-di-AMP, therein termed CabPA (*trk*) and CabPB (*trkA*), and that they also play a role in biofilm formation (102).

***Mycobacterium tuberculosis*.** *M. tuberculosis*, the causative agent of tuberculosis, is the leading cause of bacterial infectious disease deaths worldwide. Inhaled *M. tuberculosis* disseminates to regional lung lymph nodes followed by hematogenous spread to other parts of the lung and throughout the body (103). Following phagocytosis by alveolar macrophages, *M. tuberculosis* is retained in the early endosome by preventing phagosome-lysosome fusion. However, survival within the phagosome, which has a pH of 6.2 to 6.4, is essential to *M. tuberculosis* pathogenesis (104). *M. tuberculosis* encodes both Trk and Kdp potassium transport systems (105, 106), and Trk is required for adaptation to acidic pH stress and survival within macrophages (107). *M. tuberculosis* lacking the Trk system was also attenuated in a mouse intranasal infection model (107). However, several reports indicate that the *M. tuberculosis* Trk system has a unique function related to potassium acquisition and cell physiology, including no detectable role in low-potassium growth, intracellular pH homeostasis, or regulation of membrane potential (105, 107, 108). It is possible that increased *kdp* gene expression compensates for the lack of a functional Trk system (108).

M. tuberculosis responds to low-potassium environments by differentially regulating a variety of genes, the most prominent of which are those of the Kdp system (106, 107). As with most Kdp systems, *kdpFABC* expression in low potassium is dependent on KdpDE. Furthermore, membrane lipoproteins LprF and LprJ have been shown to function as accessory proteins that directly interact with KdpD and affect its kinase activity to modulate KdpE-dependent *kdpFABC* expression (106). A *kdpF*::GFP reporter showed no induction during growth under acidic pH stress or high osmolarity but was enhanced in a transcriptional repressor mutant, *rv0500A*, when grown in potassium-free media, although the mechanisms responsible remain unclear (107). An earlier study of six *M. tuberculosis* two-component regulatory systems found that deletion of *kdpDE* increased virulence, as determined by a significantly shorter survival time in SCID infected mice (109). Interestingly, numerous studies have shown that susceptibility to *M. tuberculosis* infection is linked to mutations in the potassium efflux gene *p2rx7*, which contributes to the antibacterial response of P2RX7-mediated inflammasome activation in macrophages (reviewed in reference 110).

GRAM-NEGATIVE PATHOGENS

***Salmonella enterica*.** *S. enterica* is major cause of community-acquired bloodstream infections (typhoidal *Salmonella*) and gastrointestinal disease (nontyphoidal *Salmonella*), transmitted predominantly through contaminated food and water (111, 112). Consumed *S. enterica* cells must initially survive passage through the stomach, where gastric acid presents an initial barrier to colonization (113). Under these conditions, the well-described *Salmonella* inducible acid tolerance response permits survival under low pH conditions (114) mediated, in part, through potassium/proton transport and upregulation of the Kdp system (115). *S. enterica* encodes Trk, Kdp, and Kup transport systems (116), and the latter is considered essential under acidic conditions. Consistent with other bacteria, transcription and translation of *kdpA* in *S. enterica* is highly induced after high salt challenge and potassium limitation (117, 118). Upon entering the small intestine, *S. enterica* must traverse the mucus layer, attach, and invade small intestinal epithelial or microfold (M) cells. Here, the KdpA channel protein is required for *S. enterica* invasion into colonic epithelial cells and replication within macrophages (115). In a screen for genes involved in facilitating *S. enterica* serovar Typhimurium invasion into human epithelial cells, mechanisms of potassium transport were by far the most enriched molecular function (119), indicating that the sensing and transportation of potassium is used as a cue to promote *Salmonella* invasion.

Potassium transport also plays significant roles in *S. enterica* virulence factor production and pathogenesis. Early studies found that TrkA (SapG) is required for low-potassium growth, protamine resistance, and pathogenesis in mouse models of intragastric and intraperitoneal infection (120, 121). Subsequently, Lu and colleagues found that TrkA is necessary for production of SipA and SipC, effector proteins of the type III secretion system (TTSS) of *Salmonella* pathogenicity island 1 (SPI-1) (116, 122). These downstream affects may also influence potassium-dependent host inflammasome activation (Fig. 1). In addition, potassium transport is required for *S. enteric* motility, mammalian cell invasion, and pathogenesis in both mouse and chick models of infection (116, 122). These results demonstrate that potassium uptake plays important roles in pathogenesis beyond maintaining the physiology of *Salmonella*, including a direct effect on the function of the SP-1 TTSS.

***Acinetobacter baumannii*.** The spread of multidrug-resistant *A. baumannii* has raised clinical concern worldwide as a major cause of serious infections, including ventilator-associated pneumonia, urinary tract infections, and bacteremia commonly occurring in hospitalized and/or immunocompromised patients (123). To date, Trk and Kdp systems have been identified in *A. baumannii*, with the latter being characterized in potassium transport and pathogenesis (124). The *A. baumannii* KdpDE two-component system was shown to be induced >70-fold and play a significant role during growth under potassium-limited conditions (124). Furthermore, a Δ*kdpE* mutant was shown to be significantly attenuated in lung colonization during a mouse pneumonia model of infection. Histopathological analyses showed that unlike wild-type *A. baumannii*, the Δ*kdpE*-infected lungs demonstrated markedly less congestion, edema, and neutrophil infiltration in the alveoli and interstitial tissue (124). In addition to its role in potassium sensing, this phenotype was attributed to the differential production of 135 proteins in the Δ*kdpE* mutant, including those involved in the heme pathway, capsule and cell wall synthesis, amino acid biosynthesis, and gene regulation.

***Helicobacter pylori*.** *H. pylori* colonization of the human stomach, unless treated, can persist indefinitely and cause chronic gastric diseases, such as gastritis, gastric and duodenal ulcers, and cancer (125). Gastric acid secretion largely determines the ability of *H. pylori* to colonize, as it must pass through the gastric lumen to reach the neutral pH of the gastric mucosa, its specific niche for proliferation. Here, the potassium concentration is expected to be in the low micromolar range, as it is critical for secretion of hydrochloric acid (126). Despite passage through acidic environments, *H. pylori* lacks homologues of the Kdp, Trk, Kup, and Ktr systems but encodes a two-transmembrane potassium channel, HpKchA (127, 128). Growth of a Δ*hpKchA* mutant was decreased in potassium concentrations as high as 17.3 mM, and despite not being required for acid tolerance *in vitro*, the Δ*hpKchA* mutant was completely attenuated in a 4-week murine

model of orogastric infection (127). The presence of a sole potassium channel in *H. pylori* might reflect an adaptation to the potassium-rich, competitor-free gastric environment (127).

***Francisella tularensis*.** The causative agent of tularemia, *F. tularensis* is a facultative intracellular pathogen known for its high infectivity and lethality and as a potential agent in biowarfare and bioterrorism (129). *F. tularensis* pathogenesis relies heavily on its ability to replicate within host macrophages; however, it must also survive extracellular transmission and dissemination (130). In a screen to identify novel extracellular nutritional requirements of *F. tularensis*, Alkhuder et al. identified TrkH as being required for growth under hyperosmotic conditions and media containing less than 18 mM potassium (131). While TrkH was not required for macrophage intercellular survival *in vitro*, growth and survival of a Δ*trkH* mutant was attenuated *ex vivo* in murine blood (131). Mouse survival studies further demonstrated that *F. tularensis* virulence is severely attenuated in the Δ*trkH* mutant following intraperitoneal injection and that the Δ*trkH* mutant is unable to replicate within the spleen, liver, and blood. Thus, Trk-mediated potassium uptake appears to play a fundamental role in dissemination and the extracellular phase of *F. tularensis* pathogenesis.

F. tularensis also encodes a Kdp system, but some strains and subspecies harbor deleterious mutations in the *kdpA*, *kdpB*, *kdpD*, and/or *kdpE* genes (131, 132). The sensor kinase KdpD was identified in a screen for genes required for *F. tularensis* survival in the mouse spleen following intraperitoneal injection (133). KdpD is thought to be responsible primarily for phosphorylating PmrA, which regulates the expression of the *Francisella* pathogenicity island (FPI) virulence genes (134); however, it remains to be determined if *F. tularensis* KdpD functions to sense environmental potassium concentrations.

***Pseudomonas aeruginosa*.** *P. aeruginosa* is an opportunistic and ubiquitous bacterial pathogen present in diverse environmental settings due to its minimal nutritional requirements and tolerance of extreme conditional variances (135). Despite its global prevalence, most infections are associated with health care settings, where *P. aeruginosa* is the causative agent of pneumonia, urinary tract infections, surgical site infections, and bloodstream infections in immunosuppressed patients. While resistant to multiple classes of antibiotics, the survival and pathogenesis of *P. aeruginosa* also requires the successful formation of biofilm (136). Mutation of the *P. aeruginosa* TrkHA system significantly increases sensitivity to carbenicillin and numerous aminoglycoside antibiotics (137, 138). An earlier report also identified a putative novel potassium importer (PA1207) that was also shown to be important for *P. aeruginosa* biofilm formation and virulence in a barley germination assay (139). Further investigations of Trk and other *P. aeruginosa* potassium importers are required to establish their contribution to animal pathogenesis.

***Vibrio vulnificus*.** *V. vulnificus* is an opportunistic zoonotic pathogen that causes severe wound infections, gastroenteritis, and sepsis after contact with seawater or consumption of raw shellfish (140). Survival and replication under a range of saline conditions is required in the various ecological niches that *V. vulnificus* inhabits. Moreover, virulence factor expression and survival in serum are essential to infection, including the production of capsular polysaccharide, toxins, and iron acquisition, resulting in a septicemia mortality rate of over 50% (140). Furthermore, resistance to the bactericidal effects of serum plays a fundamental role in the systemic dissemination of pathogenic bacteria. Chen et al. screened a library of *V. vulnificus* transposon mutants for decreased survival in human serum and identified a *trkA* mutant that was required for resistance to complement-mediated killing (141). The requirement for TrkA in *V. vulnificus* serum survival was confirmed in a recent report (142). TrkA is also necessary for resistance to polymyxin B and protamine, and in mouse models of lethal intraperitoneal and subcutaneous infection, the 50% lethal doses (LD_{50}) of the *trkA* mutant were 80- and 7-fold higher,

respectively, than those of wild-type *V. vulnificus* (141). In a model of elevated iron, the LD_{50} of the *trkA* mutant was 150- and 300-fold higher than that of the wild type in the intraperitoneal and subcutaneous models, respectively (141). Together, these studies clearly implicate the Trk system as a major contributor to *V. vulnificus* pathogenesis.

***Haemophilus influenzae*.** *H. influenzae* is a commensal organism of the nasopharynx and is often implicated in systemic and respiratory tract infections, meningitis, and otitis media (143). The species is divided into encapsulated and nonencapsulated (nontypeable; NTHi) strains, depending on the presence or absence of a polysaccharide capsule, respectively. Following widespread use of the *H. influenzae* type B vaccine, the vast majority of respiratory disease now arises from NTHi strains (143). According to genomic analyses, NTHi encodes a TrkHA system, but Mason et al. showed that a SapD homologue, known to provide ATPase activity to Trk potassium transporters in other bacteria (144), is also required for potassium uptake in NTHi (145). They also demonstrated that the Sap operon was upregulated upon exposure to antimicrobial peptides and that SapD was necessary for resistance to killing by human beta defensin-3 and cathelicidin LL-37 (146). Furthermore, a Δ*sapD* mutant was completely attenuated in both nasopharynx and middle ear survival using adult chinchilla models of colonization (145). It is speculated that in addition to its role in providing ATPase activity to the SapA complex, SapD provides ATPase activity to the Trk system to mediate high-rate potassium uptake. In this respect, SapD activity may counter the rapid loss of potassium that occurs after exposure to antimicrobial peptides.

Electrical signaling in bacterial biofilms. Cell-to-cell signal transmission is essential to the survival of a wide variety of biological systems. Bacterial biofilms depend on cooperative behavior and division of labor but cells also compete for limited resources (147). While quorum sensing is the best-characterized intercellular signaling process in bacteria (148), electrical signaling via ion transport is a major form of communication in many other biological systems. In recent years, the study of bacterial potassium transporters has provided fundamental insights into novel mechanisms that mediate spatial and temporal signaling within biofilms (149–151). Essentially, synchronized oscillations in membrane potential correlate with the active uptake and release of potassium (but not sodium) within and among biofilm cells. Nutrient-starved cells (i.e., glutamate) in the biofilm interior release propagating waves of potassium to temporarily depolarize neighboring cells, resulting in a cell-cell relay wave to the biofilm periphery that allows nutrients to diffuse internally (151). Beyond dictating system behavior in response to variations in nutrient availability, further studies in biofilm electrical signaling have demonstrated that such electrical signals could extend beyond the biofilm periphery to influence distant and unrelated cells (149). In this study, electrical signaling mediated through the *Bacillus subtills* YugO potassium transporter activity attracted distant *P. aeruginosa* cells by modulating their membrane potential and motility, demonstrating a mechanism of long-range, cross-species bacterial communication through gradients of potassium (149). Interestingly, *P. aeruginosa* also directed their motility toward noncellular sources of potassium, indicating that potassium alone serves as a compass rose for pathogenic bacterial motility. Taken together, these results demonstrate the fundamental role of potassium and potassium ion transport in mediating electrical signaling both within and beyond a bacterial biofilm. Importantly, potassium-mediated electrical signaling does not require dedicated receptors or signaling pathways (required for quorum sensing), thereby allowing for cross-species communication using transporters and/or channels already produced for basic cellular survival. However, the role of potassium in biofilm electrical signaling has yet to be demonstrated in any bacterial pathogen and should be considered in the focus of future studies of bacterial pathogenesis.

CONCLUSION

Potassium availability at the host-pathogen interface is required for regulating several host immune functions and antimicrobial activities. Bacterial pathogens also require potassium for virulence factor expression and antimicrobial resistance. As a result, competition for potassium is likely to be a critical factor in determining infection outcomes. Given the importance of potassium in bacterial pathogenesis and immune activity, ongoing studies will continue to identify novel mechanisms of potassium utilization during infection. The study of c-di-AMP, for example, is of active interest, as its role in modulating bacterial potassium transport implicates it as a critical determinant in pathogenesis. C-di-AMP released from bacterial pathogens elicits a type I interferon immune response, mediated by the host receptor protein STING (152, 153). Additionally, continued investigation into the contribution of potassium to bacterial colony signal transduction will undoubtedly shed new light on its role during infection. Finally, further understanding how both host and pathogen utilize potassium to combat each other may identify novel therapeutic strategies to promote a productive immune response and thwart bacterial infection.

ACKNOWLEDGMENTS

We thank Zainab Rangwala for her assistance with early drafts of the manuscript.

This work was supported by a pilot grant to C.M.G. from the University of California Riverside School of Medicine.

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