REVIEW

Bio-Communication of Bacteria and its Evolutionary Interrelations to Natural Genome Editing Competences of Viruses

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ABSTRACT

Communicative competences enable bacteria to develop, organise and coordinate rich social life with a great variety of behavioral patterns even in which they organise themselves like multicellular organisms. They have existed for almost four billion years and still survive, being part of the most dramatic changes in evolutionary history such as DNA invention, cellular life, invention of nearly all protein types, partial constitution of eukaryotic cells, vertical colonisation of all eukaryotes, high adaptability through horizontal gene transfer and co-operative multispecies colonisation of all ecological niches. Recent research demonstrates that these bacterial competences derive from the aptitude of viruses for natural genome editing.

In contrast to a book which would be the appropriate space to outline in depth all communicative pathways inherent in bacterial life in this current article I want to give an *overview* for a broader readership over the great variety of bacterial bio-communication: In a first step I describe how they interpret and coordinate, what semiochemical vocabulary they share and which goals they try to reach. In a second stage I describe the main categories of sign-mediated interactions between bacterial and non-bacterial organisms, and between bacteria of the same or related species. In a third stage I will focus on the relationship between bacteria and their obligate settlers, i.e. viruses. We will see that bacteria are important hosts for multiviral colonisation and virally-determined order of nucleic acid sequences.

1. INTRODUCTION

Bacteria communicate and therefore are able to organize and coordinate their behavior similar to a multicellular organism.[1,2] We refer to communication processes as interactions mediated by signalling processes, i.e. sign-mediated interactions. Signs are, in most cases, chemical molecules (in some cases also tactile interactions, i.e. specific behavior) which serve as signals both within and between prokaryotic organisms. Most 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.[3] 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.[4] 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.[5] More than in any other organismic kingdom it is in common use to speak about the languages and even dialects of bacteria.[6-11]

Quorum sensing is the term of description for sign-mediated interactions in which chemical molecules are produced and secreted by bacteria.[12-15] They are recognized by the bacterial community dependent on a critical concentration and in a special ratio to the population density.[16,17] These molecules trigger the expression of a great variety of gene transcriptions. Many bacteria use multiple quorum sensing codes; each may be modulated by post-transcriptional or other regulatory engineering.[18]

There are also communication processes between different species of bacteria (some term it bacterial Esperanto) and between bacteria and non-bacterial life such as eukaryotic hosts.[19] Beneath the semiochemicals (Gr.: Semeion = sign) necessary for developmental processes of great variety 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.[20-23] Also, abiotic influences serve as signs which indicate specific nutrients or other environmental circumstances such as hydro- or heatdynamic changes.

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.[24] 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.

We can differentiate three classes of signalling molecules for different purposes, i.e. signalling within the organism to coordinate gene expressions to generate adequate response behavior, signalling 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 and defence. 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.[25,26] 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.[27,28] 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[11] 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 context-dependent

meaning of signals which act as signs, and pragmatic aspects, which focus on the variety and differences of the behavioral patterns in common-goal coordination, shared knowledge, memory and mutual intentions. Apart from that, it is coherent with the presupposition by Charles Morris of any non-reductionistic analysis of language-like structures, the complementarity of syntax, semantics and pragmatics.[29]

2. BIOFILM ORGANISATION: SIGN-MEDIATED COORDINATION

Bacteria have profound effects on human health, agriculture, industry and other ecospheres. Therefore they target the multiple drugs which fight them.[30] They develop drug resistance by coordination of special defensive behavior called biofilm organization. Biofilm organization is a special kind of coordination with a high density of physical contact and contact-specific signalling.[2] 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.[31] 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 cough remembers like persistent the mucus in the bronchial tube remained.

Nutrient availability also regulates the structure of biofilm organization[32] as hydrodynamic forces.[33] Interestingly, it has been found that biofilm organization is linked with coordinated DNA release which is integrated in the biofilm.[34]

3. SEMIOCHEMICAL VOCABULARY and COMMUNICATIVE GOALS

The sum of the semiochemical vocabulary each used by different bacteria is of great variety, especially because some signalling molecules are multiple reusable components.[35] Acyl homoserine lactones (AHLs) and linear oligopeptides are used as signs in diverse processes. Cyclized oligopeptides function as virulence genes. g-Butryolactones (GBLs) are used as antibiotics and in sporulation processes. Furanosyl diester (AI-2) is used in diverse processes[36] 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.[37,38] Gram-negative bacteria use homoserine lactones (LuxR/LuxI) as signs in communication processes,[7,39] whereas Gram-positive bacteria use oligopeptides in quorum sensing communication. As in all organisms non-coding RNAs are important in higher order regulatory pathways. 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,[40,41] e.g. in controlling the quorum sensing pathways.[42]

At present, three kinds of communicative goals are distinguished: (A) reciprocal communication, active sign-mediated interactions which are beneficial for both interacting parts; (B) 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; (C) signalling to manipulate the receiver, i.e. to cause a response behavior which is one-sided – beneficial to the producer and harmful to the receiver,[38] often in that they behave against their normal goals.[43]

The three classes of intra-, inter- and metaorganismic (trans-specific) communication enable bacteria to generate and coordinate different behavioral patterns: self and non-self

identification, i.e. 'recognition' and identification of 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 non-bacterial organisms the signalling molecules bind to specialized sensor proteins which function as receptors. They transmit the message to an intracellular regulator,[44,38] i.e. the signal molecule transits the cell membrane through diffusion or by specific transport pathways. Inside the cell the signalling 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.[38] Organization of cellular production of response molecules leads to signal-dependent transcription control of DNA.

Bacteria have to distinguish between species-specific signalling and signalling which is able to modulate behaviors interspecifically.[8] With these communicative competences they are able to coordinate species-specific behavourial patterns as well as to coordinate behaviors between diverse species.

4. COMMUNICATION OF BACTERIA WITH NON-BACTERIAL ORGANISMS

Starting with beneficial symbioses between bacteria and plants we refer to the complex communication networks between soil bacteria, mychorrizal fungi and plant roots.[45-47] 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. 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 signalling molecules, either to trigger bacterial production of special molecules or to disturb bacterial communication pathways.[40,42,15]

Rhizobia bacteria are integrated into plant cells by phagocytosis when they interact symbiotically with the plant roots.[48] In other cases where rhizobia fail to fix nitrogen inside the root nodules because they are being deceptive, plants are sanctioning these rhizobia[49] and prevent their spread in order to stabilize mutualistic symbioses with bacterial colonies.[43] 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.[45,46] The full range of trans-specific communication processes between bacteria and plant roots are important for developmental and growth processes in the entire plant kingdom.[13,50]

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'.[51]

Marine eukaryotes are able to mimic bacterial quorum sensing to inhibit bacterial successful communication.[52] Interbacterial communication uses hormone-like signalling 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 signalling molecules.[53]

Living as endosymbionts as potential candidates for symbiogenesis[54-57] as documented in the origin of eukaryotic endosomes like mitochondria, indicates the important role of bacteria for the entire history of evolution.[58] 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.[59] 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,[60] most of them bacteria.

5. SOCIOBACTERIAL COMMUNICATION

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.[61,62] 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.[63,64,1] Bacteria use intraspecific and interspecific signalling in all ecological *in vivo* situations.[43] This also implies a broad variety of conflicts within and between species.[65] The mutual, neutral and manipulative aims of communication processes are special kinds of response behavior to certain degrees of beneficial up to conflictual relationships.[43]

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 genomic 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.[11,64] This functions similar to neuronal networks in higher eukaryotes. 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.[37,66]

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.[67,68]

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[11] of the context-dependent decision. The identification of non-self 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.[69] Interestingly, the prokaryotic cell–cell communication has structural analogues to cross-kingdom signalling between bacteria and fungi.[70]

Some bacterial species decide, in special cases, to form fruiting bodies of different types and shapes for sporulation. This enables these bacterial communities to more efficiently disseminate the spores. The fruiting body building is governed by context-specific rules with different roles for different sub-groups of bacterial communities for coordination.[71] 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', [65,11] which do not follow the rules for coordinating this special behavior.

One of the most interesting and best investigated phenomena of bacterial communication is the *symbiology* of multiple colonies coexistent in the human oral cavity.[72-74] 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.[75] The homeostasis is not static but is the result of a dynamic relationship between different species-colonies dependent on intervals of daily hygiene. The interacting species number approximately 500 different species.[76-78]

Each member of these communities must be capable of self and non-self distinction, and be able to distinguish between species-specific signalling and trans-specific signalling or even 'noise' (no biotic signal, no abiotic index). As a community they must be able to measure their own colony size and the size of the other colonies and distinguish 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 (i) metabolite exchange, (ii) cell–cell recognition, (iii) genetic exchange, (iv) 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. 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.[72,73]

6. COMMUNICATION PROCESSES WITHIN BACTERIA

Interestingly, prokaryotic gene order is not as conserved as the sequences which code for proteins. 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.[79,80] 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 exemplified excellently by Thomas and Nielsen.[81] Thus we can recognize the outcomes of a diversity of mobile DNA contents,[82] not a mass of individualized genetic texts, but a bacterial gene pool as a text repertoire which is available for each individual bacteria and the resource for bacterial genome innovation and evolution.[83] 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.[84-86] Important in this context of genomic innovation is not the sequence acquisition alone but also the contextualization,[87] it means also their loss.[88] It seems now that the 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.[89,90]

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.[91] 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.[92]

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.[93-97]

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 extremely 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 colonised by them, in most often cases in the form of multiple colonisations.[98] 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 colonise them. 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.

Lytic versus 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, non-lytic viruses are decisive for species diversity and host genome editing. Nearly all natural genome editing competences represented in the conservation of expression, transcription, translation and recombination with all their detailed steps seem to derive from viral aptitudes. Even the DNA replication pathways, after a period of early RNA influence,[99-101] seems to be a special viral strategy for the conservation of coded phenotypes by warding off RNA parasites.[102,92]

Since observations have become more evident that viruses are able to integrate genetic material into the host genome, it has become clear that some viruses have lytic infection lifestyles but others also endosymbiotic and even symbiogenetic lifestyles. They bestow phenotypic capabilities on the host which non-infected 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.[103]

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.[104] Most often the integration occurs by mutual neutralisation of toxic capabilities by an antitoxin of a competing genetic settler.[105] The whole range of toxin/antitoxin addiction modules we can find througout all genetic contents in living nature

most likely is of viral origin.[92] Therefore the persistence is sometimes called temperate lifestyle. A good example is the persistent virus in all Symbiodinium species being the essential endosymbiotic partner for coral animals. Coral bleaching as a worldwide phenomenon of coral disease is the consequence of dying of the coral endosymbiont because of global (water) warming. As we know now, death occurs because the persistent viruses of Symbiodinium become lytic as a reaction to the changing water temperature.[92]

Also bacteria may be infected by viruses without being harmed. If infected bacteria meet non-infected bacteria it may be that the non-infected acquires lysis; the lysogenic strain does not lyse itself, but is lethal to the non-infected one. The colonized bacteria has a virus-derived molecular genetic identity which has an advantage against the non-infected one through an acquired ability. This lysogenic bacteria, termed prophage, has an immunity function for the bacteria which the non-infected bacteria lack. Prophage is a virus that is integrated into the bacterial host genome. Both the acute lytic phages and the persistent prophages are highly abundant in oceans and in the soil and seem to be the most dynamic life form on the entire planet. Some viruses are not integrated in the host genome but persist as plasmids and replicate independently from the host genome.[92]

When we speak about the relationship of bacteria and viruses in most cases we speak about phage ecology. 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 [92] in acute lytic and in persistent phages. This is documented in the very different nucleotide words (di-, tri- and tetranucleotides). Nucleotide word frequences of acute phages are very dissimilar to those of their hosts while persistent or temperate phages share nucleotide word frequences 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 pathways need a completely different semantic content in the genome expressed in a different syntactic arrangement of nucleotides.[98]

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.[92]

Bacterial DNA does not have highly stable structures as do eukaryotes and can interact with the cellular replication and transcription. In most cases it is circular with a unique origin of replication system. 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.[92]

Bacteria as biotic matrix for natural genome editing

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.

As new research indicates the agents of horizontal 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.[106] 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.[107] Phages, plasmids, retroplasmids and transposons therefore played a crucial role in bacteria evolution.[108] 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.[66]

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 1ml 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.[91] 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.[109]

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.[110,111]

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 non-self 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 non-lytic viruses.[112,106] As phylogenetic analyses demonstrate, the main protein enzymes for natural genome editing are viral inventions and not of cellular origin.[92,103] Also, the origin of eukaryotic nucleus was thought to be an ancient prokaryote but phylogenetic analyses show that its ancestor seem to be a large DNA virus.[113-115] 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.[116-118]

Bacteria successfully escaped from selective pressure of the early RNA-world

For a long time bacteria have been considered to be the forerunners of the eukaryotic superkingdom. Although the evolution of eukaryotes did not occur by random mutations of bacterial genomes but by integration and natural genetic engineering of former free-living prokaryotes[25] the key features of the eukaryotic nucleus have less in common with prokaryotic competences than with some double-stranded (ds)DNA viruses.[98] The textbook conviction of the early 21st century on the evolutionary history of eukaryotes was that an ancient prokaryotic cell was colonised by a large dsDNA virus and afterwards by mitochondria-like and chloroplast-like bacteria which together built the first eukaryotic cell. This scenario makes sense from a cytological perspective, because prokaryotes are much simpler than eukaryotes. From the perspective of an early RNA world, however, this view changes.

A biosemiotic "virus-first"-scenario would look like this: At the beginning there were singlestranded unencapsidated RNA molecules with their aptitude to replicate themselves and through both their coding and catalytic capabilities built complex structures with multiple functions to form dsRNA genomes in a pre-protein world.[119] If we term these pre-cellular RNA replicators as viruses then ssRNA viruses evolved into dsRNA viruses. Via a reverse transcriptase function present in a RNA-dependent RNA-Polymerase[120,121] these dsRNA viruses evolved later on into dsDNA viruses. Now the stable DNA of dsDNA viruses was an advantageous competence to colonize the instable nucleotide word order in genomic contents of RNA viruses. In parallel DNA of dsDNA viruses served as appropriate habitat for infection events by retroid agents. Holding these colonization interrelations in a non-lytic but inheritable persistent status infection forced the colonised RNA viruses to establish a bi-layered cell membrane and to encapsulate the genome in a porous nuclear envelope.

Especially these steps from ssRNA to dsRNA and from dsRNA to DNA are hallmarks in the evolution of life from a prebiotic assembly of ribonucleotides into a functional agent with simple nucleotide grammar editing competences. But this has to include a self non-self differentiation capability being able to ward off competing agents through the first immune function similar to RNAi represented by repeated sequences. In parallel this would have been an advantage to colonize RNA replicators which lack this ward off capability.

Interestingly even today we can look at relics of precellular evolution in both RNA viruses and viroids. Viroids and its monophyletic sister group satellite RNAs are short circular ssRNAs whereas viroids are unencapsulated but satellite RNAs are encapsulated. We know that viroids share an extreme plasticity of their nucleotides sequences being the most rapidely evolving biological agents.[122-125] Important features of small RNAs such as RNA silencing seem to derive from viroid competences.[126-128] Most conserved competences of RNA viruses and viroids are RNA stem-loop structures which play important roles in priming and replication with an inherent self/non-self differentiation in that they determine RNA replication to viral and not to host RNA molecules.[92]

We now can imagine eukarya-like dsDNA viruses with both the ribozymatic function of endonuclease competent in RNA-splicing, excision of introns out of tRNAs,[129] integration of retroid DNA[130] and its key features, double membrane, linear chromosomes with telomere ends, intronic elements with regulatory functions,[131] segregation of transcription and translation and the subviral competences which we find in the ribonucleoprotein structures of pre-mRNA, pre-tRNA und pre-rRNA all processed by small nucleolar (sno)RNAs and small nuclear (sn)RNAs. As we know today the precursor RNAs are a highly sophisticated network of regulatory patterns each of them with a separate RNA processing pathway. Especially linear chromosomes with telomere repeats, the ancient nuclear pore complex[132] and the highly mobile genetic settlers inherent in introns being competent in RNA-splicing we do not find in any prokaryote but – interestingly - in eubacterial and archaeal phages.

Additionally prokaryotes share a circular genome with nearly intron-free genetic syntax, whereas the seemingly evolutionary later eukaryotes have linear chromosomes with telomere repeats to protect their ends against genetic invaders and highly colonised genomes by virus derived agents such as transposons, retroposons and related genetic settlers.

Although the "error-prone" coding-fidelity of the RNA world at the beginning was an advantage for fast adaptations the evolutionary target evolved into both the relatively stable DNA configuration (via the reverse transcriptase competence - the only encoded function common to *all* retroelements) and the resistant protein world necessary in high temperature environments found in the habitats of archaeal populations. Prokaryotes lack the key features of the early RNA world and therefore they would appear to be specialized fast-adapting single-celled organisms using the advantages of stable DNA storage medium coding for highly temperature resistant protein structures to protect this storage medium.

Although accelerated ssRNA processing of mRNA, tRNA and rRNAs in linear RNA genomes built core competences of natural genome editing in the early RNA world those ssRNAs without cellular habitats are extremely thermolabil and could not survive in high temperature environments.[133] The lack of RNA correction and repair and the high rate of replication combined with innovation allowed a replication rate of 1-10 x 10^6 times faster recombination events than DNA genomes.[130] RNA-based lifeforms could evolve millions of times faster than DNA-based systems. This was an advantage for the exploration and invention new sequence space, i.e. new genomic content with phenotypic competences and functions. In contrast circular genomes with few higher order regulatory elements (represented by a diversity of genetic parasites present in intron-like genomic habitats) have more advantages in a high temperature environment and could adapt faster because of their ability to exchange selected phenotypes within and between protein-coding data-sets as happens in horizontal gene transfer. So RNA cultures with eukaryote-like RNA-processing seem to predate the evolution of prokaryotes which adapted to fast-changing environmental conditions by reducing their genomic content to a DNA with nearly analog (intron-free) protein-coding data-sets. This could be the evolutionary pathway from ribozymes of the early RNA world to ribonucleoproteins via low complexity RNA-chaperones to a DNA-protein-based life.[122,133-135] That eukarya-like genomes predated prokaryotic genomes is coherent with the existence of telomeres and telomere-like functions in ancient dsDNA viruses which seem to be the ancestors of eukaryotic nucleus and are not part of prokaryotic genomes although some are found in persistent bateriophages.[136]

In the bacterial expression of target genes at the posttranscriptional level also multiple small regulatory RNAs play important roles. They are immediately available after being transcribed from the non-protein-coding sections of bacterial genomes unlike protein enzymes which must be translated too.[137-141] From the perspective of evolutionary history bacteria seemed to reduce the predated RNA-based metabolism of early eukarya-like genetic content arrangements to become specialised (in higly-selective environmental conditions such as high temperature and/or fast-changing nutrient availability) dependent on nearly intron-free DNA-protein metabolism,[142] constituting circular genomes with only one starting-point for replication. Because intron-rich linear chromosomes are the preferred habitat for persistent retroviral infections and their important role on host-genetic content (re)arrangements the invention of bacterial circular genomes must have an effective immune function against retroviral infections. The result was the evolution of organisms which successfully escaped high selective pressures of the early RNA world.

SUMMARY

For a long time bacteria have been assumed to be the most primitive organisms and consequently investigated as single-cell individuals determined by mechanistic input-output

reactions. Now this picture has changed radically. Today we know that bacteria are parts of bacterial communities which interact in a highly sophisticated manner. The medium of every bacterial interaction is communication, i.e. sign-mediated. A wide range of chemical molecules serve as signs through which bacterial communities exchange information and act in reaching a "quorum" which is the starting-point for decision-making: one of many different behavioral patterns will thereby be organised, such as biofilm organisation, bioluminescence, virulence or sporulation. Quorum-sensing is not only chemotaxis, but includes interpretation, which means that the incoming signals are measured on the background memory of the species-colony in their real life world. The interpretation before decision-making, coordination and organisation, such as fruiting body formation and cooperative hierarchical organisation, is context-dependent.

Bacteria, which in former times were viewed as lower life-forms, have now been recognised as masters of monitoring, computing, interpretation, coordination and organisation. Bacterial communicative competences are sign-mediated interactions between the same or related species, but also between non-related 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), both determining the content of the messages (semantic level of analyses), the meaning of signalling 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.

Additionally Bacteria seem to be the comfortable habitat for natural genome editing competences of persistent viruses throughout he whole history of life.

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