Chapter 1
Introduction: Key Levels of Biocommunication of Bacteria

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1.1 Introduction: Communicative Competences of Bacteria

Bacteria (prokaryotes) communicate and therefore are able to organize and coordinate their behavior similar to a multicellular organism (Losick and Kaiser 1997; Kaiser and Losick 1993; Ben Jacob and Levine 2006; Bassler and Losick 2006). But what does communication mean? In contrast to older concepts which summarize communication processes as information exchange only, nowadays communication processes are investigated as sign-mediated *interactions*, i.e., the informational content which is transported with signs triggers all kinds of different behavior. Also such different processes as production, release, uptake, and interpretation of signal molecules represent behavioral patterns. Signs are, in most cases, chemical molecules, in some cases also tactile interactions, which serve as signals both within and between prokaryotic organisms.

Bacteria are symbiotic organisms covering the whole range from mutualism to parasitism. They may be beneficial for their (eukaryotic) hosts and without them host survival would not function. Others are neutral, i.e., they do not harm the host. Many of them also cause diseases, with sometimes epidemic characteristics and, often, lethal consequences.

Bacteria represent one of the main success stories of evolution. They originated at the early beginning of life similarly to archaea which represent a different organismic kingdom (Woese et al. 1990; Koonin et al. 2006; Koonin and Wolf 2008; Koonin 2009). Bacteria are found in all ecological niches and share a common flux of their gene pool with a high rate of gene order recombination for adaptational purposes of great diversity (Pal et al. 2005). More than in any other organismic kingdom it is in common use to speak about the languages and even

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dialects of bacteria (Kaiser and Losick 1993; Swift et al. 1994; Bassler 1999, 2002; Schauder and Bassler 2001; Ben Jacob et al. 2004).

Quorum sensing is the term of description for sign-mediated interactions in which chemical molecules are produced, secreted, and uptaken by bacteria (Crespi 2001; Manefield and Turner 2002; Greenberg 2003; Tu and Bassler 2007). They are recognized by the bacterial community dependent on (a) a critical concentration and in a special ratio to (b) the population density (Daniels et al. 2004; Lerat and Moran 2004; Waters and Bassler 2005). These molecules trigger the expression of a great variety of gene transcriptions. Many bacteria use multiple quorum sensing codes; each may be modulated by posttranscriptional or other regulatory engineering (Loh et al. 2002).

There are also communication processes between different species of bacteria and between bacteria and nonbacterial life such as eukaryotic hosts (Konaklieva and Plotkin 2006). Beneath the semiochemicals (Gr.: Semeion = sign) necessary for developmental processes of bacterial communities such as division, sporulation, and synthesis of secondary metabolites, there are physical contact-mediated behavioral patterns which are important in biofilm organization (Davis et al. 1998; Fuqua and Greenberg 2002; Voloshin and Kaprelyants 2004; Parsek and Greenberg 2005). Also, abiotic influences serve as signs which indicate specific nutrients or other environmental circumstances such as dehydration or hydrodynamic changes or changes of ph-level in soil and floodwaters.

As communities of bacteria species, which are able to coordinate their behavior and have advantages over single bacteria organisms, are much more common, it is not surprising that the evolutionary drive went into rising communicative complexity (Ben Jacob 2003). We should not forget that in comparison to the first two billion years of life on earth with closed prokaryotic symbiology the rise and growth of the multicellular eukaryotes (animals, fungi, plants) was a *crucial advantage* for bacterial lifestyle to colonize vertical hosts with their great spatial and motility resources.

In general in biocommunication, we can differentiate three classes of signaling molecules for different purposes, i.e., signaling within the organism to coordinate gene expressions to generate adequate response behavior, signaling between the same or related and different species. With a limited number of molecules and a limited number of combinatorial rules, they generate quite different interactions for different purposes all mediated by signs. As in every sign-mediated interaction sign users share a common set of syntactic rules, i.e., how signs may be combined; of pragmatic rules which determine a great variety of interactional contexts, e.g., development, growth, mating, virulence, attack, or defense. The situational context of these complex interactional processes determines the meaning of signs, i.e., semantics of signals. Independent of organismic complexity, the complementarity of these three levels of semiotic rules can be identified, in principle, in every sign-mediated interaction within and between organisms (Witzany 2010). This leads to the generation of intra- and intercellular processes which enable bacterial communities to generate memory which may be inheritable but can alter epigenetically, i.e., different reading/meaning patterns of the same genetic data set with differences at the phenotypic level without altering the genetic data set.

The link between linguistics and genetics has been obvious since the detection of the universal grammar and the structural code of DNA. Chomsky's meaning-independent syntax approach lead to the broad acceptance and usage of bioinformatic methods and systems biology. Researchers in bacteria communication like (Ben Jacob et al. 2004) suggested with good reason that this approach reduces linguistic competences found in bacterial communication and has to be satisfied by both semantic aspects, i.e., the meaning of signals which serve as signs, and pragmatic aspects, which focus on the context-dependent variety and differences of the behavioral patterns in common-goal coordination, shared knowledge, memory, and mutual targets. Apart from that, it is coherent with the presupposition by Charles Morris of any nonreductionistic analysis of language-like structures, the obligate complementarity of syntax, semantics, and pragmatics (Morris 1946).

1.2 Semiochemical Vocabulary and Communicative Goals of Bacteria

The semiochemical vocabulary used by bacteria is of great variety, especially because some signaling molecules are multiple reusable components (Henke and Bassler 2004). Acyl homoserine lactones (AHLs) and linear oligopeptides are used as signs in diverse processes. Cyclized oligopeptides function as virulence genes. γ-Butryolactones (GBLs) are used as antibiotics and in sporulation processes. Furanosyl diester (AI-2) is used in a variety of processes (Sun et al. 2004) and in luminescence. cis-11-Methyl-2-dodecenoic acid (DSF) serves in virulence and pigmentation. 4-Hydroxy-2-alkyl quinolines (PQS, HAQs) are important in whole regulation processes and for virulence as are palmic acid methyl esters (PAME). Putrescine is important in swarming motility like biofilm organization. A-signal is used in early developmental processes and aggregation. C-signal is a cell surface-associated protein and serves to coordinate motility and the developmental process of building a fruiting body. Cyclic dipeptide is a secondary metabolite (Shapiro 1998; Visick and Fuqua 2005).

Gram-negative bacteria use homoserine lactones (LuxR/LuxI) as signs in communication processes (Swift et al. 1994; Schauder and Bassler 2001; Lenz et al. 2004), whereas Gram-positive bacteria use oligopeptides in quorum sensing communication. As in all organisms, noncoding RNAs are important in higher order regulatory pathways such as small RNAs and microRNAs are used by bacteria to regulate special genetic expression patterns, which play an important role as appropriate response behavior to stress or nutrient availability (Teplitski et al. 2000; Masse and Gottesman 2002; Wassarman 2002; Vogel and Sharma 2005; Majdalani et al. 2005), e.g., in controlling the quorum sensing pathways (Bauer and Robinson 2002).

At present, three kinds of communicative goals are distinguished: (1) reciprocal communication, i.e., active sign-mediated interactions, which are beneficial for

both interacting parts such as decision-making processes (Brockhurst et al. 2008); (2) messages which are produced as response on a triggering event, which may be an indicator for a receiver which was not specially targeted by the producer. A coincidental event which is neutral – except for the energy costs of production – to the producer but beneficial for the receiver; (3) signaling to manipulate the receiver, i.e., to cause a response behavior which is one-sided – beneficial to the producer and harmful to the receiver (Visick and Fuqua 2005), often in that they behave against their normal goals (Keller and Surette 2006).

The three classes of intra-, inter-, and transorganismic (trans-specific) communication enable bacteria to generate and coordinate different behavioral patterns: self and nonself identification, i.e., "recognition" and identification of self and other colonies and measurement of their size, pheromone-based courtship for mating, alteration of colony structure in formatting of fruiting bodies, initiation of developmental and growth processes, e.g., sporulation.

In receiving signals from same or related species or nonbacterial organisms the signaling molecules bind to specialized sensor proteins which function as receptors. They transmit the message to an intracellular regulator (Fuqua et al. 1996; Visick and Fuqua 2005), i.e., the signal molecule transits the cell membrane through diffusion or by specific transport pathways. Inside the cell the signaling molecule, in most cases, binds to a cytoplasmic target protein. It may be that a diffusible molecule is chemically engineered to an active signal after entering the target cell (Visick and Fuqua 2005). Organization of cellular production of response molecules leads to signal-dependent transcription control of DNA.

Bacteria have to distinguish between species-specific signaling and signaling which is able to modulate behaviors interspecifically (Bassler 1999; Federle and Bassler 2003; Waters and Bassler 2006). With these communicative competences, they are able to coordinate species-specific behavioral patterns as well as to coordinate behaviors between diverse species (Hughes and Sperandio 2008).

1.3 Transorganismic Communication of Soil Bacteria

If we look at beneficial symbioses between bacteria and plants, we refer to the complex communication networks between soil bacteria, mychorrizal fungi, and plant roots (Hayashi 2005; Imaizumi-Anraku et al. 2005). Mychorrizal fungi secret molecules in the surrounding environment which serve as nutrients for soil bacteria and trigger their activation to degrade special nutrients which are then available for mychorrizal fungi (Bonfante 2003; Bonfante and Anca 2009). Their hyphal growth serves as the developmental and growth area of plant roots, themselves being dependent on nutrients which are prepared by the mychorrizal fungi. Plant roots can also mimic bacterial signaling molecules, either to trigger bacterial production of special molecules or to disturb bacterial communication pathways (Teplitski et al. 2000; Bauer and Robinson 2002; Daniels et al. 2004).

Rhizobia bacteria are integrated into plant cells by phagocytosis when they interact symbiotically with the plant roots (Samaj et al. 2004). In other cases where rhizobia fail to fix nitrogen inside the root nodules because they are being deceptive, plants are sanctioning these rhizobia (Kiers et al. 2003) and prevent their spread to stabilize mutualistic symbioses with bacterial colonies (Keller and Surette 2006). Root exudates of different kinds regulate plant and microbial communities in the rhizosphere. This is necessary to stabilize equilibrium and inhibit the continuity of attacks by pathogenic bacteria in the soil (Walker et al. 2003; Bais et al. 2003). The full range of trans-specific communication processes between bacteria and plant roots is important for developmental and growth processes in the entire plant kingdom (Manefield and Turner 2002; Kent and Triplett 2002; Sharma et al. 2003).

Chemical molecules, which serve as signs in intercellular communication processes of bacteria, are similar to pheromones in social insects and animals. This may be an indicator of evolutionary lineages that evolved in the bacterial "chatter" (Velicer 2003). Interbacterial communication uses hormone-like signaling to sense specific host locations such as intestinal habitat. In this specialized ecosphere, a bacteria–host communication occurs which means the host cells and bacterial cells share a common meaning function for the same signaling molecules (Sperandio et al. 2003).

Living as endosymbionts as potential candidates for symbiogenesis (Margulis 1996, 1999, 2004; Margulis and Sagan 2002), as documented in the origin of eukaryotic endosomes like mitochondria, indicates the important role of bacteria for the entire history of evolution (Witzany 2005). The interactions may be pericellular colonization events but also an intracellular lifestyle. These different symbiotic interactions range from acquisition of novel genetic material to reduction in size and content connected with gene loss (Batut et al. 2004). Successful living processes of higher eukaryotes would not be viable without beneficial symbiosis with bacteria. The cell mass of an adult human assembles 20% of human origin and up to 80% of exogenic settlers (Blech 2000), most of them bacteria.

1.4 Interorganismic Communication

Interorganismic Communication is the sign-mediated interactions (coordination) between the same and the related species and includes the ability to sense self and nonself members. For a long time, it was assumed that bacteria live predominantly as monads. However, it has been recognized that this is a very rare exception (Federle and Bassler 2003; Dunn and Handelsman 2002). Bacterial colonies live, in almost all cases, not alone but in coexistence with other bacterial species self-coordinated by a diversity of sign-mediated interactions (Gray 1997; McNab and Lamont 2003; Ben Jacob and Levine 2006). Bacteria use intraspecific and interspecific signaling in all ecological in vivo situations (Keller and Surette 2006). This also implies a broad variety of conflicts within and between species (Velicer et al. 2000;

Xavier and Foster 2007). The mutual, neutral, and manipulative aims of communication processes are special kinds of response behavior to certain degrees of beneficial up to conflictual relationships (Keller and Surette 2006).

Dependent on the availability of nutrients, some bacteria suppress normal cell development which leads to the development of a different cell type, which is better suited for adequate response behavior for this situational context. It means that different environmental conditions can lead to different gene expressions within the same genetic data set. It has been shown that if the same colony is exposed several times to these changing contexts they react more immediately. This indicates that bacterial communities are able to develop collective memory and learn from the experience (Ben Jacob et al. 2004; McNab and Lamont 2003). In the case of changing environmental conditions, the suppression of cell division may lead to cell elongation which enables cell colonies to change the modus of motility. This is an important feature of socio-bacterial behavior, e.g., swarming coordination and organization for surface colonization (Shapiro 1998, 2007).

Some authors have documented altruistic strategies in mixed colony formations, which seems to be an advantage to the mixing among microcolonies. Altruistic behavioral strategies enable strengthened self-identity and a sustainable equilibrium in multilevel colonized ecological niches (Velicer and Yu 2003; Kreft 2004; West et al. 2007).

Interestingly, bacteria use a common contextual interpretation of incoming signals by each member of the colony. The response behavior is appropriate to the majority vote (Ben Jacob et al. 2004; Ben Jacob 2009) in a context-dependent decision.

The identification of nonself species is a competence which is possible through species-specific and group-specific quorum sensing and is coherent with the assumption that smaller groups of the same bacterial species are able to built types of quorum-sensing "dialects." These are important in the high density of coexistent bacterial life habitats to prevent confusion and enable more complex coordination (Taga and Bassler 2003) such as in the oral cavety of humans (see below). Interestingly, the prokaryotic cell–cell communication has structural analogs to cross-kingdom signaling between bacteria and fungi (Wang et al. 2004).

1.4.1 Interpretation and Coordination

Bacteria have profound effects on human health, agriculture, industry, and other ecospheres. Therefore, they target the multiple drugs which fight them (Camara et al. 2002). They develop drug resistance by coordination of special defensive behavior called biofilm organization (Sutherland et al. 2004; Burmølle et al. 2007; Danhorn and Fuqua 2007). Biofilm organization is a special kind of coordination with a high density of physical contact and contact-specific signaling (Bassler and Losick 2006) between members of a bacterial identity group. Biofilmorganisation in most cases depends on coordination of group members which share self (group

identity) and nonself (Bacteria which are recognized to be not part of the group). In most habitats, there is also an organization with one or more nonself groups concerning group density, i.e., symbiotic signaling. This includes the release and uptake of molecules, which serve as indicators that, e.g., signalize to certain group members to undergo apoptotic processes if group density is too high to continue population survival concerning nutrient or even living space availability. If bacteria realize a critical mass via quorum sensing, they organize a high density of communal body by moving their flagellas which may resist even strong antibiotics (Wadhams and Armitage 2004; Diggle et al. 2007a, b). Biofilms are constructed on abiotic surfaces, e.g., on stones in rivers and other aqueous surfaces, as well as biotic ones, e.g., in the respiratory track of animals. Each human who had a strong cold remembers like persistent the mucus in the bronchial tube remained.

Nutrient availability also regulates the structure of biofilm organization (Stanley and Lazazzera 2004) as hydrodynamic forces (Wuertz et al. 2004). Interestingly, it has been found that biofilm organization is linked with coordinated DNA release, which is integrated in the biofilm (Spoering and Gilmore 2006).

Bacteria decide, in special cases – to mention another coordinative pattern – , to form fruiting bodies of different types and shapes for sporulation (Ben Jacob 2009). This enables bacterial communities to more efficiently disseminate the spores. The fruiting body building is governed by context-specific rules with different roles for different subgroups of bacterial communities for coordination (Kaiser and Welch 2004). Some have to serve for motility to density, followed by direction decision and decision of cell types, cell growth and developmental stages in all the different steps until the fruiting body is ready for the sporulation event. Without communicative hierarchical organization, this would not be possible. If communication is disturbed body building is not assured, so bacterial communities have developed special strategies to single out so-called “cheaters” (Velicer et al. 2000; Ben Jacob et al. 2004; Sandoz et al. 2007), which do not follow the rules for coordinating this special behavior.

As documented into Fig. 1.1 (Kohlenbrander et al. 2002), one of the most interesting and best investigated phenomena of bacterial communication is the *symbiology* of multiple colonies coexistent in the human oral cavity (Kohlenbrander et al. 2002, 2005; Rickard et al. 2006). Bacteria on human teeth and oral mucosa establish a homeostasis of pathogenic and mutualistic bacteria by a complex system of sign-mediated interactions both species-specific and trans-specific. The dental plaque in the oral cavity of humans is a unique habitat, which is not found in any other species (Sahasrabudhe and Dewhirst 2001). The homeostasis is not static but is the result of a continous and dynamic relationship between different species-colonies dependent on intervals of daily hygiene. The interacting species number approximately 500 different species (Moore and Moore 1994; Kroes et al. 1999; Paster et al. 2001).

Each member of these communities must be capable of self and nonself distinction and be able to distinguish between species-specific signaling and trans-specific signaling or even “noise” (same molecule but without informational content). As a community they must be able to measure their own colony size and the size of the

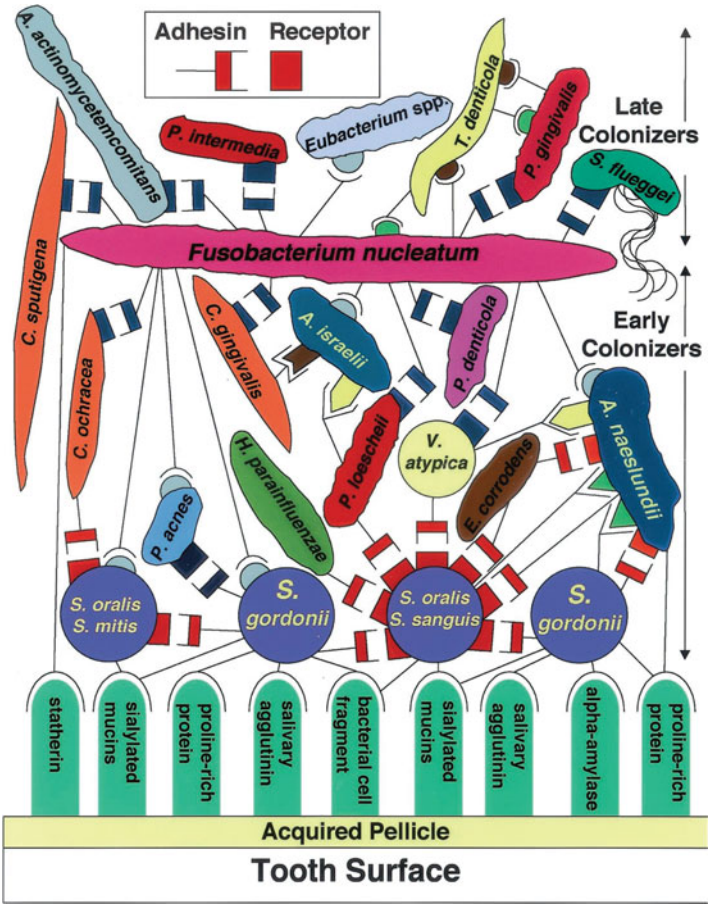

Fig. 1.1 Spatiotemporal model of oral bacterial colonization, showing recognition of salivary pellicle receptors by early colonizing bacteria and coaggregations between early colonizers, fusobacteria, and late colonizers of the tooth surface. Each coaggregation depicted is known to occur in a pairwise test. Collectively, these interactions are proposed to represent development of dental plaque and are redrawn from Kolenbrander and London (79). Starting at the bottom, primary colonizers bind via adhesins (round-tipped black line symbols) to complementary salivary receptors (vertical round-topped columns) in the acquired pellicle coating the tooth surface. Secondary colonizers bind to previously bound bacteria. Sequential binding results in the appearance of nascent surfaces that bridge with the next coaggregating partner cell. Several kinds of coaggregations are shown as complementary sets of symbols of different shapes. One set is depicted in the box at the top. Proposed adhesins (symbols with a stem) represent cell surface components that are heat inactivated (cell suspension heated to 85°C for 30 min) and protease sensitive; their complementary receptors (symbols without a stem) are unaffected by heat or protease. Identical symbols represent components that are functionally similar but may not be structurally identical. Rectangular symbols represent lactose-inhibitable coaggregations. Other symbols represent components that have no known inhibitor. The bacterial strains shown are *Actinobacillus actinomycetemcomitans*, *Actinomyces israelii*, *Actinomyces naeslundii*, *Capnocytophaga gingivalis*, *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, *Eikenella corrodens*,

other colonies and molecules that have the same chemical structure but are not part of a biotic message. Special communication patterns with detailed hierarchical steps of signal production and transmission include (1) metabolite exchange, (2) cell–cell recognition, (3) genetic exchange, (4) host signal recognition and signal recognition of same or related species. Owing to the high number of competing and cooperating species, there is a special short- and long-term community architecture established according different spatial and temporal conditions. If the communication on the intra-, inter-, and metaorganismic level is successful, i.e., the signal transmission and reception enables colonies to live in a dynamic homeostasis, then the human oral cavity will avoid cavity diseases (Kohlenbrander et al. 2002, 2005).

1.5 Intraorganismic Communication

In contrast to transorganismic (trans-species) and interorganismic (same and related) biocommunication of bacteria, we term intraorganismic communication those sign-mediated interactions within the bacterial organisms, i.e., the signaling, regulation, coordination of all processes within prokaryotic cells including all genetic and epigenetic processes.

Only some higher order regulations (operons) that code for physically interacting proteins are found in almost all bacterial (and archaeal) genomes. Recent research indicates high dynamics of new gene orders as documented in the horizontal gene transfer events with their intensive intragenomic recombination (Imaizumi-Anraku et al. 2005; Xie et al. 2004). This exchange of whole genes or gene-blocks enables bacterial lifestyles to combine several bacterial competences, i.e., phenotypes. The transformation process includes the release of naked DNA, followed by the uptake and recombination, i.e., the integration, with 17 steps identified to date (Thomas and Nielsen 2005) (see Fig. 1.2). Thus, we can recognize the outcomes of a diversity of mobile DNA contents (Bordenstein and Reznikoff 2005), not a mass of individualized genetic texts, but a bacterial gene pool as a genetic text repertoire which is available for each individual bacteria and the resource for bacterial genome innovation and evolution (Gogarten and Townsend 2005; Olendzenski and Gogarten 2009). Horizontal gene transfer is a main resource for integrating newly evolved genes into existing genomes and does not need the slow steps of chance mutations to alter the genomes but accelerated genome innovations in both bacteria and archaea (Jain et al. 1999, 2003; Brown 2003). Important in this context of genomic innovation is not the sequence acquisition alone but also the contextualization (Solomon and Grossman 1996); it means also their loss (Berg and Kurland 2002). It seems now that the

Fig. 1.1 (Continued) Eubacterium spp., *Fusobacterium nucleatum*, *Haemophilus parainfluenzae*, *Porphyromonas gingivalis*, *Prevotella denticola*, *Prevotella intermedia*, *Prevotella loescheii*, *Propionibacterium acnes*, *Selenomonas flueggei*, *Streptococcus gordonii*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguis*, *Treponema spp.*, and *Veillonella atypical* (with permission by Kohlenbrander et al. 2002)

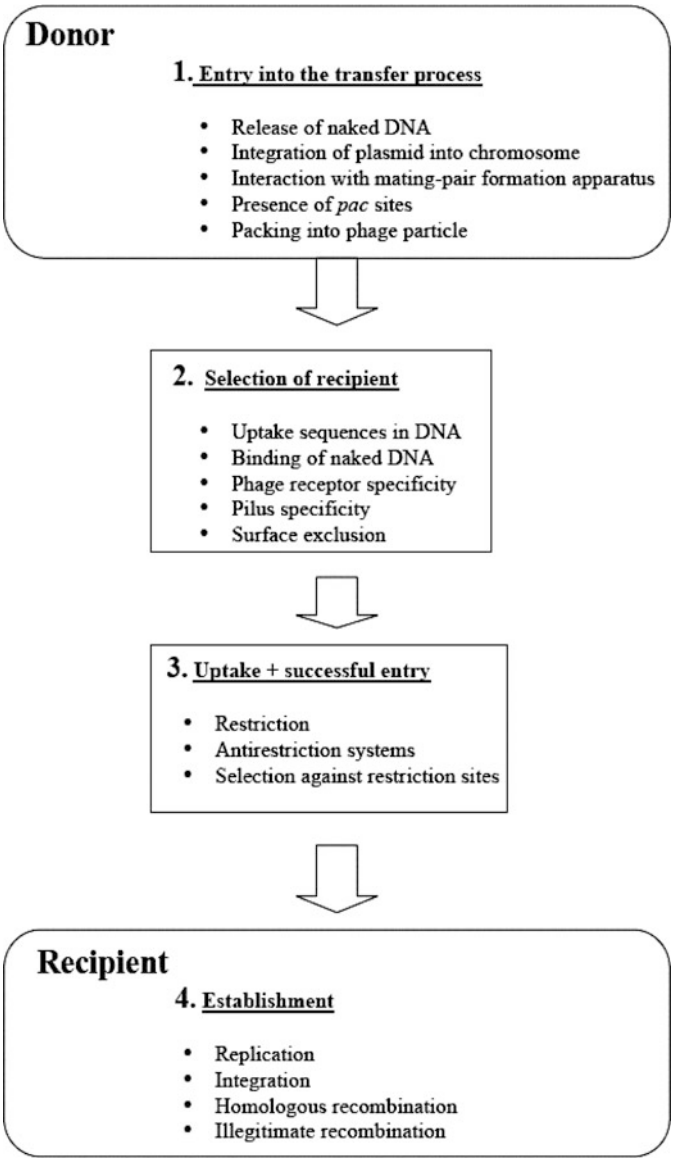

Fig. 1.2 The process of horizontal gene transfer. A schematic outlining the stages through which DNA must go on its journey from donor to recipient bacteria. The process begins with DNA in a potential donor cell becoming available and ends when this DNA becomes a functional part of a recipient cell's genome (Fig. 2 accordingly Thomas and Nielsen 2005)

phylogeny of microbial species is not a tree of life, but an evolutionary network or a ring of life, mediated by genetic exchange, i.e., acquisition and loss of genetic data sets (Rivera and Lake 2004; Kunin et al. 2005) (Fig. 1.3).

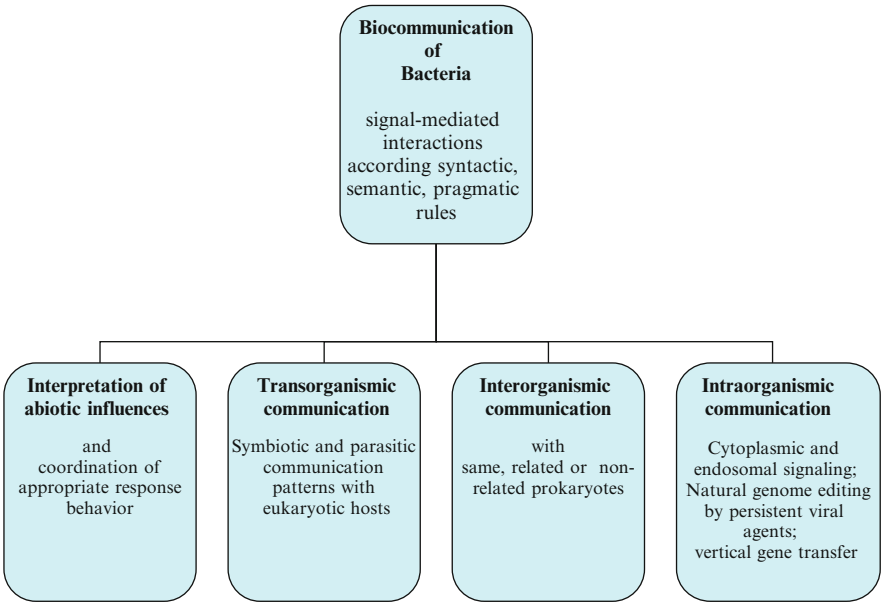

Fig. 1.3 Levels of biocommunication of bacteria

1.5.1 Intracellular Communication

Signal-dependent transcription regulation of the DNA serves for a great variety of response behavior. One of the most interesting phenomena is the fact that in the first two billion years of life on planet earth, the immense density of bacterial life has not been an event of the mass of individual organisms but their commonly shared gene pool which was in constant flux, as we now know, through investigations on horizontal gene transfer.

It means that the evolution of bacteria was not a random event of chance mutations and their selection but transfer of whole genes and gene-blocks representing real phenotypes that were transferred. This leads to different combinatorial patterns of genetic encoded phenotypes and the rise of bacterial diversity. It also enables bacterial pathogens to optimize their disease-causing coordination and is therefore targeted to special kinds of drug developments for medical purposes (Tettelin et al. 2005). New empirical data seem to suggest that the phenomenon of horizontal gene transfer is driven by viral competences inherent in bacterial settlers such as phages, plasmids, retroplasmids, and transposons (Villarreal 2005; see also Chiang and Lambowitz 1997).

For a long time, it has been proposed that tubulin plays an important role in cytoskeletal functions of eukaryotes whereas prokaryotes lack this system. Recent research has shown that tubulin is a very ancient system for genetic data set segregation also in bacteria which plays important roles in filament formation,

movement, and orientation (Graumann 2004; Graumann and Defeu-Soufo 2004; Defeu-Soufo and Graumann 2004; Gitai 2005; Guerrero and Berlanga 2007).

1.5.2 Bacterial Evolution and the Agents of Natural Genome Editing

To elucidate communicative competences of bacteria, we also have to look at the roles of viruses and their relationship to bacteria. Viruses have long been accepted only as disease causing, epidemic phenomena with lytic and therefore dangerous consequences for infected organisms. However, new research has corrected this picture. Viruses are part of the living world, in most cases integrated in the cytoplasm or the nucleoplasma of cells without harming the host. Viruses are on their way to representing the best examples of symbiotic relationships, because there is no living being since the start of life that has not been colonized by them, in most often cases in the form of multiple colonisations (Sonenshein 2006; Witzany 2010). The longest period of these symbiotic relationships during evolutionary history share viruses, archaea, and bacteria. As viruses are extremely biosphere specific, i.e., they adapt to special host tissues, the identification of various forms of, e.g., bacteria is to identify primarily the viruses that colonize them (Rohwer and Edwards 2002; Rohwer 2003). This is also the concept of "bacteriophages," in that bacteria are identified best by identifying the viruses that are associated with them. Host identification in this way is a special method called phage typing (Goyal et al. 1987; Abedon et al. 2009; Ackermann 2007, 2009).

1.5.3 Lytic vs. Persistent Viral Life Strategies

As mentioned in recent years, the lytic consequences of viral infection are a special case if viruses are not able to develop a sessile lifestyle without harming the host. In most cases, viruses living within organisms help to ward off competing parasites from the host and becoming part of its evolutionary history. Persistent viruses are decisive for species diversity and host genome editing. Nearly all natural cellular competences such as expression, transcription, translation, and recombination with all their detailed steps derived from viral competences. Even the DNA replication pathways, after a period of early RNA influence (Forterre 2002, 2005, 2006), seem to be a special viral strategy for the conservation of coded phenotypes by warding off RNA parasites (Villarreal and DeFilippis 2000; Villarreal 2005).

Since observations have become more evident that viruses are able to integrate genetic material into the host genome, it has become clear that viruses have infection lifestyles and endosymbiotic and even symbiogenetic lifestyles. They transfer

phenotypic capabilities on the host, which noninfected hosts from the same species do not possess. As endosymbiotic viruses, which are dependent on the host's replication, they are part of the host history in that they are inheritable and part of the genomic identity of the host as documented in some several 10,000 infection events in the human genome by endogenous retroviruses (Villarreal 2004).

The two viral lifestyles are not in strict opposition but, in most cases, are part of a symbiotic process. It starts with an infection by a virus. In the infected host, it arrives at an equilibrial status where the immune system does not eliminate the virus but controls its replication without fatal consequences for the host organism. The persistent status lasts during most phases of the host's life, but may return to the lytic lifestyle if the host-immune system is under stress (Villarreal et al. 2000). Most often the integration occurs by mutual neutralization of toxic capabilities by an antitoxin of a competing genetic settler (Pandey and Gerdes 2005). The whole range of toxin/antitoxin addiction modules we can find throughout all genetic contents in living nature most likely is of viral origin (Lehnherr et al. 1993; Lehnherr and Yarmolinsky 1995; Yarmolinsky 1995; Gerdes and Wagner 2007). Therefore, the persistence is sometimes called temperate lifestyle.

Also bacteria may be infected by viruses without being harmed. If infected bacteria meet noninfected bacteria, it may be that the noninfected acquires lysis; the lysogenic strain does not lyse itself, but is lethal to the noninfected one. The colonized bacteria has a virus-derived molecular genetic identity, which has an advantage against the noninfected one through an acquired ability. This lysogenic bacteria, termed prophage, has an immunity function for the bacteria which the noninfected bacteria lack. Prophage is a virus that is integrated into the bacterial host genome. Both the acute lytic phages and the persistent prophages such as T4 and lamda are highly abundant in oceans and in the soil and seem to be the most dynamic life form on the entire planet (Hendrix et al. 2000; Hendrix 2002; Chibani-Chennoufi et al. 2004; Hendrix 2008). Some viruses are not integrated in the host genome but persist as plasmids and replicate independently from the host genome (Villarreal 2005).

When we speak about the relationship of bacteria and viruses in most cases we speak about phage ecology (Abedon et al. 2009). Most prokaryotic viruses are double-stranded DNA viruses with either linear or circular genome morphology and are packaged in an icosahedral capsid. Whereas acute viruses in most cases code for their own replication, recombination, and repair proteins, the persistent phages lack such genes and use the host-cellular replication. This involves a totally different gene word order (Villarreal 2005) in acute lytic and in persistent phages. This is documented in the very different nucleotide words (di-, tri-, and tetranucleotides). Nucleotide word frequencies of acute phages are very dissimilar to those of their hosts while persistent or temperate phages share nucleotide word frequencies with the host. This means the molecular syntax from acute and persistent phages is constructed totally differently according to the different strategies. Different life strategies with different behavioral patterns need a completely different semantic content in the genome expressed in a different syntactic arrangement of nucleotides (Witzany 2010).

As the bacterial cell walls differ substantially between different types of bacteria, a different behavior is necessary for viruses for recognition, attachment, and penetration. Owing to these diverse barriers of the bacterial cell walls, the prokaryotic viruses do not enter the host cells physically but attach to the cell surface and inject their genomes through contractile tails or pilot proteins. Also, the progeny of the virus has to deal with this barrier (Villarreal 2005).

Bacterial DNA does not have highly stable structures as do eukaryotes and in most cases, it is circular with a unique origin of replication. In contrast to that viral double-stranded DNA is a linear DNA with integrated short terminal repeats. Since bacterial viruses do not use a transport technique as they need in eukaryotes to be transported out of the nucleus, bacterial viruses differ a great deal from eukaryotic viruses.

All bacteria have a restriction/modification system which is a connected form of two viral competences. Only the descendants of mitochondria lack this system which causes them not to be exposed to viral selection. It may be that they have transposed their ability to the eukaryotic nucleus which cares in a more efficient way for cell immunity (Villarreal 2005).

1.5.4 Bacteria as Global Habitat for Viruses

Horizontal gene transfer between bacteria as being responsible for genetic plasticity in prokaryotes may be a capability which is acquired by viral infections. Then, viral genetic inventions are transferred to bacteria via persistent lifestyles of viruses and are not an exchange phenomenon performed by bacteria. In contrast to the "gene-shuttle" hypothesis of HGT, i.e., the horizontal transfer of genes between bacteria via plasmids and similar transfer techniques, the infectious perspective focuzises on a vertical gene transfer (VGT) by viral swarms into the life habitat of cellular organisms such as bacteria. The advantage of the latter one is that the origin and recombination of genetic contents has its roots in viral competence of natural genome editing, whereas in HGT hypothesis, the de novo-generation and recombination of new genetic contents remains randomly derived or even unclear.

As new research indicates, the agents of gene transfer are plasmids, retroplasmids, bacteriophages, and transposons. They effect DNA movements and act in all prokaryotes. DNA movement is achieved through transformation, conjugation, and transduction. Transformation is the transfer of DNA between related bacteria mediated by encoded proteins. Conjugation is performed by conjugative plasmids, which are independently replicating genetic elements. These elements code for proteins which facilitate their own transfer (Frost et al. 2005). Transduction is a DNA transfer mediated by phages which can package host DNA in their capsid and inject it into a new host followed by integration into the host genome (Holmes et al. 2003). Phages, plasmids, retroplasmids, and transposons, therefore, played a crucial role in bacteria evolution (Chen et al. 2005). Bacteria are the most genetically adaptable organisms with enormous capabilities to react appropriately to extreme

changes of their ecological habitats. This does not stem from their high reproductive rates but from their great ability to acquire DNA segments by plasmids, bacteriophages, and transposons which transport complete and complex sets of genes from external sources (Shapiro 2007).

When we consider the age of the ocean and the dense abundance of bacterial and viral life in it, then we can say that the possibility of genetic arrangements, rearrangements, and exchange does not need long time periods to create the basics of the complexity of life, because the exchange rate is of astronomical order. If we imagine that 1 ml of seawater contains one million bacteria and ten times more viral sequences, it can be determined that 10^{31} bacteriophages infect 10^{24} bacteria per second (Tettelin et al. 2005). Since the beginning of life, this behavioral pattern has been an ongoing process. The enormous viral genetic diversity in the ocean seems to have established pathways for the integration of complete and complex genetic data sets into host genomes, e.g., acquisition of complex new phenotypes via a prophage can include the acquisition of more than 100 new genes in a single genome editing event (Ryan 2006). Similar interactive patterns are estimated to occur in soil habitats.

Owing to the virus-induced genomic plasticity of bacteria, they are an ideal global biotic matrix to evolve and develop varieties in genome editing, i.e., competent content arrangement of bacterial gene word order coherent with its regulation network. Bacteria are the smallest living organisms with relatively simple genomic structures where the competitive situation between an abundance of viral infective elements leads to the adaptation of lytic viruses to temperate viruses integrated as plasmids in cytoplasma and even persistent viruses integrated in the host genome. The viral competences can develop in this global bacterial habitat as the bacterial species due to their immense genetic flux between viral colonization events and immunity reactions such as restriction/modification (Kulakauskas et al. 1995; Hambly and Suttle 2005).

The highly conserved genome edited functions such as replication, transcription, translation, recombination, and all the substeps evolved primarily in the competitive situation between viral competences to colonize a host and to ward off competing parasites. This includes that biotic self and nonself recognition functions as we know it from diverse immunity systems are also of viral origin, i.e., the integration and all genetic/genomic modification steps that what we call natural genome editing are of viral origin. Therefore, the immense importance of horizontal gene transfer for bacterial species evolution, diversity, and competences is derived from viral genome editing competences and is, in most cases, infection induced by persistent nonlytic viruses (Villarreal 1999; Frost et al. 2005). As phylogenetic analyses demonstrate, the main protein enzymes for natural genome editing are viral inventions and not of cellular origin (Villarreal 2004, 2005). Also, the origin of eukaryotic nucleus was thought to be an ancient prokaryote but phylogenetic analyses show that its ancestor most likely was a large DNA virus (Takemura 2001; Bell 2001, 2006). Interestingly, the early genetic invention of capsid proteins detected in viruses infecting archaea seems also to be of viral origin and of common ancestry to eukaryotic and bacterial viruses (Nandhagopal et al. 2002; Rice et al. 2004;

Khayat et al. 2005). These clearly indicates that the escape theory which assumes viruses to be rements of cellular host genomes cannot be substantiated, because most of viral genes have not counterpart in cellular life (Villarreal and Witzany 2010).

1.6 The Origins of Bacterial Group Identity

1.6.1 Obligate Viral Settlers of Bacteria

In comparison to investigations on bacterial life in the ocean, our knowledge about soil bacteria is rudimentary. The number of bacterial species in soil and its dry, wet, and floating ecospheres is just an estimate, but it may be of a similar magnitude to that in the ocean (Fierer and Jackson 2006; Fierer et al. 2007). The abundance of phages infecting soil bacteria is also just an estimate. The authors in this book will give an overview on the current knowledge on the various levels of sign-mediated intra- and interorganism interactions in which soil bacteria are involved. Additionally, it is important to be aware of soil-related ecospheres such as the enteric bacterial habitat in animals and, of particular importance, the rhizosphere of plants with its unique symbiotic relationships with organisms such as rhizobial bacteria, plant roots, fungi, protozoa, insects, nematodes, and both exogenous and endogenous persistent as well as lytic viruses and their satellites and hyperparasites that are linked to all these organisms. This means that the variety of viruses which are specialized to the various organismic kingdoms, such as ssRNA, dsRNA, dsDNA, ssDNA, and retroviruses, are in constant interaction which, from today's view, is an optimal resource for evolutionary novelty and adaptation.

Soil is in most cases colonized by fungi and bacteria. Soil is a resource which is needed by all terrestrial eukaryotes, which represents a highly complex network of dependencies of different ecospheres such as flood waters, lakes, forests, dry lands, etc. In this respect, soil has a similar function to water in the ocean, in that it is the basis for all terrestrial life forms. At the basics of organic soil are bacteria with their obligate settlers, phages, and plasmids, and then the single-celled protozoa and fungi, all of which are settled by bacterial colonizers. Higher eukaryotes like animals and plants depend vitally on these settlers because, as in the case of plants, rhizosphere ecology depends on biocommunication between plant root cells (of three different types), mycorrhizal fungi, and rhizobial bacteria. Digestive processes in animals depend on intestinal bacterial colonizers, without which animals could not survive. Additionally, the oral cavity of terrestrial animals such as humans is a complex bacterial ecosphere with up to 500 different species in a symbiotic lifestyle as described above (see Fig. 1.1). One of the obligate symbiotic settlers of animal intestinal tracts is E. coli, with its obligate lytic T4 phage parasite. T4 phage shows a similarity to some eukaryotic DNA viruses (e.g., herpesvirus). Additionally, T4 phage shows genetic similarities not only to other viruses, but also to eukaryotic cells such as T4 DNA polymerase, lysozyme and, in particular, group

I self-splicing introns, which can be found in mitochondria of fungi, nuclei of protists and chloroplasts, as well as in mitochondria of plants, but not in many prokaryotes (Villarreal 2005).

Interestingly, the identity of bacterial strains is determined by their colonizing viruses, that is, their phages or plasmids, and therefore the identification of bacterial strains is called "phage typing." The knowledge that viruses colonize bacterial genomes was discovered just 60 years ago, when Salvator Luria termed this a "molecular genetic parasite," whilst Lwoff termed this hereditary virus as having a "temperate" lifestyle or called it a "prophage" (Villarreal 2005). With these, it was clear that there are two different lifestyles of viruses: a lytic acute one and a silent one (lysogenic). Later, a third was detected: a continuous and chronic virus production without lysis of the host cell and without silent persistence.

Another interesting observation was that if lysogenic bacterial strains and non-lysogenic strains were mixed, the noninfected were lysed but the lysogenic were not. This seemed to be an advantage in that the infected bacteria were protected by their prophage, whereas the noninfected were not. The identity of the infected bacterial strains is therefore another one as those of the noninfected. In competitive situations, infected bacteria have an immunity advantage in comparison to noninfected bacteria. The genetic identity is virus-derived (Villarreal 2005). With this identity, the bacteria host is able to identify and preclude other competing genetic parasites. Defective phages can also be a part of this identity. Although they are not able to produce infective viruses, they can effectively preclude infection from the host by related parasites.

The most abundant bacteria-infecting viruses are the T4 phage and the lambda phage (Tetart et al. 2001; Desplats and Krisch 2003). If the bacterium is lysogenic, they integrate in the host chromosome. When viruses integrate in the host cytoplasma, rather than in the host chromosome, they are known as episomes. Episomes are exogenous genetic elements, such as plasmids, which replicate independently of the host genome and are derived from transposable elements, i.e., viruses. The overwhelming majority of bacterial phages are dsDNA viruses of linear or circular genomes. Of these, 96% are tailed and the remaining 4% are isometric. Whereas lytic phages such as T4 code for their own replication, recombination and repair, persistent pages use the host system instead. The next most common bacterial phages are the ssDNA viruses with rolling circle replicons, whereas dsRNA viruses and ssRNA viruses are found very rarely. Whereas bacterial DNA is circular with a unique origin of replication, and most dsDNA genes from viruses are linear with terminal repeats, it has been found that these repeats facilitate replication via circular theta forms and RCR intermediates (Villarreal 2005).

As an immunity function, it is common for all prokaryotes to use a restriction/modification system. The restriction system acts as endonuclease which degrades unmodified DNA and its counterpart modification, i.e., methylase which covalently modifies DNA protecting it from degrading endonuclease. Prokaryotes that undergo symbiogenesis, such as mitochondria in eukaryotic cells, lack the restriction enzyme, which seems to be an indicator for lacking phage-selective pressure within the new host habitat.

In vivo bacteria are the most genetically adaptable organisms in that they can change their genetic molecular syntax very rapidly due to their high clonal reproductivity. The ability to acquire complete and complex genetic datasets from the outside also enables genetic adaptation. This has been termed horizontal gene transfer in that it is assumed to be an exchange and transfer system of genetic elements within microbial ecospheres. In reality, this seems to be virus-infection driven and leads to an altered genetic (molecular) syntax of the host which does not originally stem from the genetic lineage of the bacterial population. In this respect, we should speak of a vertical gene transfer (VGT). This is a very important fact as phage–phage interactions can lead to phage immunity for the host and rapidly infected bacteria may acquire multiple drug resistances and also virulence.

There are several examples of phages that can be colonized by other phages which are phage-specific colonizers rather than host-specific. This means a different lifestyle. In some cases, it is well documented that these phage–phage interactions are complementary and provide features which are absent in phages that are not part of these interactions. This means that a bacterial host which has been colonized multiple times will have a variety of features not available to a less infected bacterial host of the same species. If, for example, a bacterium acquires a virulence-associated prophage, this means that it will be able to acquire more than 100 new genes in one infection event (Villarreal 2005).

1.6.2 The Role of Persistent Viruses in Gene Word Order of Bacteria

The ability of bacteria to communicate and coordinate via quorum sensing processes depends on a variety of features which assemble group identity, that is, the ability to sense group members as part of self and nongroup members as nonself agents. A coherent exchange of signaling molecules ensures the ongoing processes. Each of these capabilities must be genetic because they are determined by the production, release, uptake, and interpretation of protein products which are genetically encoded. In order to understand this, there are questions that need to be answered, such as: what is the genetic make-up of a bacterial population, what are the adaptational purposes for changing these genetic datasets and finally, what agents are involved in the natural genome editing of bacteria, i.e., determine their genetic content arrangement?

The behavioral patterns demonstrate an intense relationship between bacteria and viruses in that the viruses colonize bacterial cells as exogenetic (plasmids) or endogenetic (phages) parasites. Episomal (plasmid) persistent viruses replicate independently of the host genome whereas the replication of endogenous parasites depends on host-genome replication. Parasitism reaches from lytic to nonlytic lifestyles. The nonlytic persistent lifestyle of phages determines the gene word order (molecular syntax) of the bacterial genetic text. Additionally, it is necessary

to look at a great variety of phage–phage interactions which can result in multiple alterations within the host genome. Also, parasites of parasites of parasites (hyperparasites) are not rare but common, so that the interrelationships between several viral strains within the bacterial cell have to be mentioned. In this respect, the traditional process described as horizontal gene transfer – a gene transfer from one bacterium to another – is not the only source of change of genetic content arrangements. More important seems to be the content arrangements generated by phages/plasmids and their interrelation partners of competing/colonizing parasites or their defectives. As mentioned above, the gene transfer can assemble up to 100 new genes within one single event, which is a completely different contribution to evolutive novelties than single randomly derived point mutations could cause. Because of the abundance of phages/plasmids in the bacterial world, this could be seen as the rule more than the exception and has important consequences on previous thoughts on prokaryote evolution.

Bacteria are undoubtedly the best adaptational organisms on earth. An abundance of fast-arranged genetic variations together with genetic adaptations occurs and can resist any environmental circumstances, for example, intense heat and radiation. The acquisition of complex genetic datasets by virally derived infection events seems to be the main source of evolutionary adaptational processes, and this was not in the focus of bacterial research within the last few decades. This means that the main genetic resources did not derive from direct cellular predecessors or from the genetic lineage of the bacterial population horizontally, but is the result of natural genome-editing activities of viruses.

1.6.3 Infection-Driven Group Identity and Group Immunity

If a bacterial strain is persistently infected by a phage and brought into a competitive situation with a bacterial strain which is not infected by the same virus, the noninfected strain will undergo lysis. This means that infection and colonization of bacteria are interconnected with the acquisition of an immunity function which does not destroy the infected one by the noninfected one. Infected bacteria share a common immunity which noninfected bacteria do not have. Phage colonization in a nonlytic persistent lifestyle has a symbiotic function which protects host cells and host strains. Colonized bacteria now have a virus-derived genetic identity (Villarreal 2005), which is dissimilar to that of noncolonized bacteria of the same strain. Members of virally colonized bacterial colonies are able to sense the different identity of bacteria that are colonized by different viruses and can also identify those that are noncolonized. Colonized bacteria can also sense other genetic parasites. If we look at the interactions of viruses and bacteria, we therefore have to look at three different but interconnected levels of relationships:

- Acute lytic and persistent viruses to the prokaryotic hosts
- Acute lytic and persistent viruses to other acute host viruses

- Acute lytic and persistent viruses to other persistent host viruses.

These interrelated processes are highly dynamic and constantly changing processes because the competition between viruses with their high mutation rate (gene word-order-plasticity) to reach a persistent status, which includes the exclusion of related parasites, is an ongoing process.

Persistent endogenous viruses do not need genes for their own replication, recombination, and repair, whereas acute lytic viruses show a strong tendency to encode these features by themselves.

1.7 Transfer of Viral Competences as Modular Tools

1.7.1 Molecular Identity Markers

One of the important features of lytic T4 phages is their ability to modify nucleotide sequences at a high frequency. Interestingly, this ability to modify molecular syntax, such as the exchange of hydroxymethylcytosine for cytidine, serves to mark the molecular identity of the phage genome distinctly from the host genome. Additionally, this marked phage DNA is protected from phage-encoded restriction endonucleases II and IV that degrade unmodified host DNA. Marking is an identity sharing action which serves for both the self/nonself identification/differentiation and as a kind of immune function. As a third advantage, the modification prevents restriction by Mcr endonucleases. Lytic phages that mark their genome through modification are able to distinguish self from nonself (host) DNA (Villarreal 2005).

1.7.2 Persistent Phages Determine Bacterial Identity

In contrast to the T4 phage which is a well investigated acute (lytic) bacterial virus, phage lambda is a typical persistent virus. Persistent viruses have enormous impact on host genomes including recombination, immunity, and identity, including identification competence of (nonself) competitors. This identification competence is important for any population determining the variety of coordination processes within habitats with multiple bacterial populations, such as the human oral cavity (see above). The phage family of lambda seems to represent a large genetic pool which interacts continuously in the exchange and deletion, as well as in the assembly, of a variety of genes. For example, lambda and related P2 as well as P22 can recombine with each other although the core genes of lambda viruses are not conserved. However, they differ completely in the area of immunity. As a common feature of phage parasites, the persistent colonization of bacteria by

phages prevents infection by phage-related parasites. In this respect, the phage colonization of bacteria results in a symbiotic interaction with the immune function of the host that clearly determines host identity (Villarreal 2005). Persistent viruses have a bistable genetic switch that only allows the expression of genes which are associated with immune functions. With the expression of only one gene (cI), a lambda lysogen is immune to super-infection by phages related to lambda. Interestingly, other related persistent phages (P2, P22) differ in mechanisms of gene expression associated with immune function (Villarreal 2005). It seems likely that the most selective pressure on a persistent phage is that of resisting super-infection by related phages. In this respect, it can be understood why 12% of the P22 genome is dedicated to preventing growth of competing related phages.

Also P2 is a prevalent colonizer of E.coli and is much more prevalent than the lambda phage (Bertani and Deho 2001). Like other prophages, P2 integrates near to various tRNA sites (7bp anticodon loop) in a site-specific manner. Although P2 can be reactivated and is therefore not seen as defective, its lifestyle is clearly symbiotic in that it protects host bacteria from infection by competing (related) viruses. The fitness advantage for persistent P2 is that the host is not damaged by infection of lytic viruses. Interestingly, the feature of host immunity against competing viruses is derived from a persistent retrovirus in P2, whereby the reverse transcriptase coding element disrupts competitor genomes. This clearly represents a genetic agent that identifies and destroys nonself genetic competitors. P2 is activated to produce virions only if another infection by a satellite P4 family occurs, which as a defective phage propagates P2 activity (Villarreal 2005). P4 can be parasitized by a retron (a defective retrovirus). The result of this hyper-hyper-parasitation is phage R73, which is nearly identical to P4 but contains a retron (Villarreal 2005). It is important to notice, that this is only one example of an abundance of highly complex networks of interconnected relationships and interactions between various phages and their parasites. This is the real precondition for the evolution of higher order regulatory networks as it is found in eukaryotic life cycles. Also, the retron of P4 depends in its persistence on addiction modules, such as homing endonuclease genes and introns and inteins. Only the presence of the mobile intron element prevents homing endonuclease genes and therefore protects the host genome from P4 infection (Villarreal 2005).

The lysogenic lifestyle (nonlytic but persistent) of bacterial viruses is the result of a counterbalanced effect of two or more infection events on bacterial host genomes. If one of these counterparts is deleted or silenced, the other will be activated to produce virions or even a toxic component. This feature is of crucial importance for the host-population because it can kill host organisms and therefore also has consequences for host population density as well as symbiotic partners. On the other hand, it is important to notice that host identity is extended in an evolutionary sense because hosts of the same species, which are not infected by lysogenic phages, do not possess this immune function which protects them from infection by competing parasites. The investigation of biocommunicative competences of soil bacteria therefore crucially depends on identifying the persistent invaders of soil bacteria which determine their phenotypic features.

1.7.3 Addiction Modules Function as Counterbalanced Viral Competences

Addiction modules can be defined as features that consist in general of a stable toxic component which is counterbalanced by an unstable component which inhibits and suppresses the toxic component (Lehnherr et al. 1993; Yarmolinsky 1995; Lehnherr and Yarmolinsky 1995; Engelberg-Kulka and Glaser 1999; Rawlings 1999). Both are necessary to transfer a feature to the host without harming the host. In the case of a restriction/modification module, this means that, for example, 52 restriction enzymes are counterbalanced by 52 modification enzymes. This indicates how complex addiction modules are constructed and how difficult it can be to understand the evolution of such phenotypes (Villarreal 2009).

Several kinds of addiction modules are known. First of all and most prominent in bacteria life is the aforementioned restriction/modification addiction module, which is a common feature in the immune function. One part consists of an antitoxic modification enzyme, which is an unstable beneficial (protective) agent (Hayes 2003). The counterpart consists of a toxic restriction enzyme component, which is a stable but harmful (destructive) agent. Another kind of addiction modules consists of two related features. There is an antitoxic antipore-toxin which represents the unstable protective agent and a toxic component with a toxic pore which represents the stable but destructive agent. A third kind of addiction module consists of the antitoxic viral immunity component and the toxic component of viral-mediated lysis. This third kind is the most obvious viral-derived immune function because it necessarily consists of a persistent genetic parasite and an external lytic phage. Interestingly, one of the most common episomal phages, P1, is much more complex than other phages in that it assembles up to 100 genes and several addiction modules. This is necessary because of plasmid stability in daughter host bacteria and for the coordination of both cellular and host DNA replication (Lehnherr et al. 1993). This involves the integration of three different immune regions. One of these is a very efficient restriction-modification addiction module. Daughter cells which have lost the P1 episome will undergo postsegregational killing as a result of the toxic restriction enzyme not being balanced any further by a modification enzyme, which is lacking (Hazan et al. 2001; Villarreal 2009).

As mentioned above, the P1 prophage is interesting because it must express genes that orchestrate both replication of the viral DNA and of the host DNA. This is also seen in the P1 competence of highly coordinated DNA replication and segregation control. P1 achieves plasmid stability by coordinating plasmid and host chromosome replication (Villarreal 2009). In parallel, P1 has to partition stable viral chromosomes and additionally host daughter cells. This ability indicates that P1 can differentiate between self (viral DNA) and nonself (host DNA). In the case of the host E. coli, it also prevents competing genetic parasites. This clearly contradicts the selfish DNA hypothesis in that these behavioral patterns are symbiotic as they benefit both the virus and its host.

An important feature of these bacterial colonizers is that they are often colonized themselves. Secondary and tertiary genetic parasites (parasites of parasites of parasites) are further important features because they represent more complex capabilities which are transferred to the host that would otherwise not be present (e.g., introns of T-even phages). Interestingly, this type of virus–virus interaction is an important contributor to bacterial features.

In the case of P1, the restriction/modification addiction module is interconnected with methylated imprinting. The imprinted DNA is protected against this immune system whereas nonimprinted (unmarked) copies are destroyed. The imprinting must be transferred actively after replication to daughter cells by an epigenetic identity tag. If this epigenetic imprinting is disturbed by other parasitic elements, the counterbalanced addiction module will become out of balance. The antitoxin will not function and the stable encoded toxic part of the module will kill the cell (Villarreal 2009). Although a great number of restriction/modification addiction modules depend on site-specific methylated DNA against site-specific endonucleases, this is a rather costly process in terms of energy.

1.7.4 The Persistent Viral Lifestyle of Plasmids and the Role of tRNAs

Plasmids have a similar lifestyle to that of episomal persistent phages (Blaisdell et al. 1996; Brüssow and Hendrix 2002; Ding and Hynes 2009). Both are derived from viruses and both share a nonlytic but persistent lifestyle (Oshima et al. 2001). Both lack genes coding for virion production and most of them require a helper virus (satellite or another hyperparasite) for their mobilization. Both provide an advantage to their host that identifies and wards off competing parasites. Additionally, most of them share the coding of a specific integrase that leads DNA integration at specific sequence sites (syntax-identification competence) which is associated – interestingly – with specific tRNA genes. Both persistent lifestyles also transfer and incorporate virulence factors to their host, which are in most cases transferred as a singular transfer event. This can include the transfer of gene blocks with dozens of complete genes, with the result of a great variety of phage-related toxins. These virus-derived toxin genes have no host counterparts which clearly indicates their viral origin. Such toxins and other virulence factors are identity markers because they reproductively isolate their hosts from host counterparts or host relatives by postsegregational killing (Villarreal 2009).

Bacteriocins are well-studied plasmid encoded toxins (Riley 1998; Bull and Regoes 2006), which are highly active against related bacterial strains that lack this plasmid. This makes evolutionary sense because the generation of new and perhaps better strains in most cases serves as an advantage in colonization or even for adaptational purposes. Additionally, plasmids can code for restriction/modification addiction modules. Interestingly, some plasmids serve as acquisition sites

(traps) for other plasmids, transposable elements, addiction modules, and also immune modules. Such large plasmids are sometimes a kind of second chromosome. Transposable elements, which are clearly derived from viruses, are ancestors of plasmids (Cohen 1976; Villarreal 2009).

Let us return to the relationship between plasmids and phages to host tRNA. Interestingly, both the integrases of mobile plasmids as well as those from phages use the same tRNA integration sites. The pathogenicity islands, which are of great medical importance and represent a specific plasmid-mediated gene word order, affect immune identification and alter regulation of cell physiology (Hacker and Kaper 2000; Hayes 2003). More than 50% of them are associated with tRNA at a sequence junction at the site of integration. This seems to be an indicator that persistent phages are also involved, because phage integrases target tRNA DNA sequences (Villarreal 2009).

If we look at bacterial speciation, for example the relationship between E. coli and B. subtilis, then we can identify 230 regions which are quite dissimilar. Most of these regions are flanked by tRNA sequences which mark integration events. This means that the majority of speciation of these two species is the result of genetic infection events. Additionally, this is an indicator that tRNA not only plays a role in the transfer to translation, but that it also plays a role in higher order regulatory functions in general (Wegrzyn et al. 2001). Until recently the role of this kind of noncoding RNA, with its ancient and long lasting evolutionary history, was clearly underestimated (Maizels and Weiner 1993).

1.8 Swarming Group Behavior and Group Identity

Over decades bacteria were investigated as single organisms. Since the 1990s, this has changed significantly. The common behavioral patterns such as biofilm organization, mating, virulence, movement (fruiting body for sporulation), feeding, and colonization demonstrated that bacterial groups (colonies) are the rule rather than the exception (living in blooms, mats, biofilms). This indicates communication processes in which bacteria exchange signaling molecules (or tactile experiences) with the sensing of population density, nutrition availability, temperature, and light. Competition between related bacterial strains drives evolution and diversity. A group identification competence is necessary and will be the result of different modes of stable (persistent) infection by phages and plasmids – often mixed – via addiction modules. These phenotypes, such as restriction/modification, pore-toxins/antipore-toxins, endonuclease/antisense RNA, and holins/antiholins, serve as identity modules as well as immune modules and help to exclude bacterial strains which do not share these features (Villarreal 2009).

Viral infection changes molecular identity, immunity, and group identity of bacterial swarms. Quorum sensing as one of the sign-mediated coordination

processes based on chemotactic competences (Nadell et al. 2008a, b; NG and Bassler 2009; Mehta et al. 2009) is associated with memory and learning and coordinated movement (Ben Jacob 2009). Besides the addiction modules, specific surface receptors are necessary to sense small pheromone molecules and coordinate programmed cell death as a common strategy of nonselfish group behavior (Villarreal 2009). Programmed cell death in prokaryotes is a strategic behavior in that it protects bacterial strains from group (self) members which are successfully attacked and lose their group identity (Yarmolinsky 1995; Engelberg-Kulka and Glaser 1999). This results in the addiction modules being out of balance whereby the unstable antitoxic part does not function and leads to toxic results.

According to the abundance of prokaryotes in all ecological habitats and the highly dynamic gene flux, which depends on the infection rates with phages and plasmids, the relationship between viruses and prokaryotes is one of the most intense living processes on earth (Hendrix 2002). In particular, the complex multigene solutions and the high rates of natural genome editing (generation, combination, recombination, repair) serve for a wide variety of issues of host identity. Additionally, the viral inhabitants of prokaryotes are in constant interaction with competing parasites and their satellites, such as multiple hyperparasites. The focus of investigations on prokaryotes in general should be upon these interrelationships and the highly dynamic interactions between prokaryotes and the network of genetic parasites and hyperparasites. The prokaryotic social competences on which their group identity, group signaling, group behavior, and immunity depend are part of these interactional networks with viruses. An important fact is that these features cannot be separated into single investigations, just as the investigation of the syntax of a single word cannot result in an appropriate description of the function of a language. This indicates that the most basic natural genome editing processes are not the result of simple solutions but in contrast include highly relevant genetic order arrangements and dynamic rearrangements according to the adaptational purposes of their host organisms (Villarreal 2009).

Interestingly, the ability to identify self (members of a population which share same addiction modules) and nonself (members sensing others than self identity) can be lost when their identity is temporarily modified, such as when they are attacked by competing parasites, resulting in a slight genetic rearrangement. This results in (self) members killing other (self) members. Even a slightly changed genetic syntax can initiate attack upon (self) members (Villarreal 2009).

Addiction modules, such as restriction/modification, are also used as toxins against lytic phages in that lytic DNA is fragmented and (self) DNA is protected against degradation. Interestingly, some sporulating bacteria and unicellular eukaryotes (dinoflagellates) use controlled DNA fragmentation as a normal step in the cellular differentiation process. This is an indicator for a further addiction module wherein the previously destructive role of special toxins is used as an advantageous process for differentiation (Villarreal 2009).

1.9 Genetic Content Operators and Viral Gene Factories

These interactional networks may have serious consequences on our understanding of early evolution of RNA replicators into the cellular era of last universal common ancestors (LUCAs) (Witzany 2010). Both the coding competences to encode information about the genetic content operators and their catalytic function for synthesis (the catalytic phenotype and its genotype) need a high density of swarms that compete and interact. The former picture of a single LUCA which serves as matrix for replicating agents is not useful because coding competences in every natural language are no *solus ipse* features but depend on an interactional network. This is the precondition for creating sequence data and sequence abundance (Witzany 2010). Sequence generating creativity is the result of competing genetic parasites in that the creation of de novo sequences is a crucial factor for host group identity and group immunity. "As soon as the first replicator evolves parasitic replicators could also have evolved" (Villarreal 2009). The emergence of competent nucleic acid editors is interconnected with slightly different replicators which parasitize each other. This sign-biocommunicative community is highly selective and in parallel dependent on one another. This seems to be in agreement with the fact that viruses not only create and acquire new genes in very high rates within various viral lineages but the viruses within their host can act as gene factories. It seems most likely that the adaptational competences in the prokaryotic world are the result of this creative force of viral natural genome editing.

On the other hand, the vast viral genetic content available in the ocean as well as in soil habitats demonstrates that viruses both assemble and mix (arrange and rearrange) new genetic contents (Osborn and Boltner 2002; Kimura et al. 2008). In this respect, viruses are the masters of genetic content innovation and they fulfill this important role by creating interactional networks with complementing genetic parasites, epiparasites, and hyperparasites (Weitz et al. 2008). Some viral inhabitants of prokaryotes need helper functions by other parasites, which then parasitize the virus in order to make a specific phenotype available. It is necessary to look at a large pool of phages which colonize all of the prokaryotes and represent one of the most abundant genes for proteins on this planet, such as receptors and pore-forming proteins. Some phages change the expression of encoded phenotypes and create a diversity of receptors. In the case of the Bordatella phage, it has been shown that two variable gene regions are used to create a wide variety of receptors by a phage-encoded reverse transcriptase, which is an indicator of retroviral infection of the phage itself. The Bordatella phage not only provides a benefit for the host in its capability to create variable gene products for both the host and phage self-identification, but is also clearly a forerunner of the vertebrate adaptive immune system (Villarreal 2009).

If these interconnected networks in real-life habitats are reduced to laboratory settings for the purpose of study, the conditions for interactions are changed dramatically. We then investigate simple prokaryotes without the interactional context of their persistent parasites, competing parasites, or complementary epi- as

well as hyperparasites. We would then have no idea how these viral agents contribute to host fitness.

If we look at a special kind of such parasites of phages, we can identify RNA sequences which act as introns in the phage genetic content. They themselves are encoded in DNA. The three groups of introns are group I introns, group II, and group III introns. They date back to the early RNA world and play important roles as transposable elements that act as regulatory elements and ward off genetic parasites. They are now recognized as stable persistent virus-like agents (homing endonucleases) that serve as identity parts for host immunity. Additionally, these homing endonucleases serve as sequence specific toxins (holins) that can kill related bacterial strains which have not been colonized by these particular parasites (Young 2002; Ziedaite et al. 2005; Villarreal 2009).

1.10 Conclusion

Bacteria, which in former times were viewed as lower life-forms, have now been recognized as masters of monitoring, computing, interpretation, coordination, and organization. Bacterial communicative competences are sign-mediated interactions between the same or related species, but also between nonrelated species according to different situational contexts (pragmatic level of analyses) and the coherent combinatorial patterns of signals according to the molecular syntax (syntactic level of analyses).

The situational context determines the content of the messages (semantic level of analyses), the meaning of signaling molecules for a bacterial community which shares a common background memory and a competence for culture-dependent interpretation which is an advantage for adaptational purposes. Maybe this concept of investigations can be applied to other kingdoms in the future to reach a unifying perspective for transdisciplinary research beyond the borders of increasing specialization.

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