Here we evaluate our current understanding of the function of the nervous system in *Hydra*, a non-bilaterian animal which is among the first metazoans that contain neurons. We highlight growing evidence that the nervous system, with its rich repertoire of neuropeptides, is involved in controlling resident beneficial microbes. We also review observations that indicate that microbes affect the animal’s behavior by directly interfering with neuronal receptors. These findings provide new insight into the original role of the nervous system, and suggest that it emerged to orchestrate multiple functions including host-microbiome interactions. The excitement of future research in the *Hydra* model now relies on uncovering the common rules and principles that govern the interaction between neurons and microbes and the extent to which such laws might apply to other and more complex organisms.

1. Introduction

What is the nervous system for? Until recently, the answer to this question was very obvious. Nervous systems evolved to function as sensory inputs, integration units, and motor output. From the beginning of animal evolution around 540 million years ago, the “invention” of a nervous system allowed animals to perceive signals from the environment and to respond to them by, for example, moving in an active, organized fashion.[1,2] In vertebrates, nerves in the somatic system connect the brain and spinal cord with muscles and sensory receptors in the skin. In addition, the autonomic nervous system regulates processes such as blood pressure and the rate of breathing. Billions of years before the “invention” of the nervous system in organisms such as Cnidaria, prokaryotes shaped (and continue to shape) the Earth. Animal evolution, therefore, appears intimately linked to the presence of microbes.[3] A continuously increasing number of studies universally demonstrates that individuals from sponges to humans are not solitary, isolated entities, but consist of complex communities of many species that likely coevolved during a billion years of coexistence.[4] We refer to these associations, that can be analyzed, measured, and sequenced, as “metaorganisms.” The metaorganism concept considers the dynamic communities of bacteria, archaea, fungi, and viruses on epithelial surfaces as integral to the functionality of the host (Figure 1A).[5,6] From the above it is obvious that animals that invented the first nervous system during evolution did so as metaorganisms and in the context of a complex colonizing microbiota. One such early emerging organism is *Hydra*, a freshwater polyp belonging to the phylum Cnidaria, which is the sister group of Bilateria (Figure 1B).[7] Importantly, since the Cnidaria branched off before the emergence of the mesoderm in the Bilateria lineage (Figure 1B), any specialized migrating immune cells of mesodermal origin are absent in *Hydra*.

Here we review recent findings that provide new perspectives on the intricate dialogue between the *Hydra* polyp and its microbiota and the nervous system. We outline the emerging concept of the central role that the nervous system plays in mediating the *Hydra*-symbiont communication and speculate on the possible evolutionary trajectories of early nervous systems. We conclude that nervous systems have multiple functions and evolved as much to control the microbiota as to function as sensory inputs, integration units, and motor outputs.

2. Main Text

2.1. *Hydra* Has a Simple Nervous System

*Hydra* possesses one of the anatomically simplest nervous systems—a diffuse nerve net spread throughout the body with no signs of centralization (Figures 2 and 3A). It is made up of about 6,000 nerve cells belonging to two morphological types—sensory and ganglion neurons.[9,10] The neurons constantly develop from the multipotent interstitial stem cells, and are assembled into two apparently autonomous nerve nets intercalated into the ectodermal and endodermal epithelial layers.[11,12] In spite of this morphological simplicity, *Hydra* demonstrates a surprisingly rich behavioural repertoire: spontaneous periodic contractionstion and extension of the body and tentacles, contractions in response to mechanical stimuli and light, complex feeding behavior and somersaulting locomotion (refs. [13–16]; for recent review see ref. [17]). All these behaviors are under the control of the nervous system, as evidenced by experiments on neuron-ablated polyps.[18,19] In addition to this conventional role in coordinating motor activities, the nervous...
system in Hydra appears to be orchestrating other organismal functions, such as development, tissue homeostasis, and immune function. However, the mechanisms behind these non-conventional functions remain largely unclear. The combination of diverse in vitro techniques, such as in situ hybridization, immunofluorescence, and electrophysiological measurements, and recently developed in vivo imaging and behavioral recordings, promises deep insights into the molecular architecture and function of the nervous system in Hydra (for review see ref. [17]).

2.2. Hydra Harbours a Stable Microbiota

As in other animals, the epithelial surface of Hydra is densely colonized by a stable multi-species bacterial community (Figures 1A and 3A).25-27 The presence and structure of this microbiota is critical for the tissue homeostasis and health of the polyps.25 Remarkably, each Hydra species supports long-term associations with a different set of bacteria, suggesting that the host imposes specific selection pressure onto its microbiome, and regulates its microbiota density, species composition, and spatial structure.27-28 Until very recently, the epithelial cells of Hydra were considered as prime regulators of the microbiome.26,29,30 In fact, ectodermal and endodermal cells were shown to express components of signaling pathways for bacterial recognition, such as TLR and NLR,27 and to produce antibacterial factors by epithelial cells. In line with that theory, AMPs of the arminin family were later found up-regulated in Hydra polyps depleted of nerve cells.38

Using a similar approach, Fraune et al. showed that eliminating nerve cells dramatically changes the composition of the microbial community on Hydra in vivo.36 Animals lacking neurons demonstrated a 10-fold reduced abundance of β-Proteobacteria accompanied by a 10-fold increased abundance of Bacteroidetes (Figure 3D). Interestingly, the overall density of bacteria on Hydra remained unaffected. Although these findings provided evidence for the significance of nerve cells in host-microbiome interactions, it remained unclear whether the observed changes were due to the loss of some neuron-derived antibacterial factors, or due to altered epithelial immune response unleashed from the nerve cell control.

2.3. Hydra Neurons Shape the Microbiota

First hints of the non-conventional roles of Hydra’s nervous system were found in Hydra polyps depleted of neurons. Early observations of KasaHara and Bosch in 2003 revealed a strong correlation between the number of neurons in Hydra and the antibacterial activity of the tissue in vitro (Figure 3B and C).35 In fact, Hydra tissue lacking neurons had a drastically enhanced antibacterial activity against Gram-positive Bacillus subtilis and Gram-negative Escherichia coli bacteria. This suggests that neurons may actively take part in regulation of the polyp’s antibacterial response and negatively control the production of antibacterial factors by epithelial cells. In line with that theory, AMPs of the arminin family were later found up-regulated in epithelia of Hydra polyps depleted of nerve cells.38

Figure 1. A) Multicellular animals are metaorganisms composed of the macroscopic host and synergistically interdependent bacteria, archaea, viruses, and numerous other eukaryotic species including fungi, and algal symbionts. This host-associated microbiota is continuously interacting with the environmental microbes, which can colonise the host transiently or permanently. Adapted with permission. Copyright 2013, Annual Reviews, Inc. B) Hydra belongs to the phylum Cnidaria, the sister group of Bilateria. The first nervous system emerged before the radiation of Eumetazoa, and hence the emergence of the nerve system predates the origin of the mesoderm and specialized immune system.
column. Additionally, NDA-1 is highly potent in killing Gram-positive bacteria. Strikingly, other neuropeptides, such as *Hydra*-specific Hym-357 and Hym-370 and a member of the highly conserved RFamide family, all previously characterized as classical neuromodulators eliciting motor activity, turned out to be also potent against Gram-positive bacteria (Figure 3G).\textsuperscript{37} Taken together, these findings indicate that distinct nerve cells contribute to the composition and spatial structure of *Hydra’s* microbial community by expressing a variety of neuropeptides with distinct antimicrobial activities.

Figure 2. A) The *Hydra* nervous system is a simple diffuse nerve net, as revealed here by expression of the RFamide neuropeptide (green). Local condensation of RFamide-positive neurons is observed around the mouth opening (hypostome) of a polyp. Two morphological types of nerve cells compose the nerve net – sensory (S) and ganglion (G) neurons. Muscular fibres of the epithelial cells are detected by phalloidin (red). B) A ganglion neuron with characteristic multiple projections located on the mesoglea, between the muscular protrusions of the epithelial cells. DNA in the nuclei is detected by TO-PRO (blue) C) A sensory neuron located between the epithelial cells, reaches the epithelium surface with its sensory cilium (arrow), the projections are located between the muscular protrusions of the epithelial cells. Note the secretory vesicles filled with the RFamide neuropeptide (green) in both, ganglion (B) and sensory (C) neurons.
Figure 3. Key observations providing evidence for the intricate dialogue between the nervous system in *Hydra* and its commensal microbiota. A) Nerve cells are localized within both epithelial layers of *Hydra*, ectoderm and the endoderm. Some neurons reach the surface of epithelium, where they secrete antimicrobial peptides and contribute to production of the glycosalyx. This complex mucus layer is the major habitat for *Hydra*-associated symbiotic bacteria. B,C) Depletion of the interstitial lineage, including the neurons, in *Hydra* polyps increases the antibacterial activity of the tissue. Normal *Hydra* sf-1 strain polyp (B) and a sf-1 animal depleted of neurons (C) with corresponding radial diffusion assays against *Escherichia coli* (insets on B and C). Adapted with permission.[35] Copyright 2002, Elsevier. D) Elimination of the neurons leads to drastic changes in relative abundances of β-Proteobacteria and Bacteroidetes. Adapted with permission.[36] Copyright 2009, Society for Applied Microbiology and Blackwell Publishing Ltd. E–F) Neurons produce antibacterial substances and shape the microbiome. In situ hybridisation (E) and immunochemical staining (F) reveal the production of the antimicrobial neuropeptide NDA-1 by sensory and ganglion neurons in the hypostome of *Hydra*. The sensory cilia of the neurons (arrows) revealed by phalloloidin staining of the actin fibres (red) reach the epithelium surface and likely receive bacterial cues. C) Not only NDA-1, but also myoactive Hym-370, Hym-357, and RFamide-like neuropeptides have distinct antibacterial activities. Reproduced under the terms and conditions of the Creative Commons Attribution license 4.0.[37] Copyright 2017, the authors, published by Springer Nature. H–J) The specific associated microbiota affects behavior in *Hydra*. Normal *Hydra* polyps with undisturbed microbiota show regular spontaneous body contractions (H and I; full body contractions marked with blue arrows). Removal of specific microbiota reduces the contraction frequency (on J: Germ-free), while recolonization with a mixture of the five main bacteria in equal proportions (5 Bact.), or with natural *Hydra* microbiota (Convent.) substantially restores the normal behaviour. Reproduced under the terms and conditions of the Creative Commons Attribution license 4.0.[24] Copyright 2017, the authors, published by Springer Nature.
2.4. Microbes Affect the Nervous System and Behavior in *Hydra*

The communication between the microbiota and the nerve cells in *Hydra* appears to be bi-directional. Recently, we showed that symbiotic bacteria modulate the nervous system activity and behavior in *Hydra*. Germ-free animals display strongly reduced and less regular spontaneous body contraction frequencies (Figure 3H–J). Importantly, the effects can be partly restored by reconstituting the native microbiota in its natural species composition and proportions. These findings strongly suggest that it is not the presence of a microbiota per se, but its precise species structure that modulates the behavior of *Hydra*. Further, we showed that a soluble molecule produced by bacteria may be involved in the contraction frequency modulation. Because disturbances in the microbiota primarily affect the regularity of contractions, we suggested that bacterial products may target the pacemaker neurons, which are responsible for timing of contractions in *Hydra*. Further, our studies indicate that the presence of a microbiota is essential for another behavior in *Hydra*—the feeding response (Murillo, Klimovich, Bosch, in prep.). In the absence of specific bacteria, the feeding response of the polyps is significantly shortened. Taken together, these findings provide a clear indication that the symbiotic bacteria may have a broad impact on *Hydra* neuronal activity, behavior, and physiology.

2.5. Commonalities Between *Hydra’s* Immune and Nervous Systems

*Hydra* has an elaborate innate immune system: operating mainly with a plethora of antimicrobial peptides, mostly secreted by multi-functional epithelial cells, it shapes the colonizing symbiotic microbiome. We proposed earlier that the *Hydra’s* immune system may have evolved not so much to defend against pathogens but to keep the metaorganism in balance. Interestingly, the observations presented above suggest that neurons in *Hydra* perform similar functions to the immune system in addition to their role in controlling body motility. Neurons produce antimicrobial peptides that contribute to shape the species-specific microbiome. Both systems therefore appear to be essential regulatory units within a given metaorganism. Both the immune and the nervous system in *Hydra* actively monitor the environment and recognize and respond to microbial cues, exhibiting a fairly high degree of plasticity. We note that these emerging commonalities are consistent with findings in more complex animals and in agreement with the view that the immune and nervous systems may represent analogous evolutionary solutions.

2.6. Rethinking the Role of the Nervous System

The importance of the above-cited findings stretches beyond *Hydra* biology, and may shed light on the evolution of the nervous systems in the animal kingdom. All multicellular animals emerged in a world that was already densely populated by microbes, and all extant animals are multiorganismal and colonized by a large number of symbiotic microbes. Animal evolution, therefore, is deeply influenced by the presence of microbes. The emergence and evolution of the nervous system must be also considered in the context of host-microbe interactions. Appearance of the first nervous systems provided early metazoans an unprecedented benefit in terms of sensory input and motor output. The emergence of the first nerve cells was one of the major evolutionary transitions in the history of multicellular life and, remarkably, predates the emergence of the mesoderm (Figure 1B). Hence the nervous system predates the first specialized cell types performing immune function (i.e., macrophage-like circulating haemocytes or blood cells). A variety of studies on bilaterian models has revealed that the
host-associated microbiota is in a permanent dialog with the host enteric and central nervous systems: these insights were the foundation of the “microbiota-gut-brain” axis paradigm. Our recent studies demonstrate the existence of such communication in non-bilaterian animals as well, and suggest a universal role of the nervous system in mediating host-microbe interactions throughout the Metazoa. This ubiquity indicates that the neuron-bacteria interactions have a deep evolutionary origin, dating back to the emergence of the nervous system itself.

This thinking casts a new light on the ancestral role of the nervous system, and supports the view that it was not restricted to conventional sensory-motor coordination. First, neurons might have emerged as a cell type capable of monitoring the environment and sensing the presence of microbes, and even discriminating their species identity. Some common or species-specific microbial products may serve as cues received by the neurons via specific receptors and downstream signalling cascades. Second, the neurons might have been able to adjust the animal’s internal vital processes (i.e., development, physiology, tissue homeostasis, and behavior) to the presence and state of the microbiota. Third, the nervous system might have had an immunomodulatory effect by tuning the immune response of epithelial cells. Finally, the neurons themselves might have imposed selective forces onto the host-associated microbiota. In this way, the first nervous systems seem to have mediated the complex interactions between the host and its microbiota, hence maintaining the holobiont.

This view indicates a shared functionality between the immune system and the nervous system, pointing to a common evolutionary origin and suggesting that the nervous system evolved as much to sense and control bacteria as to coordinate movements. With the emergence of mesoderm in the Bilateralian lineage, the “immune” function of the neurons was partly delegated to these specialized cell types and ultimately lead to the advent of the adaptive immunity. This is consistent with the view of a common origin of the immune and neuroendocrine system, proposed based on the structural conservation of molecules comprising the two systems. The rich diversity of extant cnidarians, that colonized aquatic habitats worldwide over 650 mya of evolution, is evidence of how the neuronal integration of a holobiont promoted its fitness.

2.7. Next Steps Toward Understanding Mechanisms and Function

While the crucial role of the nervous system in host-microbiome interactions is increasingly appreciated, the mechanisms underlying these interactions remain unclear. Hydra provides a perfect opportunity to study microbe-neuron interactions, since both the microbiota and the nervous system are of limited complexity and both are experimentally fully accessible. We find the following questions worth addressing in order to get insights into mechanisms and function.

2.7.1. What is the Nature of the Microbial Molecules Recognized by the Neurons?

One could expect common microbe-associated molecular patterns (MAMPs), such as flagellin, LPS, or peptidoglycan, to serve as cues received by the neurons via specific receptors and downstream signalling cascades. Indeed, studies on mammalian models provide evidence for these MAMPs being recognized by both enteric and nociceptor neurons. However, the specificity of bacterial effects onto Hydra behavior suggests that these cues might be more complex and even species-specific. One might expect to find interactions, similar to those described in Hydra and Acropora, where compounds produced by certain members of the complex bacterial biofilms (like tetrabromopyrrole or a yet not identified lipophilic substance) induce larval settlement and metamorphosis. Remarkably, in both cases sensory neurons directly bind the inducer and trigger metamorphosis by secreting a GLW-family neuropeptide. Strikingly, studies on vertebrate models provided evidence that intestinal microbiota is able to produce molecules structurally similar or identical to neurotransmitters, such as serotonin, acetylcholine, glutamate, and GABA, and thus has a potential to directly modulate the neuronal activity. We propose that a systems biology approach based on deep transcriptomic and metabolomic analysis of microbes associated with Hydra, combined with a survey of existing complete genomic sequences of all major colonizers of Hydra (Fraune and Bosch, unpublished), may lead to identification of the bacteria-derived neuroactive molecules. Of particular importance is the possibility of testing these compounds in vivo, in relatively simple experimental set-ups.

2.7.2. Which Neuronal Receptors and Signaling Cascades Are Triggered by the Bacterial Cues?

Genomic and transcriptomic studies have revealed that Hydra possesses a surprisingly diverse repertoire of receptors, including over eight hundred conventional G-protein coupled receptors, hundreds of NLRs, multiple tyrosine-kinase, and nuclear hormone receptors. However, only few receptors have been cloned and functionally characterized so far, and most of the receptors remain orphan. Moreover, neuronal localization of these receptors remains elusive. Therefore, deep analysis of the transcriptomes from Hydra nerve cells will be instrumental in revealing the neuronal receptor toolkit. Further, systematic attempts to deorphanize the receptors, is to identify their ligands, downstream cascades and cellular effects, are necessary. A very productive approach is exemplified by studies that unexpectedly revealed several DEG/ENaC-family ion channels to function as receptors for neuropeptides. The group of channels-receptors may be of particular interest, because findings in mammals provide evidence for their potential of activation by bacterial products; furthermore, they can elicit immediate cellular responses such as ion currents and membrane depolarization.

2.7.3. What Do Nerve Cells Receiving Bacterial Cues Look Like?

In spite of its anatomical simplicity, the nervous system of Hydra appears functionally complex. On the one hand, diverse sub-populations of neurons have been described based on their...
non-overlapping expression patterns of neuropeptide genes.\[12,20\] Behavioral and electrophysiological studies also suggest that distinct cell sub-populations within the nerve net are responsible for particular behaviors such as spontaneous body contractions, response to light, and feeding behavior.\[13,14,64,65\]

Our recent findings strongly indicate that the activity of one particular population – the pacemaker neurons responsible for timing of spontaneous body contractions – is modulated by the presence of specific microbiota.\[24\] Molecular profiling of the Hydra nerve net with single-cell resolution combined with functional analysis of putative receptors may provide cues on functional heterogeneity of the neurons and existence of certain bacteria-sensing sub-populations.

2.7.4. How Do Neuron-Derived Effector Molecules Shape the Microbiota?

While previous studies have identified a few neuropeptides that have antibacterial activity,\[137\] these are, clearly, a minute fraction of the Hydra neuron-derived effectors that may mediate the host-microbiome interplay. A systematic approach to identifying peptide signalling molecules in Hydra revealed over 800 short peptides and estimated about half of them to be neuron-derived.\[66\] Additionally, multiple genes coding for non-conserved (orphan) peptides have been identified in Hydra genome. Together, these datasets represent a rich source of potential novel antimicrobial factors, and a systematic screen for their activity and expression pattern must now be performed. Further, detailed in vivo functional assays may elucidate the role of the peptide in shaping the microbiota composition and localization, yet the available toolkit is as yet limited to constitutive overexpression and knock-down. Development of new tools for temporal and spatial control of neuronal function, such as specific promoter-driven systems, CRISPR/CAS9 and optogenetics, will be necessary.

2.7.5. How Does the Microbiota Affect Development?

One line of evidence indicates that the nervous system modulates development in Hydra. First, neurons appear to control morphogenetic processes, such as proportion regulation, tentacle number, and bud detachment.\[119,67-69\] Second, nerve cells may exert control on tissue homeostasis by regulating stem cell proliferation and differentiation.\[70,71\] On the other hand, the microbiota of Hydra shows a remarkable dynamics during ontogenesis.\[28\] In a newly hatched polyp, Gram-positive bacteria dominate the microbial community, but disappear later in the adult polyp. Strikingly, these shifts correlate with changes in the nerve cell density during the ontogeny of Hydra.\[72\] A plausible explanation would be that certain microbes promote the neurogenesis in early Hydra development, in a way similar to the effects that the gut microbiota exerts on development of the nervous system in vertebrate models.\[73,74\] Finally, our recent data suggest that the transcriptional factor FoxO serves as an intracellular hub-protein, and controls both bacterial colonization and stem cell activity in Hydra.\[144\] Therefore, microbiome and tissue homeostasis are deeply integrated at the molecular level. In order to obtain deep insights into the mechanisms mediating the microbiota effects on development, diverse morphogenetic processes (budding, regeneration, sexual induction) and tissue maintenance functions (cell proliferation, differentiation, and apoptosis) have to be compared between germ-free Hydra and polyps colonized with different microbial consortia. Neuron-ablated polyps may provide a useful tool to prove the causal involvement of the nerve cells. Further, following the development of Hydras from germ-free embryos in axenic conditions (i.e., in the absence of microorganisms) is essential to address causality. Parallel molecular profiling of the Hydra tissue, especially the neurons, may be particularly insightful.

2.8. Understanding the Gut-Brain Axis Requires “Brainless” Models

A growing body of evidence in animals supports the concept that the gut microbiota influences cognitive processes, emotional states, and behavior.\[64,57,73\] Changes in the gut microbiota or intestinal exposure to specific bacteria can modulate the peripheral nervous system in animals, as evidenced, for instance, by gut motility disturbance in germ-free mice.\[41,76,77\] More strikingly, the intestinal microbes extend their effects onto the central nervous systems (CNS), resulting in altered brain functioning and suggesting the existence of a microbiota-gut-brain axis.\[43\] There is strong evidence from animal studies that gut bacteria influence brain chemistry and development, and that the enteric nervous system, including the sensory vagus nerve, appears to be able to differentiate between non-pathogenic and potentially pathogenic bacteria, and may play a critical role in mediating the effects of gut microorganisms on behavior.\[41,75,78-81\] Because the nervous system has constant bidirectional communication with the immune system, the effects of bacteria on the nervous system cannot be disassociated from effects on the immune system. This type of crosstalk occurs regularly and can have profound neurological and immunological effects. However, the exact molecules responsible for host-microbe communication remain largely unknown. The complexity of both microbiota and nervous systems in vertebrates is daunting. Simple animal models such as Hydra therefore may help to examine and understand the basic principles governing the microbiome-host crosstalk mediated by the neurons – even if they only partly reflect the human situation.

The unique experimental accessibility of Hydra provides a way to identify molecular mechanisms and to prove causality. Combining this mechanistic understanding with a body of knowledge on development, stem cell biology, and neurophysiology promises a truly holistic understanding of the Hydra holobiont. This may be of particular importance in light of Hydra’s non-senescence and unlimited lifespan.\[82\] Furthermore, the understanding of fundamental mechanisms and a comparative evolutionary approach will clarify the role of neuro-microbe interactions in animal health and disease. In particular, there is increasing evidence that multiple neurologic diseases in humans, such as Parkinson’s disease, multiple sclerosis, and gut motility disorders,\[40,81-85\] are correlated with gut microbiota disturbances. The management of such
disorders will benefit from a deep understanding of the cellular and molecular pathways of the neuro-microbial dialogue.

Lastly, we fully agree with Dobzhansky’s famous statement “Nothing in biology makes sense except in the light of evolution”[86] and conclude that from the beginning of animal evolution, neurons received signals from microbes; and they themselves interacted with microbes by secreting antimicrobial neuropeptides.

Acknowledgments

The authors apologize to those authors whose work we were unable to cite due to space restrictions. This work was supported by the Deutsche Forschungsgemeinschaft (DFG) (CRC1182 “Origin and Function of Metaorganisms,” DFG grant BO 848/15-3), and grants from the DFG Cluster of Excellence program “Inflammation at Interfaces”. T.C.G.B. gratefully appreciates support from the Canadian Institute for Advanced Research (CIFAR).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

AMPs, commensal microbiota, host-microbe interaction, Hydra, metaorganism, nerve system, neuropeptides

[1] G. O. Mackie, Am. Zool. 1990, 30, 907.
[2] G. Jekely, Proc. R. Soc. B Biol. Sci. 2011, 278, 914 LP.
[3] T. C. G. Bosch, D. J. Miller, The Holobiont Imperative: Perspectives from Early Emerging Animals. Vol. 10, Springer, Vienna 2016, p. 973.
[4] M. McFall-Ngai, M. G. Hadfield, T. C. G. Bosch, H. V. Carey, T. Domazet-Loso, A. E. Douglas, N. Dubilier, G. Eberl, T. Fukami, S. F. Gilbert, Proc. Natl. Acad. Sci. 2013, 110, 3229.
[5] P. J. Turnbaugh, R. E. Ley, M. Hamady, C. M. Fraser-Liggett, R. Knight, J. I. Gordon, Nature 2007, 449, 804.
[6] T. C. G. Bosch, M. J. Mcfall-ngai, Zoology 2011, 114, 185.
[7] M. J. Telford, R. R. Copley, Trends Genet. 2011, 27, 186.
[8] T. C. G. Bosch, Annu. Rev. Microbiol. 2013, 67, 499.
[9] O. Koizumi, Can. J. Zool. 2002, 80, 1678.
[10] H. Bode, S. Berking, C. N. David, A. Gierer, H. Schaller, E. Trenkner, Wilhelm Roux’Archiv für Entwicklungsmorphologie der Org. 1973, 171, 269.
[11] H. R. Bode, Trends Genet. 1992, 8, 279.
[12] O. Koizumi, N. Sato, C. goto, Hydrobiologia 2004, 530, 41.
[13] L. M. Passano, C. B. Mcclough, J. Exp. Biol. 1964, 41, 643.
[14] L. M. Passano, C. B. McCullough, J. Exp. Biol. 1965, 42, 205 LP.
[15] G. Wagner, J. Cell Sci. 1905, 2, 585.
[16] W. F. Loomis, Ann. N. Y. Acad. Sci. 1955, 62, 211.
[17] T. C. G. Bosch, A. Klimovich, T. Domazet-Loso, S. Gründer, T. W. Holstein, G. Jekely, D. J. Miller, A. P. Murillo-Rincon, F. Rentzsch, G. S. Richards, Trends Neurosci. 2017, 40, 92.
[18] R. D. Campbell, J. Cell Sci. 1976, 21, 1.
[19] B. A. Marcum, R. D. Campbell, J. Cell Sci. 1978, 29, 17 LP.
[20] G. N. Hansen, M. Williamson, C. J. P. Grimmelikhuijzen, Cell Tissue Res. 2000, 301, 245.
[21] D. L. Gonzalez, K. N. Badhiwala, D. G. Vercosa, B. W. Avants, Z. Liu, W. Zhong, J. T. Robinson, Nat. Nanotechnol. 2017, 12, 684.
[22] F. Vitale, D. Vercosa, A. V. Rodriguez, S. S. Pamulapati, F. Seibt, E. Lewis, J. S. Yan, K. Badhiwala, M. Adnan, G. Royer-Carfagni, Nano Lett. 2017, 18, 326.
