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Kin recognition in bacteria

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Abstract

The ability of bacteria to recognize kin provides a means to form social groups. In turn these groups can lead to cooperative behaviors that surpass the ability of the individual. Kin recognition involves specific biochemical interactions between a receptor(s) and an identification molecule(s). To ensure that nonkin are excluded and kin are included, recognition specificity is critical and depends on the number of loci and polymorphisms involved. After recognition and biochemical perception, the common ensuing cooperative behaviors include biofilm formation, quorum responses, development and swarming motility. Although kin recognition is a fundamental mechanism through which cells might interact, microbiologists are only beginning to explore the topic. This review considers both molecular and theoretical aspects of bacterial kin recognition. Consideration is also given to bacterial diversity, genetic relatedness, kin selection theory, and mechanisms of recognition.

Keywords

kin recognition; kin selection; relatedness; greenbeard; bacteriocin

INTRODUCTION

All cells interact with other cells. These interactions begin with the birth of a cell, but after septation the extent of interactions varies widely. Some cells stay in continuous contact with neighbors, whereas others rarely interact. The ability of a cell or a multicellular individual to recognize its surrounding neighbors provides important clues about opportunities for exploitation, cooperation, or competition. One type of recognition is identification of others as like oneself. Recognition of kin allows the formation of groups of genetically related individuals in which combined functions exceed the capabilities of an individual. In turn, these advantages can increase the reproductive fitness of the individuals. The study of kin recognition originated with animal research (33, 50). Some animal species, using their five senses, memory, and brain cognition, along with local enviornmental clues, can identify others that are related to themselves. However, because of the complexity of kin recognition in animals, our understanding of it at the molecular level is lacking. In contrast, microbes

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offer an experimentally accessible path to identify the genetic determinants and molecular interactions responsible for kin recognition. In this review, I discuss the nascent field of kin recognition in bacteria from molecular and evolutionary perspectives.

Bacterial kin recognition involves three steps (Figure 1). First, individuals recognize one another by receptor-ligand or receptor-receptor binding. Second, recognition leads to a signal or biochemical perception. Third, there is a behavioral response. Because brain cognition is typically involved in animal kin recognition, studies in these species are largely limited to observation of behavioral changes. That is, kin recognition is indirectly observed as the differential treatment of full siblings as compared to nonkin. In part because of these difficulties, studying kin recognition in animals can be problematic (44, 99). In contrast, bacterial kin recognition involves a molecular event(s) that can be directly observed—e.g., kin cells that adhere together. The end result of these interactions is a cooperative behavior that increases the fitness for the participating individuals.

TYPES OF RECOGNITION

In this review, I categorize kin recognition as either general or specific. General recognition involves low levels of specificity. For example, recognition may simply involve the presence or absence of a single receptor type. Thus recognition occurs when both cells contain the receptor, and discrimination occurs when one cell lacks the receptor. In contrast, specific recognition involves multiple recognition types. For instance, with polymorphic receptors that have different binding affinities, kin recognition depends not only on the presence of the receptor but also on its type (allele). As the diversity of receptor polymorphisms increases, the specificity of recognition correspondingly increases. Specific kin recognition can also occur when multiple loci are involved in recognition. Because bacterial kin recognition depends on interactions between molecules, e.g., proteins, the limits on specificity depend on chemical diversity. In contrast, recognition based on brain cognition potentially offers greater precision. For instance, a human might be able to identify a kin among a thousand or even a million different individuals. Although bacteria cannot discriminate between individuals (e.g., clonemates), such resolution is not necessarily relevant when cells are genetically identical. Instead, what might be critical is the ability of bacteria to differentiate between clonemates and conspecific strains (genetically distinct environmental isolates that belong to the same species) and other species. Examples of general and specific recognition, as well as greenbeard recognition, an evolutionary concept, are described below.

DIVERSITY IN NATURAL HABITATS

Describing his observations about microbiology, Baas Becking formulated the hypothesis that “everything is everywhere, but the environment selects” (25). Although not absolute, this statement captures salient features about microbial ecology. For instance, in similarly located tree canopies, the bacterial communities differ widely depending on the tree species (environment) (60). Additionally, microbes are easily dispersed by the movements of wind, water and animals. In a recent study, atmospheric clouds were shown to be a microbial mixing pot of diverse species at high concentrations (10^5 bacteria per milliliter) (58). Not surprisingly, hurricane winds further aerosolize particles, leading to even greater diversity

and densities of microbes (26). These initial mixtures, once deposited by the winds, are then refined by environmental selection.

Bacteria often live in crowded and diverse habitats in which they interact with neighbors (1). In soils, densities reach 10^9 bacteria per gram (36), whereas in the human gut they can reach 10^{12} organisms per gram (53). Bacterial diversity also tends to be high in these environments. For example, the human gut contains ~10^3 species (and ~10^4 strains) (8, 53), and a gram of soil might contain 10^4 to 10^6 species (36, 75). Two groups also examined conspecific differences and found another ~50-fold increase in diversity at the species level (87, 88, 96, 97). These studies, involving *Myxococcus xanthus* and *Bacillus subtilis*, found not only genetic differences among isolates but also the formation of different social groups. These findings suggest that bacteria use recognition tools to form communities with increased fitness.

EVOLUTIONARY THEORY

Evolutionary biologists have played an important role in bringing the topic of microbial kin recognition to the forefront (34, 89, 95, 104). Attracted to simpler and faster models, some evolutionary biologists transitioned from more complex systems, e.g., insects and mammals, to microbes. Microbes not only allow evolutionary experiments to be conducted in the lab but also facilitate the understanding of behaviors and kin recognition at the molecular level. The influx of evolutionary biologists has also introduced a different language and set of questions to the field of microbiology.

Kin Selection and Cooperation

The underlying theme of kin recognition is that it provides a platform for individuals to identify others that are closely related and then form a cooperative group. At face value, the notion that individuals cooperate appears to be at odds with natural selection: Individuals compete for survival. However, the finding that cooperation is common in all kingdoms has inspired research on social evolutionary theory for the last 50 years. Central to this field is William Hamilton's seminal work that provided a conceptual framework for social and cooperative behaviors (47, 48). Central to his work is Hamilton's rule, which states, in accordance with Darwinian principles, that cooperative behaviors can occur when $r > c/b$, where r is the coefficient of relatedness between individuals, c is the fitness cost to the actor, and b is the fitness benefit to the recipient (72a, 104). Thus a cooperative act by an individual can be explained when r and b values are high relative to c. In a bacterial clonal population, clonemates have identical genomes, and thus $r = 1$. From a kin selection viewpoint, there is a reason ($r = 1$) for clonemates to cooperate. They are facilitating the propagation of the same genes. As the value of r decreases, the benefit to the recipient needs to correspondingly outweigh the cost of the deed to the actor for the cooperative behavior to evolve within a kin selection framework.

Although Hamilton's rule provides important insights into how cooperation evolves, the utility of Hamilton's rule has limits from an experimental perspective. For instance, evolutionary theory has not provided a framework for how to measure r in bacteria that are not clonemates. With diploid organisms, r is frequently measured as the probability of two

individuals sharing a gene relative to the whole population (39, 67). For instance, the *r* coefficient for two brothers is defined as 0.5, whereas two individuals randomly selected from a population would have an *r* coefficient of 0. Although the literature typically describes *r* in the context of genes, with diploids its description really pertains to alleles; for example, two brothers would share an identical gene set, but half of their alleles will differ. In bacteria there are not only allelic differences but also a wide variation in gene content between conspecific individuals (discussed below).

A particularly relevant idea for bacterial kin recognition that has emerged from the field of social evolution is the concept of a greenbeard gene. The idea originated with Hamilton (48) and was significantly embellished by Dawkins (23, 24) and others (39, 72a, 103). A greenbeard gene or locus has three features: (*a*) a recognizable trait, (*b*) the ability to recognize others that bear the same trait (gene/allele), and (*c*) the ability to confer a cooperative or helpful behavior on those individuals that bear the same trait. Although the greenbeard was originally conceived as a hypothetical gene, Haig (45, 46) made the idea concrete by suggesting that homotypic cell surface receptors could perform all of these functions. As described below, several recent reports describe greenbeard functions in bacteria, and this type of recognition may constitute a major form of kin recognition in these organisms. Because greenbeard involves a single locus, there is also the potential for nonkin to be recognized. For instance, if a single greenbeard locus was horizontally transferred to an unrelated bacterium, that recipient would now recognize the donor or siblings thereof. In this scenario, recognition is instead called greenbeard or kind recognition (89), because the individuals are related only at the greenbeard locus; the rest of their genomes are not related. Although nonkin greenbeard recognition is theoretically plausible, the extent to which it occurs in nature is unknown. As described above, greenbeard recognition can be either specific or general, depending on whether the locus is polymorphic.

Darwinian Selection

It is important to note that, from a theoretical perspective, kin recognition and kin selection not necessarily have to be invoked to explain cooperative behaviors; there are other theoretical explanations for how cooperation might evolve (67). In Darwinian theory the underlying principle is that individuals compete for limited resources and that the most fit prevail. This leads to the conclusion that individuals will tend not to assist their neighbors but instead will antagonize them. Bacteria are no exception—they compete. Perhaps the clearest example of this is the propensity of bacteria to antagonize or kill their neighbors. This behavior is frequently directed toward conspecific relatives (16, 55, 74). Because related strains share genes, traits, and niches, they are strong competitors for shared resources. This leads to a conundrum: Does a bacterium antagonize a close relative or cooperate with it? Before we consider this, it would first be useful to discuss bacterial relatedness.

BACTERIAL RELATEDNESS

The concept of species, and hence relatedness, in bacteria is different from relatedness in plants and animals, which is typically described in terms of sexual reproduction. Bacteria

undergo asexual reproduction; they divide by binary fission. This results in genetically identical offspring. However, microbial communities are far from monocultures; populations rapidly diverge by mutation and horizontal gene transfer, as well as environmental conditions that continuously mix populations (64). For this reason, understanding bacterial relatedness is important in the context of kin recognition.

Individual bacterial strains are similar if they belong to the same species. Classically, bacterial species are defined as a group of wild strains that share phenotypes (77). This definition has been augmented by 16S rRNA classification, which defines bacterial strains as belonging to the same species when their 16S rRNA sequences are ≥98.7% identical. Strains whose 16S rRNA identity is <98.7% are generally viewed as distinct species. However, the highly conserved nature of 16S rRNA genes results in poor resolution between strains and species. An alternative criterion for relatedness classification is DNA-DNA hybridization (DDH) (77). A DDH value of 70% is a widely accepted standard to delineate species. Today, with the availability of genome sequences, DDH is being replaced with average nucleotide identity (ANI), which is a measure of homology between shared sequences. For species cutoff values, 70% DDH correlates to 95% ANI (43). However, two strains can share a high ANI value, e.g., 96%, yet their shared genome content might be only 70% (43).

Ussery and colleagues carried out a global analysis of a species by comparing over 60 *E. coli* genomes (63). Genome size ranged from 4.57 to 5.93 Mbp, a nearly 30% difference between the smallest and largest genomes. The pangenome consisted of 15,741 gene families, and only 993 gene families were represented in every (core) genome (Figure 2). Since *E. coli* strains contain about 5,000 genes, each strain contains only a third of its species's pangenome. From this analysis, one can conclude that a group of conspecific strains that share a similar gene content, a measure of relatedness, should be defined as a genovar (72). A genovar is a more precise indication of relatedness than serovar (which describes antigen relatedness) and in this review suggests $r > 0$.

DISCRIMINATION AGAINST RELATED INDIVIDUALS

Although I have described what may be viewed as two very different paths—bacterial killing of related individuals and kin recognition—the ability to discriminate against (antagonize) others can lead to outcomes that are similar to those of kin recognition (Figure 3). That is, the removal of competing bacteria from a habitat creates a population that is more closely related. In this regard, bacteria are well known for their ability to produce a diverse array of toxins that kill or inhibit other bacteria (16, 74, 81). Bacteriocins are one common class of toxins that have a narrow range of activity that is directed toward related strains. For example, colicins, a well-known class of bacteriocins made by *E. coli*, target *E. coli* strains (16). Bacteriocins are released into the environment by either transport systems or cell lysis (16, 74). Once released, bacteriocins bind to specific cell surface receptors on target cells and then kill by a variety of mechanisms. Producer cells and clonemates are resistant to their own bacteriocin(s) because they make a cognate immunity protein(s). Because bacteriocin systems are relatively simple and provide an effective means for dominating an environmental niche, nearly all bacteria produce bacteriocins (57, 74, 107). For toxins to be effective, they need to be unique to help ensure that other cells in the population are not

resistant. Because of this selective pressure, there is a diverse array of polymorphic toxins (55, 107). Toxin modules that are homologs to bacteriocins are also found associated with bacterial delivery systems. Such systems include type VI secretion (T6S), contact-dependent inhibition (CDI; discussed below), and others (49, 55, 81). As discussed below, polymorphic toxins have likely contributed to diversification of kin recognition systems (87a).

Discrimination Against Clonemates

Considering the increased competition among genetically similar bacteria, as noted above, it is perhaps not surprising that discrimination is not restricted to distant species and relatives but also includes self. A number of examples have emerged in which bacteria kill their clonemates. *Paenibacillus dendritiformis* produces a bacteriocin called sibling lethal factor that functions in territoriality behavior, where approaching bacterial swarms repel each other or form demarcation lines between colony swarms (9, 10). *Bacillus subtilis* and *Streptococcus pneumoniae* similarly produce bacteriocins that kill clonemates in response to starvation and stress, respectively (17, 18, 32, 42). Although clonemate competition is not readily explained by kin selection theory, it may be more prevalent in bacterial populations than originally thought, but this has not yet been confirmed.

Precision of recognition can be increased when recognition and discrimination functions are combined (Figure 4). Examples of such recognize and verify systems are given below.

BACTERIAL KIN RECOGNITION

Myxobacteria and Outer Membrane Exchange

The roots of bacterial sociobiology research can be traced back to myxobacteria (30). These terrestrial microbes exhibit complex social behaviors that culminate in the production of multicellular fruiting bodies. Because these bacteria form multicellular aggregates from cells in their environment, they use forms of kin recognition to identify partnering siblings (100). In support of this, fruiting bodies derived from natural sources tend to consist of clonemates and closely related strains (59, 86). Although the mechanism for clonemate selection is poorly understood, early studies showed that myxobacteria isolates antagonize one another from joining a fruit, apparently through bacteriocin activity (86). Other mechanisms may also contribute to clonemate selection.

One of the best understood kin recognition systems in bacteria is called outer membrane exchange (OME). OME is a process by which myxobacteria transiently fuse their outer membranes and exchange their outer membrane proteins and lipids (Figure 5*a*) (13). OME is initiated when two cells make contact on a solid surface (101). The ensuing exchange is robust, as partnering cells share private goods in essentially equal amounts (68). Because a substantial amount of outer membrane material is exchanged, OME can repair damaged cells (93). For instance, if one cell lacks an outer membrane protein essential for motility, it can be functionally rescued for that defect by a partnering cell that contains the corresponding protein (Figure 5*a*,*c*). Similarly, if one cell contains defective lipopolysaccharide (LPS), another cell with wild-type LPS can repair the defective cell by OME (92). Based on these and other findings, we hypothesize that one role of OME is to

help create a population that is more homogenous by sharing outer membrane components. In turn the whole population benefits because it is more fit to conduct multicellular functions (93).

OME requires two cell surface proteins, called TraA and TraB, that must be present on both partnering cells (69). TraA/B forms the machinery to catalyze the fusion of the outer membranes, although the mechanistic details are not well understood. Importantly, the TraA cell surface receptor is the recognition determinant (70). For recognition to occur, the partnering cells must have identical or very similar receptors, providing for a homotypic interaction. Among environmental isolates, *traA* is polymorphic (Figure 5*b*). In studies from a limited set of *M. xanthus* isolates, six distinct TraA recognition groups were identified (Figure 5*b*) (70). Based on an expanded study consisting of a bioinformatic and functional analysis of 100 *traA* alleles from a diverse pool of myxobacteria, we propose that this collection represents ~50 distinct TraA recognition groups (P. Cao, R. Awal, R. Muller, D. Wall, unpublished manuscript). By extending this dataset, we hypothesize that in nature there are hundreds of different TraA recognition groups and that these polymorphisms determine recognition specificity. Thus by simply swapping *traA* alleles recognition can be reprogrammed in *M. xanthus* cells (Figure 5*C*) (70). Recently, we reengineered TraA specificity by site-directed mutagenesis (P. Cao & D. Wall, unpublished manuscript). In some cases single–amino acid substitutions changed recognition specificity, whereas in other cases alleles were created with unique specificities. Thus TraA is a kin recognition determinate in which simple polymorphisms can lead to completely altered specificities.

The polymorphic nature of TraA recognition raises Crozier's paradox (21, 38, 52), which states that genetic variation should erode because larger cooperative groups are more fit than small groups. So for TraA, how can diversity be maintained if the sharing of private goods by OME leads to beneficial outcomes? That is, members of a large population will share more frequently and will incur more benefit than those in small groups. In turn, *traA* alleles that represent small groups should be driven to extinction (52). We think the answer to this question lies in the nature of the goods that are exchanged. Recently, we discovered that, along with beneficial goods, harmful toxins (bacteriocins) are also exchanged (28). Thus indiscriminate pairing of individuals leads to lethal outcomes. Stated another way, OME represents a dual model involving the recognition and verification of partner identity (Figure 4). In this scheme, to guard against lethal OME events, TraA polymorphisms are selected for and maintained to provide recognition specificity that helps ensure that OME only occurs between clonemates.

The properties of TraA match the definition of a greenbeard locus (23, 24). Consistent with this, we found that a *traA* allele from an *M. fulvus* isolate was phylogenetically related and functionally compatible with some *M. xanthus traA* alleles (Figure 5*b*) (70). At face value, TraA recognition can thus occur between distinct species, a characteristic of greenbeard (kind) recognition (89). However, there are caveats to this conclusion. First, *M. fulvus* and *M. xanthus* are closely related, and it is unclear whether these isolates actually represent distinct species. Second, although TraA recognition and OME occur, the cells involved do not necessarily remain viable (28, 70), because OME involves a verification step with a toxin at a different locus. In conclusion, TraA has greenbeard qualities; however, a

successful OME outcome also depends on genetic relatedness at other loci in the genome, a requirement for kin recognition.

Adhesins and Contact-Dependent Inhibition

The specific adhesion of sibling cells represents a direct form of bacterial kin recognition. Some adhesins recognize the same adhesin on adjacent cells, and thus kin recognition occurs through homotypic receptors. Examples of homotypic receptors include members of the autotransporter family, a subclass of the type V secretion system, in which a single polypeptide facilitates its own transport across the outer membrane (22). TibA and Ag43 are members of the autotransporter family and share homology in their adhesin domains, which contain repeat sequences (51, 85). Crystal structures have shown that self-associated Ag43 proteins bind by a Velcro-like handshake (51). Expression of these adhesins in *E. coli* results in self-recognition manifested as autoaggregation or cell clumping. Ag43 expression also results in self-associated chains of cells, suggesting that adhesins are concentrated at cell poles (94). The ability of TibA/Ag43 to recognize clonemates allows those bacteria to form social groups in the form of biofilms or aggregates that can protect cells from environmental insults.

Some adhesins are multifunctional. A case in point is CDI, a system that is widely distributed in alpha-, beta- and gammaproteobacteria (5). The CDI system is also a member of the type V secretion family and belongs to the two-partner secretion subclass. The CDI system uses large and extended adhesins (CdiA) on the cell surface. Related cells are recognized when they attach to cell surface receptors. The C terminus of CdiA proteins is highly polymorphic and contains different types of toxin modules (5). Thus upon binding to related cells, toxins are delivered to the recipient. If the recipient does not contain the cognate CdiI immunity protein, because it is not a clonemate, then its growth is blocked. CDI is thus another example of a recognize-and-verify system that increases kin selectivity (Figure 4).

Importantly, the function of CDI is not simply to antagonize related strains. CDI also functions to assemble multicellular biofilm communities (3, 37). CdiA recognition occurs by binding to heterologous cell surface receptors as well as through homotypic interactions (79). Such CdiA-CdiA interactions illustrate a greenbeard recognition mechanism. By recognizing and verifying other cells, the CDI system helps to ensure that biofilms consist of clonemates.

Other interesting aspects of the CDI system involve its distribution and receptor recognition. A genomic analysis determined that *cdi* loci are found in 90 of the 576 sequenced *E. coli* genomes (78). These polymorphic loci are thus part of the accessory genome and are typically associated with genomic islands. The best-characterized CDI system is from *E. coli* EC93, in which CdiA was shown to bind BamA as the cell surface receptor (6). BamA is an essential β-barrel protein involved in outer membrane protein folding (6). Although BamA homologs are universally found in gram-negative bacteria, the specificity of CdiA to binding to BamA is in extracellular loops 6 and 7, whose sequence conservation are species restricted to *E. coli* (80). Surprisingly, these surface-exposed loops are identical in hundreds of *E. coli* isolates. This finding is unexpected, as cell surface sequences are under selective

pressure to diversify and these loop sequences are not essential for BamA function (71, 80). Although it is unknown why loops 6 and 7 are invariant in *E. coli* but are polymorphic in other species (80), their utilization allows CdiA-EC93 to selectively recognize fellow *E. coli* strains for CDI functions.

Proteus Territoriality

Proteus mirabilis exhibits a behavior known as territoriality (7, 11, 40). The behavior is seen on swarm agar plates on which different motile isolates frequently form demarcations called Dienes lines when the swarm colonies meet. In contrast, two sibling colonies will merge their swarms in the absence of Dienes lines. The Dienes lines are thus thought, in part, to reflect a molecular identification system(s) for self/nonself recognition to ensure that territories are inhabited by fellow clonemates. Interestingly, the selectivity of *Proteus* discrimination is high, because in one study Dienes typing of 204 isolates resulted in 98 distinct compatibility groups (83). Discrimination, in part, is correlated with the production of bacteriocins (40, 84). Thus isolates that are sensitive to a particular bacteriocin are killed, and this outcome seems to contribute toward Dienes line formation. However, not all Dienes lines are attributed to bacteriocins. In these cases, boundary formation seems to depend on cell-cell recognition. To identify genetic determinants involved in recognition, Gibbs and coworkers (41, 102) conducted forward screens. They found three gene clusters that govern self-recognition in *P. mirabilis*. One gene cluster encodes homologs of the T6S system (*tss*). The T6S system is a transport apparatus that delivers effector proteins to other cells (81). Frequently the effectors are toxins and can be homologous to bacteriocins. A second gene cluster is called *idr* and encodes putative cytotoxins delivered by *tss*. Both *idr* and *tss* are involved in growth inhibition, and similar results were independently reported (2). The role of the third gene cluster, *ids*, is less clear. The *ids* gene cluster contains two genes that are polymorphic, suggesting a role in recognition (41). The *ids* genes are not required for competition with foreign strains but are required for nonlethal interactions with the parental strain (102). Biochemically, the polymorphic proteins IdsD and IdsE interact in an allele-specific manner through their transmembrane domains (15). Additional studies are needed to elucidate the molecular mechanism by which IdsD-IdsE binding leads to behavioral changes manifested as territoriality. Although T6S systems are typically associated with aggressive behaviors, they may also be involved in nonantagonistic interactions (81), and perhaps Ids is one example of this exception.

As microbiologists turn more attention toward how bacteria interact, we have an increasing number of examples of territorial behaviors, as judged by demarcation lines, between conspecific isolates (65, 87, 87a, 97). As seen with *P. mirabilis*, the resolution of discrimination is high even among isolates that originate from the same location and that are highly related (87, 97). These findings suggest that kin recognition and discrimination systems are widespread in the bacterial kingdom. Moreover, these findings suggest that the diversification of social groups within ecotypes may contribute to the stability of the overall population (Figure 6).

Recognition from Afar—Diffusible Signals

Kin recognition does not require direct cell-cell contact; recognition can be perceived through diffusible signals. Recognition by diffusible signals provides the advantage that it allows individuals to decipher the composition of kin in a local population. A limitation is that the identity of adjacent cells is not necessarily known. Quorum sensing is an example of how many bacterial species recognize their kin and their population densities in local environments. In turn, quorum signaling, which is mediated by diffusible autoinducers, is used to regulate diverse cooperative behaviors, including bioluminescence, competence, virulence, biofilm formation, and motility, among others (35, 82). Quorum-sensing studies in gram-negative bacteria have found that acylated homoserine lactones (acyl-HSLs) represent a major class of signaling molecule, whereas gram-positive bacteria typically carry out this function with oligopeptides (66, 82). The specificity of recognition is derived from receptors that selectively bind their cognate signaling molecules. In the case of acyl-HSLs, their chemical structures vary depending on substitutions, saturation, and overall length of the acyl chains (35, 90). Quorum sensing in gram-negative bacteria can result in general kin recognition at the species level or can be more specific. For example, some *Vibrio cholera* and *Pseudomonas aeruginosa* strains make two and three types of signaling molecules, respectively, which adds complexity and specificity to the recognition process and to the regulatory control of gene expression (82, 98).

Gram-positive bacteria do contain polymorphic quorum-sensing molecules and cognate receptors (66, 91, 105). For instance, *Staphylococcus aureus* uses quorum sensing to control the expression of the *agr* virulence regulon. In *S. aureus* there are four known kin recognition groups that are determined by allelic variation in the peptide signal derived from AgrD and the cognate coevolved receptor, AgrC (66). The interaction between the signal and AgrC is highly specific, as a single amino acid substitution can change specificity. Interestingly, an AgrD variant that does not function as a cognate signal with a particular AgrC variant will block the expression of the *agr* regulon in that strain (56, 66). This antagonism prevents an established infection from being invaded by another *S. aureus* strain. In evolutionary terms, social antagonism may contribute to the diversification and hence selectivity found in kin recognition systems (31). Similar polymorphic recognition systems are found in *B. subtilis* and *S. pneumoniae* quorum control of natural competence and in *Enterococcus* spp for pheromone-controlled conjugation (4, 19, 29, 54, 88).

In other paradigms, the ligand and receptor that mediate kin recognition may have additional functions. One example is *Rhizobium* spp. that associate with plants where the roots form protected nodules, excluding other microorganisms. Here *Rhizobium* cells differentiate into bacteroids that fix nitrogen for the plant. In this mutualistic interaction, the plant in turn provides bacteroids with nutrients that the bacterium uses to synthesize rhizopines, which are metabolites that are unique to *Rhizobium* spp. (27, 76, 106). *Rhizobium* spp. located outside of nodules and that are not differentiated can selectively take up and use rhizopines as a carbon/energy source. In essence this is a form of greenbeard recognition in which rhizopines represent the specificity ligand that binds catabolite enzymes (receptor) and results in their utilization (benefit) (106).

In an interesting twist on kin recognition, Mougous and colleagues propose that *P. aeruginosa* recognizes danger in its environment by the lysis of kin cells (61, 62). In this scheme, sensor kinases/response regulators (RetS/GacS/A) detect a diffusible signal that originates from the lysis of siblings. In turn, this activates a response to the danger by the induction of a regulon that includes the T6S system, a weapon used to attack hostile bacteria (a likely source of the danger). This response is one of many examples whereby different bacterial groups induce bacteriocin/toxin production in response to competition or stress as an apparent counterattack measure (20).

PERSPECTIVE

Kin recognition in bacteria is a frontier in science. Currently there are few labs that are making a concerted effort to study this topic. However, there is a growing appreciation that bacteria recognize their neighbors and this leads to important social functions, such as multicellular development, biofilm formation, and quorum sensing (57, 82, 100). Given the vast and unknown diversity of bacteria, there are likely many examples where kin recognition is involved in unforeseen microbial processes, whether in the human body or the environment.

An advantage of studying kin recognition and kin selection in bacteria is the ability to understand each step at the molecular level (Figure 1). Experimental methods in bacteria allow hypotheses to be tested and bacterial systems to be reengineered. In addition, with the advent of next-generation sequencing and other sensitive molecular techniques, particular ecological, evolutionary, and mechanistic questions can be explored in natural populations.

FUTURE ISSUES

1. **Experimental**
2. How are bacterial populations spacially organized and how do they interact in natural habitats?
3. With the large diversity of bacterial species, what other types of cooperative behaviors and kin recognition systems have evolved? Do some recognition systems rely on multiple loci, instead of a single polymorphic receptor, to confer specificity of recognition?
4. When kin recogntion governs cooperative behavoirs how is selectivity of recognition maintained when Cozier’s paradox says it should erode?
5. Can cooperative behaviors and fitness gains be precisely defined and quantified?
6. **Definitions**
7. Can evolutionary theory provide a matrix or a protocol to measure relatedness in bacteria beyond clonemates?
8. What constitutes a kin group within a bacterial species?

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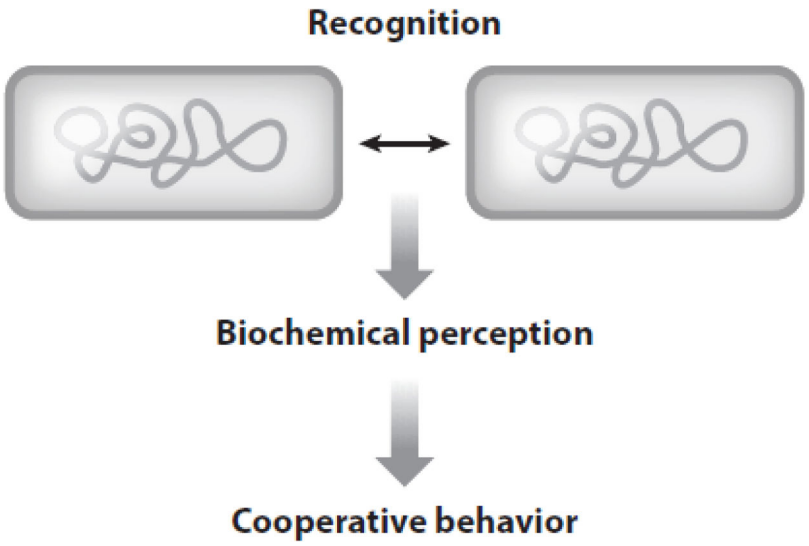

Figure 1.
Bacterial kin recognition involves three steps.

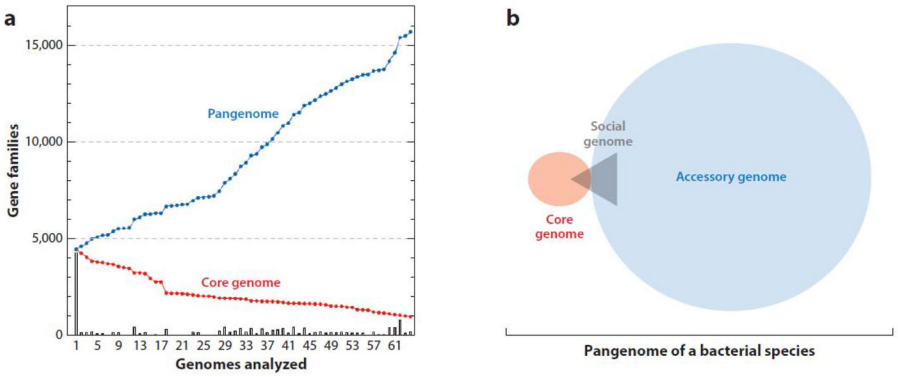

Figure 2.

Core genomes and pan genomes among conspecific strains. (*a*) Plot of 61 completed *Escherichia coli* genomes showing a cumulative count of common (core; *red*) and total (pan; *blue*) gene families as a function of the number of analyzed genomes. The bars represent the number of unique (new) gene families as genomes are added along the x-axis. Genomes 62–64 are phylogenetically distant strains. Adapted with permission from Reference 63. (*b*) Schematic illustration comparing types of genes. The core genome consists of genes shared by conspecific isolates that are presumably important for the survival of the species. Accessory genes provide adaptation advantages for growth under different conditions or in different niches. Strains that share accessory gene sets belong to the same genovar. The social genome (*gray*) can allow kin recognition and cooperative behaviors; it includes genes that can belong to the core or accessory genome.

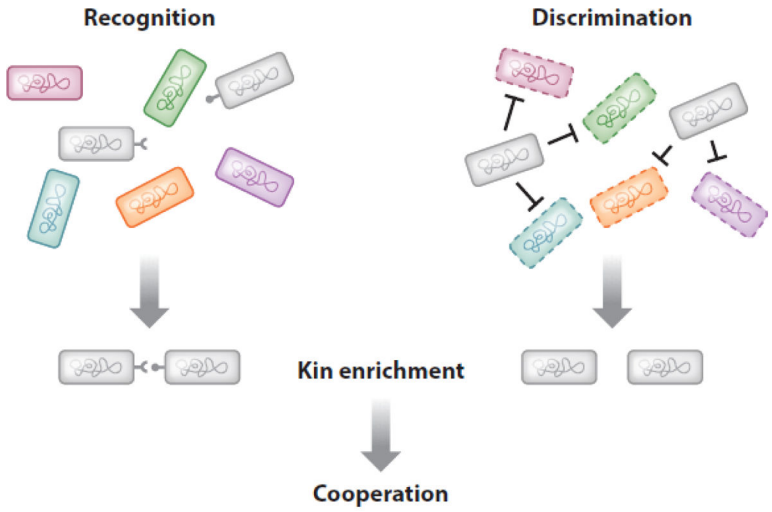

Figure 3.
Two paths that lead to kin enrichment. The recognition model is based on binding affinities between related cells. The discrimination model is based on antagonism (bacteriocin production). Colors indicate distinct genovars/strains; dashed borders represent cells inhibited by blue cells.

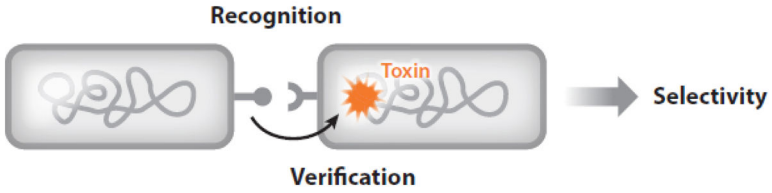

Figure 4.

The recognize-and-verify model for kin recognition. The first stage involves receptor-ligand binding. During the second stage (verification), a polymorphic toxin (*orange*) is delivered to the recognized cell. Clonemates will express a cognate immunity factor and survive, whereas a cell that is not a clonemate will lack immunity and die.

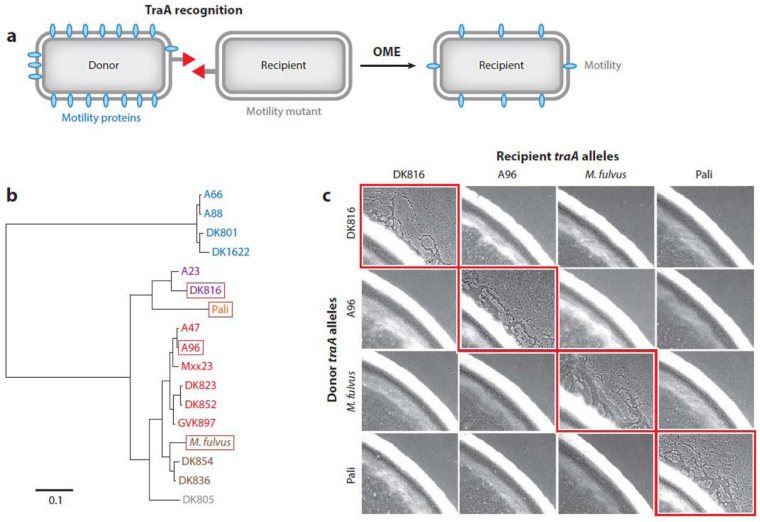

Figure 5.

Kin recognition and outer membrane exchange (OME) in myxobacteria. A) A model of OME. Two cells have compatible TraA proteins (*red*) for recognition, which leads to membrane fusion and bi-directional cell component exchange. Here, the 'recipient' lacks a particular outer membrane motility protein and can move only once it receives that protein (*blue*) from the donor. (*b*) A phylogenetic tree showing the relatedness of *traA* alleles from different isolates. The tree contains six functionally distinct recognition groups that are color coded; those in red boxes pertain to panel *c*, which shows phenotypic assays demonstrating kin (allele)-specific recognition by TraA. Colony edges contain 1:1 mixtures of isogenic donor and recipient strains that contain the indicated *traA* alleles. All strains contain mutations that block motility; however, motility in the recipients can be restored by OME (see panel *a*). OME occurs only between identical *traA* alleles (*red boxes*). *M. fulvus* = *Myxococcus fulvus*. Panels *b* and *c* adapted with permission from Reference 70.

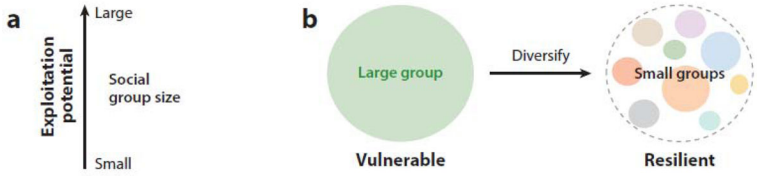

Figure 6.

(*a*) Larger kin groups are less stable. A single individual cannot be socially exploited, whereas a large social group can. Exploitation mechanisms include social cheats and the propagation of a phage infection in a social group. (*b*) A model suggesting that large social groups are under environmental and exploitation pressures that tend to lead to diversification. In contrast, a collection of smaller groups provides overall population resiliency for two reasons. First, if an exploitation phenotype develops, it is limited to one social group. Second, different groups (genovars; see accessory genes, Figure 2) expand the genetic diversity, which in turn increases the potential, of the entire population, to adapt when faced with changing environmental conditions and competitors. The relative size of each group is dynamic and will temporally fluctuate depending on the conditions. For ecological examples of niche diversity and diversification, see References 73, 87, 87a, 97 and 97a.