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Detection of acyl-homoserine lactones by *Escherichia* and *Salmonella*

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Abstract

Escherichia and *Salmonella* do not synthesize quorum sensing signaling molecules of the *N*-acyl-L-homoserine lactone (AHL) type but they can detect AHLs produced by other species of bacteria. AHLs are present in the bovine rumen but not in the remainder of the gastrointestinal tract. Enterohemorrhagic *E. coli* (EHEC) responds to AHLs extracted from the bovine rumen. *Salmonella* fails to detect AHLs in the gastrointestinal tracts of pathogen-free mice or pigs, suggesting that AHLs are not present. However, *Salmonella* does detect the AHL production of *Yersinia enterocolitica* in mouse Peyer's patches. In response to AHLs, EHEC represses flagellar genes and the LEE pathogenicity island while it activates the acid fitness island, whereas *Salmonella* activates the *rck* operon and a gene, *srgE*, encoding a putative Type III secreted effector.

Introduction

Bacteria can communicate with their own species and other species using small diffusible molecules. The presence of these molecules is thought to indicate the population density of a species and/or the diffusion characteristics of their environment. This process has been termed quorum sensing, efficiency sensing, or in a broader context, telesensing [1**,2]. Within small confined volumes, or spaces with low rates of diffusion, the accumulation of quorum sensing molecules indicates either a high Manuscript population density or alternatively, a low population density that has been producing quorum sensing molecules for a sufficient length of time [3]. The quorum sensing molecules, which are typically freely diffusible across bacterial membranes, are detected by transcription factors that control significant cell processes such as host interaction, bioluminescence, conjugation, competence, sporulation and biofilm formation [4,5]. In this review we will concentrate on recent advances in our understanding of one type of quorum sensing by *Escherichia coli* and *Salmonella enterica*, the detection of *N*-acyl-Lhomoserine lactones (AHLs).

LuxR and AHLs

The prototypical quorum sensing system is the production and detection of AHLs by *Vibrio fischeri* [4,5]. LuxI synthesizes the AHL signal molecules and LuxR is the transcription factor that detects the presence of AHL. The LuxR-AHL complex activates the transcription of the *luxICDABE* operon required for bioluminescence. The regulation of this operon is important to the symbiotic relationship between *Vibrio fischeri* and its host, the squid *Euprymna scolopes* [6,7].

Homologs of LuxR and LuxI have been found throughout the Gram-negative bacteria. A particular LuxI homolog predominantly synthesizes one or two AHL variants, although other variants are produced in lesser quantities. The AHL synthesized by a particular LuxR homolog can have an acyl chain length of between 4 and 18 carbon atoms (abbreviated here as C4, C6, etc.) (Figure 1). Additionally, the 3 position of the acyl chain can be either unmodified or modified with a carbonyl or hydroxyl group (abbreviated here by placing "oxo" or "OH" in front of the acyl chain length, eg., oxoC8). Although the acyl chain is most commonly present in the fully saturated form, varying degrees of saturation can also be found. The LuxI protein of *Vibrio fischeri* produces an AHL with a fully saturated acyl chain length of six and a carbonyl group at position 3 (*N*-(3-oxohexanoyl)-L-homoserine lactone, abbreviated here as oxoC6). The LuxR homolog typically has a binding preference for the AHL synthesized by its cognate LuxI enzyme. The variations in AHL structure produced and detected provide some degree of species specificity to the system.

The LuxR homolog of *Escherichia* and *Salmonella*, SdiA

Escherichia, *Salmonella* and related bacteria such as *Klebsiella*, *Enterobacter*, and *Citrobacter* encode a single LuxR homolog named SdiA, but lack a corresponding LuxI homolog and do not produce AHLs [8]. Thus, SdiA is considered an orphan or solo LuxR homolog [9]. The SdiA proteins of *Escherichia* and *Salmonella* detect AHLs produced by other species of bacteria [10,11,12**,13*,14,15*]. SdiA of *Salmonella* can detect an unusually wide range of AHL structures, but preferentially binds oxoC8 (Figure 1) [16,17]. SdiA can also detect AHLs that are not modified at position 3 and can detect chain lengths of 4 to 12 (C4, C6, C8, etc.). The detection sensitivity of SdiA for the various AHLs is in the range of 1 nM to 1 μM. Even the detection of non-ideal AHLs with micromolar sensitivities may be physiologically relevant since *Salmonella* can detect *Pseudomonas aeruginosa*, an organism that produces primarily C4 and oxoC12, when studied using a cross-streak assay on LB agar plates [17]. The cross-streak assay was also used to demonstrate that *Salmonella* can detect *Aeromonas hydrophila*, an organism that produces C4 [18] and *Yersinia enterocolitica*, which produces a mixture of C6 and oxoC6 [19].

The SdiA regulon of *Salmonella*

There are over 2600 serovars of *Salmonella enterica* and it is likely that the SdiA regulon is different among the serovars. The *sdiA* gene of *Salmonella enterica* serovar Typhimurium (*S*. Typhimurium) regulates two loci, the *rck* operon and the *srgE* gene (Figure 2). The *rck* operon is encoded on the 90 kb virulence plasmid of *S*. Typhimurium, pSLT, and contains six genes *pefI*, *srgD*, *srgA*, *srgB*, *rck*, and *srgC*. PefI, SrgD, and SrgC are homologous to transcription factors and PefI exhibits regulatory effects on the neighboring *pef* operon (plasmid encoded fimbriae) [20]. SrgA is a DsbA homolog that is involved with folding of the PefA fimbrial subunit and the SsaC (SpiA) protein of the SPI2-encoded Type III secretion system (TTSS2) [21,22]. Rck is an outer membrane β-barrel protein that confers resistance to complement killing, adhesion to fibronectin and laminin, and a zippering-type of host cell invasion [23–26,27*,28*]. The *srgE* gene appears to be a single gene horizontal acquisition in the chromosome [29]. A computer algorithm suggests that this gene is likely to encode a Type III secreted effector [30]. Interestingly, the *rck* operon is not expressed at temperatures below 37°C whereas *srgE* can be expressed at lower temperatures [29]. The temperature requirement of the *rck* operon and the apparent host interaction functions of the entire SdiA regulon suggest that SdiA is important in the host, rather than the external environment.

Salmonella SdiA activity in nature

Salmonella can detect the AHL production of numerous bacterial species during growth on agar plates, but the organisms detected in nature and the environmental settings and consequences of these detection events are largely unknown. The most obvious hypothesis, that *Salmonella* detects the gut environment by sensing the AHLs produced by the resident gut flora, turns out to be incorrect. A *Salmonella* strain that reports SdiA activity failed to respond in any region of the gastrointestinal tracts of a guinea pig, a rabbit, a cow, 5 mice, 6 pigs, or 12 chickens [12**,18]. However, this reporter strain did detect AHLs in mice colonized with the AHL-producing pathogen *Yersinia enterocolitica* [12**]. The signaling between *Salmonella* and *Yersinia* occurred primarily in the Peyer's patches. This interspecies signaling required both the *sdiA* gene of *Salmonella* and the *yenI* gene (a *luxI* homolog) of *Yersinia enterocolitica*. These data indicate that the normal flora of animals does not produce AHLs, and that *Salmonella* is detecting the AHL production of specific pathogens instead. The microbial communities of the gastrointestinal tract are some of the most diverse and highly concentrated communities known. The lack of AHL in this environment is surprising. However, maybe it is the lack of AHL signaling by the normal flora that allows AHL-mediated quorum sensing to be of use to pathogens like *Yersinia enterocolitica*. If the normal flora produced high concentrations of AHLs, then *Yersinia* would not be able to use AHLs to measure its population density.

Yersinia enterocolitica has LuxR and LuxI homologs named YenR and YenI. In vitro, *yenI* does not affect the quantity of Yop effectors secreted into the culture supernatant [19]. Instead, *yenI* is required for expression of the flagellin protein, FleB, and for swimming and swarming motility [19]. In BALB/c mice, which are susceptible to lethal *Yersinia* infection, a *yenI* mutant has no discernible fitness or virulence defect [12**]. In CBA/J mice, which are resistant to lethal *Yersinia* infection, the *yenI* mutant has a mild fitness defect. In competition with the wild-type, the *yenI* mutant is recovered from feces in 10-fold lower numbers than the wild-type for the first seven days of infection, but the two strains are recovered in equal numbers for the next 21 days [12**]. It should be noted that in both the BALB/c and CBA/J mouse experiments, the animals were also infected with *Salmonella*, which may have affected the *yenI* mutant phenotypes [12**]. No other virulence phenotypes have been published for the *yenI/yenR* quorum sensing system of *Yersinia enterocolitica*. It is possible that more significant virulence phenotypes for these genes will be observed with other animal models or when virulence is examined in more detail.

But why does *Salmonella* detect AHL signals from *Yersinia*? More importantly, is *Yersinia* an organism that *Salmonella* detects in nature? If so, in which animal(s) does this detection normally occur and for what purpose? The identification of the "natural" scenario for AHL detection by a solo LuxR homolog is not straightforward, especially when discussing an organism with a very broad host range like *S*. Typhimurium. For example, one hypothesis was that *Salmonella* uses *sdiA* to detect the AHL production of plant pathogens in produce [15*]. This hypothesis was based on the observation that *Salmonella* SdiA is able to detect the AHL production of *Pectobacterium carotovorum* in vitro. However, during coinfection of produce, *Salmonella* was unable to detect the AHL production of *Pectobacterium*. It was determined that the environmental conditions present in produce are not correct for *sdiA* expression [15*]. A second hypothesis is that the function of *Salmonella* SdiA is to detect the AHL production of *Aeromonas hydrophila* in turtles [18]. SdiA becomes activated when *Salmonella* transits through the gastrointestinal tract of turtles and the only AHL producing organism that could be cultured from these animals was *Aeromonas hydrophila* [18]. However, in competition assays between the wild-type and *sdiA* mutant strains, the *sdiA* mutant had no fitness phenotype in turtles suggesting that this may not be the environmental setting where *sdiA* is important. One caveat is that the *Salmonella* serovar used for the

experiments, Typhimurium, is not commonly associated with reptiles, leaving open the possibility that *sdiA*-dependent detection of *Aeromonas* may be relevant to other serovars.

This leads back to the question of whether the detection of AHL production by *Yersinia* is the "natural" function of *sdiA* in *Salmonella*. In competition experiments between wild-type and *sdiA* mutant *Salmonella*, both strains are recovered in equal numbers from the feces of CBA/J mice infected with *Yersinia* [12**]. As with the turtle experiments, this suggests that *Salmonella* does not benefit from the detection of *Yersinia* in mice. However, it was possible that only a few *Salmonella* cells were detecting *Yersinia* AHLs and the benefit conferred upon those cells could not be detected among the much larger population of *Salmonella* that had not detected AHLs. Therefore, the competition was repeated with *Salmonella* strains in which the *Yersinia yenI* gene was incorporated into the *Salmonella* chromosome (so that all members of the *Salmonella* population would detect AHLs). In this $yenI^+$ background, the $sdiA^+$ *Salmonella* quickly and dramatically outcompete an isogenic *sdiA* mutant in CBA/J mice [12**]. Both the *srgE* gene and the *rck* operon are required for this phenotype. This indicates that the SdiA regulon is indeed functional and advantageous when expressed in the mouse. This experiment has not been performed with turtles.

Although possible, it seems unlikely that the "natural" function of *S*. Typhimurium SdiA is the detection of *Aeromonas* in turtles or *Yersinia* in mice. However, a natural reservoir for both *S*. Typhimurium and *Yersinia enterocolitica* is swine. Roughly 15% to 25% of animals are infected with either organism on U.S. swine farms. Therefore, *Salmonella* and *Yersinia* should encounter each other on a regular basis in these animals. Preliminary results indicate that *Salmonella* can detect *Yersinia* in pigs (Ahmer, unpublished). Further work is needed to determine the prevalence and consequence of this interaction in nature.

The role of SdiA in *E. coli* and other bacteria

The role of *sdiA* in other *Salmonella* serovars is unknown, although it is known to be present in all 101 serovars that have been examined to date [31]. The role of *sdiA* in other genera like *Citrobacter, Enterobacter*, and *Klebsiella* is also unknown, although we have identified AHL-responsive fusions in *Enterobacter cloacae* and *Klebsiella pneumoniae* (Ahmer, unpublished). In *E. coli*, the SdiA regulon is entirely different than the regulon in *S*. Typhimurium. SdiA activates the *gad* genes of the acid fitness island of *E. coli* K-12 and EHEC [10,13*,14]. SdiA also represses flagellar genes and the genes of the LEE pathogenicity island (LEE) of EHEC [14,32]. A model has been proposed in which EHEC SdiA detects AHLs in the bovine rumen where acid resistance is increased and LEE expression is repressed [14]. AHL is no longer encountered beyond the rumen allowing the LEE to be expressed so that the recto-anal junction can be colonized [14]. The organisms that produce AHLs in the rumen have not been identified. It was also determined that AHL can induce lambda prophage induction in an *sdiA*-dependent manner and that environmental prophages respond to AHL as well [33**].

The bovine paradox

There is an apparent contradiction in the observations that AHL can be chemically extracted from the bovine rumen but a *Salmonella* reporter of SdiA activity failed to respond in this environment [14,18,34,35*]. The *Salmonella* reporter was recovered from only a single calf so it is possible that this particular animal was of the wrong age or on the wrong diet to have AHLs in its rumen. It also appears that the time of year plays a major role in whether or not AHLs are found in the rumen [35*]. Another possibility is that the *sdiA* gene of *Salmonella* is not expressed in this particular environment. This was found to be the case when the same *Salmonella* reporter system failed to detect the AHL production of *Pectobacterium carotovorum* in a tomato soft rot [15*]. The *sdiA* gene was not expressed so SdiA was not

available to detect AHL. Further research is required on the parameters affecting AHL concentration in the bovine rumen, the role of AHL in the rumen community, and on the regulation of the *E. coli* and *Salmonella sdiA* genes.

The gene downstream of *sdiA* may also respond to other bacteria

Interestingly, in all of the bacterial genera that contain *sdiA*, a gene named *sirA* (*Salmonella* invasion regulator) is located downstream [36,37]. In fact, *sirA* is distributed more broadly than *sdiA*, being present throughout the gamma-proteobacteria. In other genera, the *sirA* ortholog is known as *gacA*, *uvrY*, *varA*, *letA*, etc. SirA is the response regulator of a two component regulatory system that responds to short chain fatty acids (SCFA) [38,39**, 40**]. Since *Salmonella* produces SCFA, SirA is active in pure culture. However, in the host, *Salmonella* and other *sirA*-encoding organisms may use SirA to detect the SCFA production of the normal flora [38]. Thus, both SdiA and SirA may respond to signals from other bacterial species.

Conclusions

SdiA of *Escherichia* and *Salmonella* functions to detect the AHLs produced by other bacteria. The scenarios in which this occurs in nature, however, are still largely unknown and many questions remain. It is clear that the gastrointestinal tracts of most animals, excluding the bovine rumen, do not contain AHL. It appears that EHEC uses *sdiA* in the bovine rumen to repress the LEE pathogenicity island and to increase acid resistance. What organism(s) are producing the AHLs and what role do the AHLs play in the rumen community? Is detection of bacteria in the rumen the only scenario in which *sdiA* provides a benefit to EHEC? What are the scenarios in which *sdiA* provides a benefit to the other serogroups of *E. coli*? What are the scenarios for *Citrobacter*, *Klebsiella*, and *Enterobacter*? Is the role of *sdiA* in *Salmonella* truly to detect the AHLs of other gastrointestinal pathogens like *Yersinia enterocolitica*? If this is true, in which eukaryotic hosts do these bacterial interactions occur? How is pathogenesis altered when *Salmonella* detects *Yersinia* or other pathogens? What are the scenarios in which *sdiA* provides a benefit to the other 2600 serovars of *Salmonella*, many of which have different host ranges and disease manifestations? Are all of these scenarios similar or has each bacterial species or serovar adapted SdiA to a very specific situation? So far, the EHEC and *S. enterica* serovar Typhimurium scenarios look quite different. How is the *sdiA* gene regulated so that SdiA protein is not available for AHL detection in inappropriate environments like the tomato soft rot? Clearly, the study of AHL detection by *Escherichia* and *Salmonella* has only just begun.

Acknowledgments

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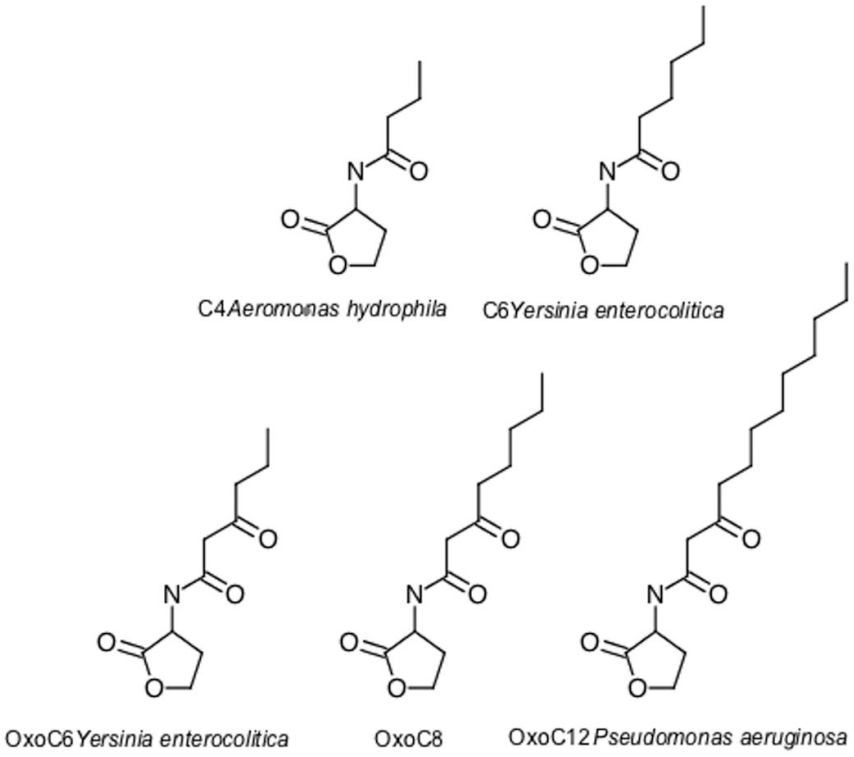

Figure 1.
Structures of some AHLs that can be detected by SdiA. The organisms listed next to the structures have been shown to produce those particular AHLs. Those organisms can also be detected by *Salmonella sdiA*-dependent biosensor strains in a cross-streak assay.

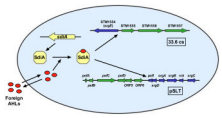

Figure 2.
The SdiA system of *Salmonella enterica* serovar Typhimurium. AHLs produced by other bacterial species diffuse across the membrane and are bound by SdiA. SdiA then increases the expression of the genes colored blue. These genes include *pefI, srgD, srgA, srgB, rck* and *srgC* found on the virulence plasmid, pSLT. STM1554 (*srgE*) is a chromosomal gene regulated by *sdiA* that appears to be a single gene horizontal acquisition that may encode a Type III secreted effector.

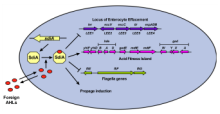

Figure 3.
The SdiA system of EHEC. AHLs produced by other bacterial species diffuse across the membrane and are bound by SdiA. SdiA then increases the expression of the acid fitness island and induces prophage induction. SdiA also represses flagellar genes and the LEE pathogenicity island.