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Acid attack: how *Escherichia coli* strains resist acid stress

Lindsey Miller

Abstract

The systems used by *Escherichia coli* to combat heightened levels of acidity within their environment are varied and complex. Four distinct systems used by *E. coli* to resist acid-induced stress were identified in 2004 by Foster (1), though six now are known today. These systems include the glucose-repressed, glutamate-dependent, arginine-dependent, lysine-dependent, ornithine-dependent, and serine-dependent acid resistance systems. Each system is also known by its corresponding abbreviation, AR1-AR6. What is known about each system varies due to identification date, complexity of the pathway, and amount of research completed. Within this paper, each system will be identified and the pathway defined, combining the published research from a variety of studies to create a comprehensive explanation of the six known acid resistance systems used by *Escherichia* coli to survive acid stress.

Introduction

Escherichia coli is a gram-negative bacillus bacteria that is widely known for being present in the human microbiome, where it can live as a symbiont with the host or as a pathogen (2). *E. coli* uses cattle as a major reservoir, especially the O157:H7 strain, but has also been found in other livestock such as sheep, goats, and pigs (3). While inhabiting a host, *E. coli* is most often found within the digestive tract (4), the large intestine specifically (5). It is considered a commensal microbe most of the time, inhabiting the GI tract of its host without any ill effects to the host. However, some strains are considered pathogenic as they attack and cause issues for the host. In order to colonize the human host, pathogenic *E. coli* must survive the acidic secretions of

lysozymes attempting to kill off invaders. *E. coli* need to maintain a neutral cytoplasmic pH in order to properly function (6), and while the pH in the large intestine can range from 5.7 to about 6.7 (7), lysozyme secretions are often very acidic at about a pH of 4-5 (8). Pathogenic E. coli strains can also be found outside of the large intestine, such as in the urinary tract, meaning that environmental pH may differ, possibly adding additional acid stress (2). In order for the bacterium to not only survive, but thrive and grow under such acidic conditions, *E. coli* has multiple pathways and systems that allow for acid resistance under acid stress conditions. These systems include the glucose-repressed, glutamate-dependent, arginine-dependent, lysine-dependent, ornithine-dependent, and serine-dependent acid resistance (AR) systems. This literature review will explore the workings of these systems (reference Figure 1 for overview) and how they help *E. coli* strains with acid resistance.

Figure 1

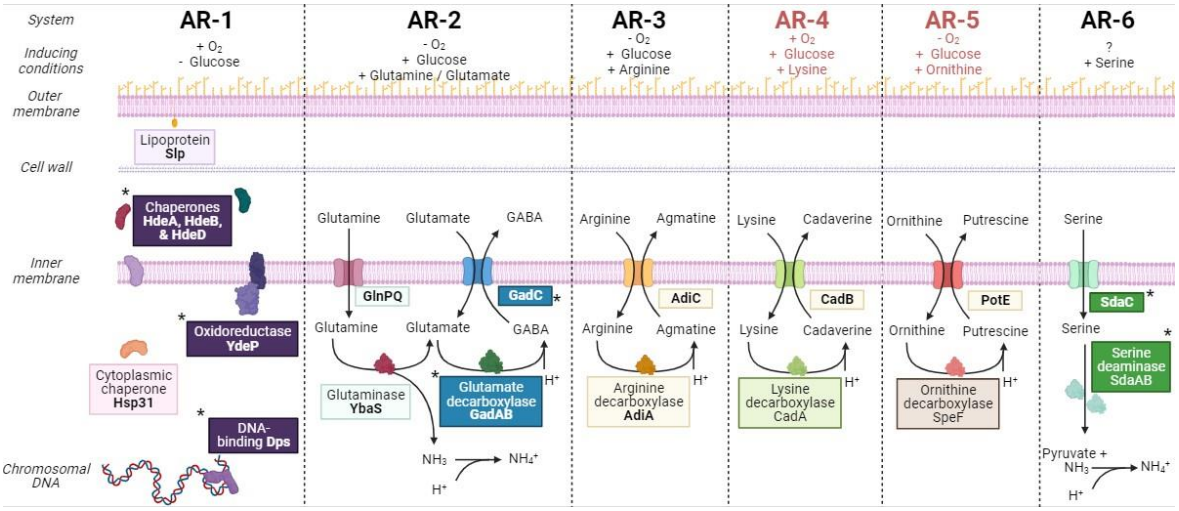

Figure 1: overview of the six acid resistance systems identified in *Escherichia coli*. Each system depicts the important proteins, substrates, and products within its overall pathway (9).

Physiological effects of acid stress in *E. coli*

Environmental conditions with acidic pH can be detrimental to bacteria. A low pH can cause DNA depurination (10), where adenine and guanine are lost from DNA due to the N-glycosidic bonds are cleaved (11). Changes in environmental pH can cause disruptions in hydrogen bonding, resulting in misfolded proteins (12). The intracellular metabolic activities of bacteria can be changed, including nutrient transport and protein phosphorylation, when in acidic pH environments (13). If the intracellular pH of the bacterium is lowered due to acidic conditions, pH homeostasis and cellular metabolism can be disturbed, causing the cell to be unable to perform essential tasks for survival (14). The intracellular pH could be lowered if the outer membrane is disrupted and becomes permeabilized, which is an effect of some acids such as lactic acid produced by muscle cells and red blood cells (15). All in all, acid stress can cause a variety of negative effects on bacterial cells, making it vital for bacteria like *E. coli* to have acid resistance systems.

Glucose-repressed/oxidative acid resistance system (AR1)

As the name suggests, the glucose-repressed (also called the oxidative) AR system is repressed by glucose, meaning it needs glucose to be absent to be activated (1). Another requirement for using this acid resistance system by *E. coli* during

stationary phase includes RNA polymerase sigma S (*rpoS*) (16). The genes necessary for acid resistance using this system change depending on environmental conditions (17); however, under stationary-phase induction using the σ^S sigma factor, the module activator GadE and related GadX expression are part of the glucose-repressed AR system (18). It must also be noted that RpoS works with Crl, a regulator protein that increases RpoS activity (19), in order to moderate RpoS regulon expression during stationary-phase acid stress, along with other kinds of environmental stress (20).

Beyond *rpoS*, the σ^S sigma factor, and the CrI protein, other proteins involved in this acid resistance system are relatively unknown. As seen in Figure 1, there are many proteins linked to the glucose-repressed AR system. The Slp protein is a lipoprotein with unknown function that is connected to acid resistance within *E. coli* (21). The YdeP, YdeO, and YhiE proteins have been preliminarily linked to acid resistance in *E. coli* (22). Proteins in the Hde family (HdeA, HdeB, and HdeD) are chaperone proteins that specifically help protect periplasmic proteins during acid stress (22)(23)(24). Hsp31 is another protein connected to protein protection during acid stress (25). During a variety of different kinds of stress, the DNA-binding protein Dps binds to the DNA (26) and can protect the DNA from damage by the stressor (27). However, further details on the specific roles and pathways Slp, YdeP, YdeoO, YhiE, HdeA, HdeB, HdeD, Hsp31, and Dps are involved in are scarce or relatively nonexistent, making their ties to *E. coli* acid resistant undetermined until further research is completed.

Glutamate-dependent acid resistance system (AR2)

The glutamate-dependent AR system is much like those before it. Similar to the arginine-dependent AR system, the glutamate-dependent AR system is comprised of the decarboxylases GadA and GadB as well as the antiporter GadC (28). Once exposed to acid shock, the antiporter imports glutamate into the cytoplasm, the decarboxylases consume a proton while converting glutamate into γ-aminobutyric acid (GABA), and the decarboxylated product of GABA is exported out of the cell by the antiporter (29). Unlike the arginine-dependent AR system, there are many existing carboxyl protonation forms that GadC may encounter, which would result in different proton movements (29). To combat the possibility of increasing acidification within the cell, GadC selects the substrates for the exchange using a charge-based mechanism with Glu0 or Glu- being exchanged for GABA+ (29); this ensures that acidification within the cell is reduced, creating acid resistance within and for the bacterium.

The decarboxylated product of GABA carries a “virtual proton”, a proton that is short lived to the point of being undetectable but still exhibits the characteristics of a proton (30). The virtual proton is present in all acid resistance systems that utilize a decarboxylase and helps to decrease intracellular acidity as it is pumped out of the cell (30). This enables the cell to maintain a more suitable pH to continue normal functions and survive acidic environments.

Glutamine, another amino acid, can play an important role in this AR system. Glutamine can be imported into the cell by GadC and converted into glutamate through enzymatic deamidation by glutaminase YbaS (31). Once the glutamine is converted into glutamate, the steps described above can occur with the same acid resistance outcome. Additionally, through the enzymatic deamidation of glutamine into glutamate,

ammonia is made and can be exported out of the cell to further aid in raising the intracellular pH (31).

Some research suggests that the enzymes used in the glutamate-dependent AR system are also used in the glucose-repressed AR system. Experimentally, it was deduced that the Gad decarboxylation enzymes, that contribute to glutamate-dependent acid resistance, are also used for glucose-repressed acid resistance but with an internally derived glutamate source (32). Furthermore, YdeO overlaps between the glucose-repressed and the glutamate-dependent AR systems, but due to the genes associated with YdeoO expression (hdeA, hdeD, slp-yhiF) not being needed under normal conditions to induce acid resistance, it is undetermined whether the two systems are the same, different, interconnected, or if this is a brand new acid resistance system (33). It can be difficult to separately categorize what belongs to the glucose-repressed AR system and what belongs to the glutamate-dependent AR system as the glucose-repressed system tends to act as a catchall for miscellaneous evidence related to acid resistance that doesn't fit into other known AR systems. The two appear to share some enzymes, but until the glucose-repressed AR system is better defined, a true distinction cannot be made.

Figure 2

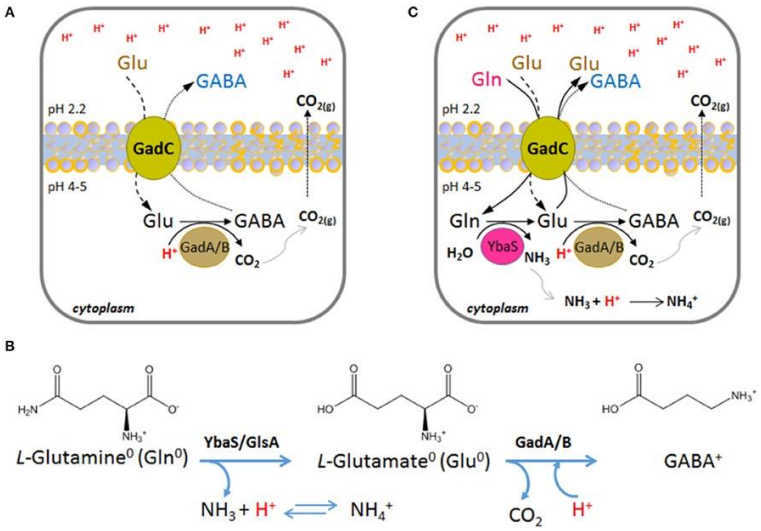

Figure 2: (A) illustration of the two systems in *E. coli* using glutamate to confer acid resistance- glutamate to GABA and glutamine to glutamate to GABA. (B) depiction of the compounds in the glutamine to glutamate to GABA pathway (34).

Arginine-dependent acid resistance system (AR3)

The arginine-dependent AR system is comprised of a decarboxylase (arginine decarboxylase, or ADC), an antiporter (adiC) and the gene that encodes for the aforementioned proteins (adiA) (35). Anaerobic conditions, low pH, and high concentrations of arginine are needed to induce this system (36). When the bacterium is subjected to acid shock by its environment, adiC takes in extracellular arginine as fuel for ADC to use to produce agmatine, which is exported by adiC (37). This helps to raise the pH of the cell to maintain a more neutral pH in an acidic environment.

Figure 3

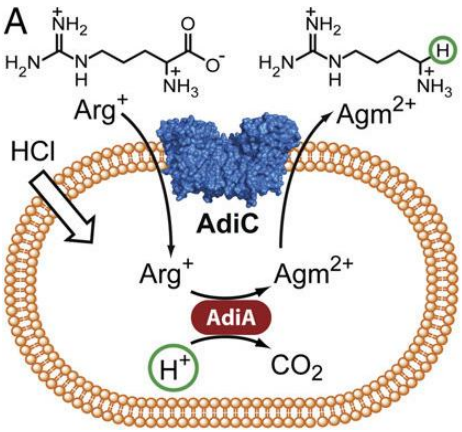

Figure 3: image depicting arginine-dependent AR system and the mechanism of converting arginine to agmatine (38).

Lysine-dependent acid resistance system (AR4)

The lysine-dependent AR system is often studied alongside glutamate- and arginine-dependent AR systems. Low pH, anaerobic conditions, and high concentrations of lysine are necessary to induce the system, just like the arginine-dependent AR system (36). Also like the arginine-dependent AR system, the lysine-dependent AR system relies on the use of a decarboxylase (cadA), which is encoded on an operon called cadBA (39). cadA is expressed to a high enough concentration during anaerobic conditions to assist the bacterium survive the acidic environmental conditions, while aerobic conditions appear to limit the expression of cadA (40). This may be due to a different promoter being used during anaerobic conditions or a higher level of induction necessary of Pcad, the promoter used during aerobic conditions (41). The lysine decarboxylase converts L-lysine into cadaverine, consuming a proton and raising the pH in the process (40). In the presence of lysine, cadB, a protein encoded on the cadBA operon, acts as an antiporter, importing lysine and exporting cadaverine out

of the cell (42). This exchange of products in and out of the cell raises the intracellular pH, enabling the bacterium to survive in less-than-ideal conditions like the acidic environment of a host's stomach.

The product of lysine decarboxylase, cadaverine, is a metabolite of human cells as well as some bacterial cells (43). In humans, cadaverine has multiple physiological effects, such as cell growth and differentiation as well as regulation of gene expression (44). Additionally, higher expression of lysine decarboxylase and cadaverine can help regulate early breast cancer (43). Accumulation of cadaverine can also have toxicological effects in humans such as hypotension and bradycardia(44). In conjunction with nitrites, cadaverine can produce nitrosopiperidine (45), a known carcinogen (46). Within bacterial cells, cadaverine is associated with the synthesis of some siderophores (47), aiding the cells with obtaining and storing iron. *E. coli*, however, has a low cadaverine tolerance with the accumulation of cadaverine causing inhibited cell growth (48), increased cell lysis (48), decreased nutrient uptake (49), and decreased exportation of harmful metabolites (49). Due to the identified negative effects of cadaverine, some bacterial species, like *Shigella* species, don't use the lysine-dependent AR system (50), relying on other AR systems instead.

Figure 4

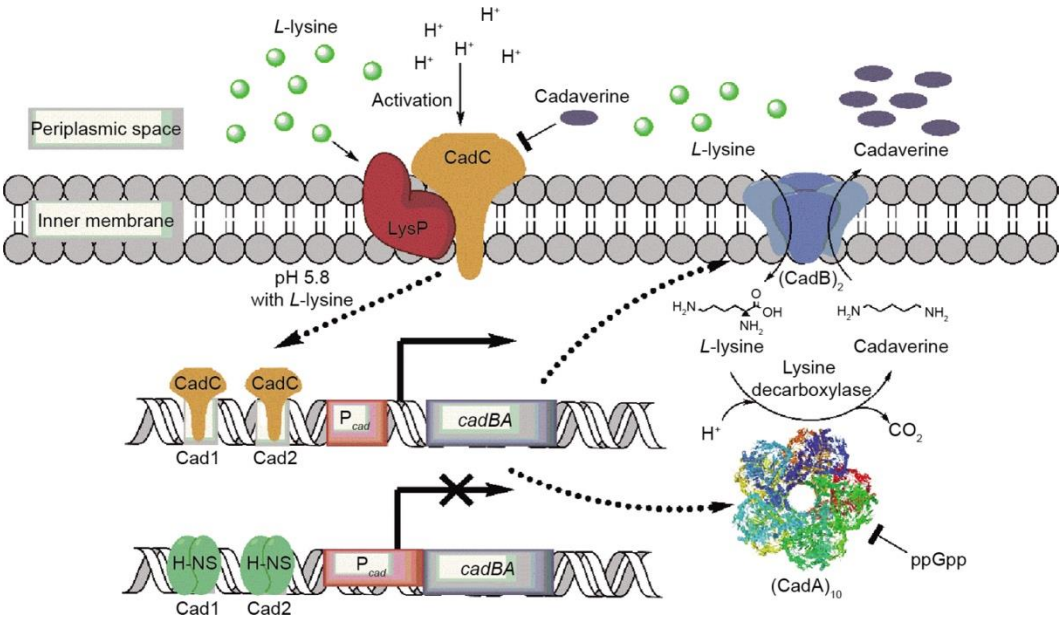

Figure 4: illustration of lysine-dependent AR system and the regulation of cadaverine synthesis (49).

Ornithine-dependent acid resistance system (AR5)

The ornithine-dependent AR system is comprised of an ornithine decarboxylase, sometimes referred to as ODC or SpeF, and an ornithine-putrescine antiporter, PotE. The inducible ornithine decarboxylase can be found on the *speF* gene and the ornithine-putrescine antiporter can be found on the *potE* gene (51). PotE imports ornithine into the cell, ODC/SpeF converts ornithine into putrescine, and PotE exports the putrescine out of the cell. In acidic environments, the synthesis and exportation of putrescine helps to protect the *E. coli* cells (52). PotE can also import putrescine into the cell under specific conditions (53), though this is not applicable to surviving acid stress. It should also be noted that SpeB, another protein in the Spe family, synthesizes putrescine from agmatine (54), and SpeE synthesizes spermidine from putrescine (55). This web of

product synthesis allows the bacteria to make use of environmental resources into a variety of useful products to best fit their needs.

Figure 5

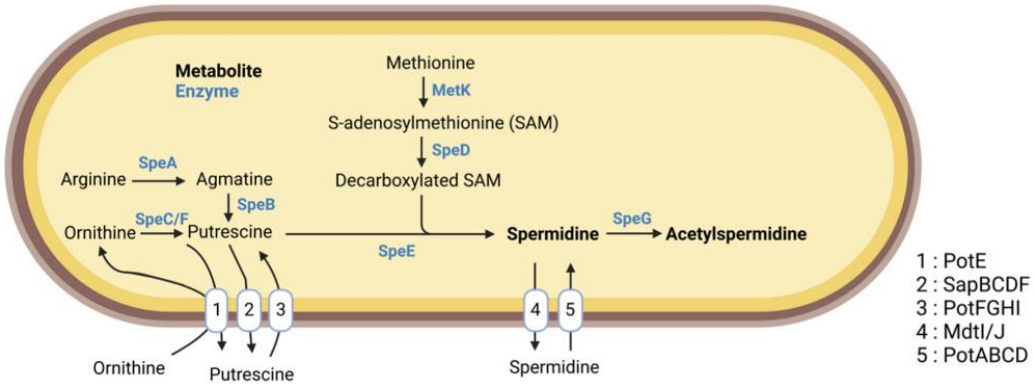

Figure 5: illustration of polyamine synthesis in a strain of E. coli (E. coli Nissle 1917), added in to demonstrate ornithine and putrescine uptake/secretion and uses (56).

Serine-dependent acid resistance system (AR6)

The serine-dependent AR system is a novel metabolism within *E. coli* identified recently in a paper by Wiebe et al in 2022. Previously, the assumptions made in studies of *E. coli* postulated that L-serine is deaminated by proteins SdaA and SdaB under aerobic conditions, producing ammonia and pyruvate (57). However, the metabolic role of this process was unknown as most of the pyruvate is exported from the cell (58). Through multiple experiments, it was determined that serine deamination is a serine-dependent acid resistance system. Serine is imported into the cell through the SdaC transporter and deaminated by SdaA and SdaB to produce ammonia and pyruvate, which activates the BtsS-YpdB system (59). This system helps to maintain homeostasis within *E. coli* cells, especially related to carbon sources and surviving stressors (60).

When the genes that encode the proteins SdaA and SdaB were deleted, the mutant strains of *E. coli* had decreased relative cell survival rate comparable to the decreased cell survival noted in other acid resistance mutants, and the BtsS-YpdB system was not activated due to the lack of intracellular pyruvate (59). More research needs to be done on this pathway as an acid resistance system due to its recent discovery to better understand the pathways and mechanisms involved.

Figure 6

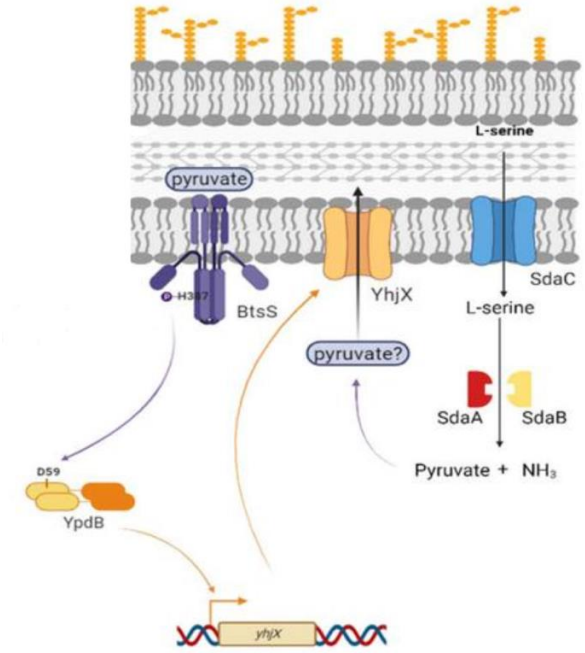

Figure 6: image depicting proposed serine-dependent acid resistance system as illustrated in Wiebe et al (59).

Conclusion

In this paper, six of the acid resistance systems in *Escherichia coli* have been highlighted and expanded upon to understand the inner workings and machinery. By

understanding how *E. coli* works to resist acid stress, microbiologists and others in related fields can take advantage of these systems to select for or against *E. coli* survival. There are many uses for this knowledge, but it is especially relevant due to the issue of antibiotic over-usage today which works to kill off bacteria in the body, including helpful and mutualistic bacteria that are harmful to eradicate within the patient. Understanding these systems can assist with furthering medical treatments for pathogenic *E. coli* infections, as well as medical treatments for other conditions while attempting to maintain a healthy microbiome including mutualistic or commensal *E. coli* strains. Stress responses, such as responses to acid stress, can contribute to antibiotic resistance. Notably, the bacterial efflux system and H^+-ATPase help bacteria to resist acid stress as well as increase resistance to antibiotics by pumping out harmful molecules and raising the intracellular pH (61). Targeting acid resistance system pathways would decrease the bacteria's ability to regulate intracellular pH when met with acidic conditions, such as lysosomal secretions from the human's immune system cells, making them more susceptible to the harmful effects of the acidic conditions (61). Additionally, targeting the pathways would decrease the bacteria's ability to pump out harmful molecules, allowing the molecules to do their job such as antibiotics working to kill off pathogenic bacteria. To properly target the right pathways and proteins, the pathways need to be well understood, necessitating further knowledge on acid resistance systems in bacteria to combat antibiotic resistance.

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