

The prospects for Symbiogenetics: emergence of superorganismal genomes and reconstruction of cellular evolution (mini-review)

Nikolay Provorov¹ and Igor Tikhonovich^{1,2}

¹All-Russia Research Institute for Agricultural Microbiology, shosse Podbel'skogo, 3, Saint Petersburg, 190608, Russian Federation

²Saint Petersburg State University, Universitetskaya nab., 7–9, Saint Petersburg, 199034, Russian Federation

Address correspondence and requests for materials to Nikolay Provorov, provorovnik@yandex.ru

Abstract

The superspecies systems of heredity that arise *via* coevolution of phylogenetically distant organisms are represented as the subjects of Symbiogenetics, a new research field addressing integration of the heterologous genomes. Evolutionary mechanisms responsible for this integration include: a) interspecies altruism based on the symbionts' refusal from autonomous lifestyle; b) inheritance of symbionts by hosts as of acquired genetic determinants (pangensis). Under impacts of these factors, endosymbionts may be transformed into the cellular organelles which have lost biological and genetic individuality and sometimes lack their own genomes. The genomically truncated organelles which have retained the abilities for reproduction and metabolism are considered as the models to reconstruct the early stages of cell evolution, including the emergence of its genome.

Keywords: Symbiogenetics, organellogenesis, hologenomes and symbiogenomes, pangensis, biological altruism, open genetic systems, biological and genetic individuality, natural selection

Introduction

For a long time, the major approach to study variability and heredity was represented by genetic analysis based on the dissection of “hereditary material” into the elementary units — genes, cistrons, mutons, recons, codons, etc. (Benzer, 1957; Lobashev, 1967; Inge-Vechtomov, 1983). This reductionist research demonstrated that the units of heredity are organized into the complicated systems wherein epistatic or complementary gene interactions are implemented (Bingham, Groose, Woodfield, and Kidwell, 1994; Phillips, 2008). These interactions were revealed not only within genomes of individual organisms but they also cover the inter-species (symbiotic) communications, both mutualistic (Nutman, 1946) and antagonistic (Flor, 1946) (Table 1) suggesting that the superorganismal genetic systems (SOGS) are formed by non-related species. In this paper, SOGS are addressed as the subjects of a distinct discipline, Symbiogenetics which considers cooperative interactions responsible for development and evolution in the majority of living creatures (Tikhonovich and Provorov, 2012).

Historically, Symbiogenetics emerged at the border of ecological genetics, which addresses the impacts of environmental factors on genome operation (Inge-Vechtomov, 2015), and of symbiogenesis theory, which assumes the eukaryotic cell origin *via* integration of distant prokaryotic species (Mereschkowsky, 1910; Margulis, 1996; Provorov, Tikhonovich, and Vorobyov, 2018). Developing this theory, L. Margulis and D. Sagan proposed Symbiogenetics as a field of evolutionary research addressing the interspecies genomic integration (Sagan, 2021). Importantly,

Citation: Provorov, N. and Tikhonovich, I. 2023. The prospects for Symbiogenetics: emergence of superorganismal genomes and reconstruction of cellular evolution (mini-review). *Bio. Comm.* 68(1): 49–55. <https://doi.org/10.21638/spbu03.2023.105>

Authors' information: Nikolay Provorov, Dr. of Sci. in Biology, Professor, Chief Researcher, orcid.org/0000-0001-9091-9384; Igor Tikhonovich, RAS Academician, Dr. of Sci. in Biology, Professor, Director for Science of ARRIAM, Dean of Faculty, orcid.org/0000-0001-8968-854X

Manuscript Editor: Pavel Skutschas, Department of Vertebrate Zoology, Faculty of Biology, Saint Petersburg State University, Saint Petersburg, Russia

Received: June 2, 2022;

Revised: October 25, 2022;

Accepted: October 26, 2022.

Copyright: © 2023 Provorov and Tikhonovich. This is an open-access article distributed under the terms of the License Agreement with Saint Petersburg State University, which permits to the authors unrestricted distribution, and self-archiving free of charge.

Funding: Research is supported by the Russian Science Foundation, grant No. 19-16-00081P.

Ethics statement: This paper does not contain any studies involving human participants or animals performed by any of the authors.

Competing interests: The authors have declared that no competing interests exist.

Table 1. Gene interactions in free-living and symbiotic organisms

Types of interaction	Organisms	
	Free-living	Symbiotic
Epistatic	Suppression by the gene from an allelic pair of the gene expression in the other allelic pair	“Gene-for-gene” partners’ interactions in symbiotic (mostly parasitic) systems based on the interactions of virulence and defense systems
Complementary	Participation of several non-allelic genes in the development of a phenotypic trait	Functional integration of partners’ genomes in symbiotic (mostly mutualistic) systems based on the inter-organism signaling and metabolic interactions

Symbiogenetics should not be considered as a paraphrasing for “genetics of symbiosis”: it is a fundamental area which follows a holistic approach to study the variability and heredity in super-species communities (Tikhonovich and Provorov, 2009). Integration of diverse species represents a basic adaptive strategy which relays on the universal properties of hereditary material displayed at different levels of its organization. Common mechanisms for the genome operation provide the opportunities for merging distant organisms (prokaryotes and eukaryotes, bacteria and archaea) into the new biological units, “holobionts” (Zilber-Rosenberg and Rosenberg, 2008).

Hologenomes and symbiogenomes: open genetic systems

Previously we suggested that in symbiotic systems, the units of heredity are represented not by singular genes (as in free-living organisms) but by over-gene systems, e.g., by pairs of genes which belong to the interacting species (Tikhonovich and Provorov, 2012). Developing the approaches of “inter-organismal genetics” coined by W.Q. Loegering (1978), who suggested for symbiosis an innovative phenotype represented by emergent traits (von Bertalanffy, 1968), we proposed a distinct symbiotic genotype encoding for this phenotype. It may be addressed in terms of genomic complementation (Tikhonovich et al., 2015) suggesting that co-evolutionary processes should not be restricted to signaling and metabolic partners’ interactions: in course of their cooperation, communalized systems of heredity are established.

To address the symbiotically emerged composite genomes, the notion of “hologenome” was suggested, which underlies the SOGS composed of all genes harbored by a multicellular eukaryotic host and its microbial cohabitants (Rosenberg and Zilber-Rosenberg, 2018). Given the enormous diversity of symbiotic interactions implemented by microbes with plants and animals, this notion should be diversified since the genetic control of provisionally emerged transient associations differs greatly from the control of obligatory, vertically transmitted symbioses. This is why, we consider “symbiogenome” as a basic product of facultative symbiosis in which the specialized partners’ genes are involved. In

historical perspective, the provisionally formed symbiogenomes tend to be reorganized into the stably maintained hologenomes: during the permanent partners’ coexistence, all their genes are involved in cooperative adaptations.

In the model N_2 -fixing legume-rhizobia system, symbiogenome involves the genes encoding for partners’ signal exchange (e.g., bacterial *nod* genes for synthesis of lipo-chito-oligosaccharidic Nod factors + plant *NFR* genes for their reception) and for metabolic cooperation (e.g., bacterial *nif/fix* genes for nitrogenase synthesis + plant *GS/GOGAT/AAT* genes for assimilation of the N_2 fixation products). For these genes, coevolution was demonstrated at the population and phylogenetic levels (Andronov et al., 2015; Igolkina et al., 2019; Shatskaya et al., 2019) resulted in a marked increase of holobiont integrity and in an improved efficiency of its operation.

Analysis of diverse microbe-plant interactions including legume-rhizobia symbioses, arbuscular mycorrhizae and endophytic/epiphytic associations, demonstrated that at least some genes used by host plants for cross-talking with their microbial cohabitants are universal for the land plants (Tikhonovich et al., 2015). It seems possible that from the very beginning of their natural history, plants acquired the gene systems for managing various microbial symbionts which diversified broadly to meet the phylogenetic and ecological radiation of their hosts. Due to adaptations towards swiftly changing environment, plants gained a range of mechanisms for recruiting the beneficial symbionts from the associated (rhizospheric, endophytic) communities which harbor a variety of genes encoding for the host-beneficial nutritional and defensive functions.

Composite systems of heredity, formed on the basis of host genomes and metagenomes of associated microbial communities, evolve as: symbiogenomes → hologenomes → mosaic host genomes. In this evolution, the SOGS integrity increases since at the early stages of partners’ coevolution, it is mostly functional: despite the cytological separation of partners’ genomes, their genes are expressed in the same coordinated manner as in a unitary organism (Provorov, Tikhonovich, and Vorobyov, 2018). The subsequent evolution of SOGS towards the structural integrity is associated with partners’ gene

Table 2. Open and closed genetic systems

Organisms	Genetic systems	
	Open	Closed
Prokaryotes	Pangenomes in the majority of free-living species composed of the core and accessory parts	Pangenomes in some species, mostly in the obligatory, vertically transmitted symbionts and cellular organelles
Eukaryotes	Hologenomes and symbiogenomes composed by the host genomes and (meta)genomes of associated microbial communities	Nuclear-cytoplasmic systems of heredity (cellular genomes)

exchange, which, upon transformation of symbionts into cellular organelles, is manifested as the endosymbiotic transfer of microbial genes to the host chromosomes.

The bacterial genomic reduction occurring in the obligatory symbioses' evolution represents an ongoing process: at its initial stages, many genes which control cell metabolism and development are eliminated from the vertically transmitted symbionts followed by genes responsible for the genome maintenance and expression lost by cellular organelles. In this reductive evolution, bacteria gave up their biological individuality — the ability for autonomous existence, and later the genetic individuality — the ability to maintain and express their own genomes. Importantly, some limitations in biological individuality may be registered for facultative symbionts characterized by a pronounced specialization towards their hosts. These limitations are illustrated by the loss of phototrophy in *Bradyrhizobium* spp. (Oda, Larimer, and Chain, 2008; Rey and Harwood, 2010) or of negative regulators of symbiosis which determine the *ex planta* survival in *Rhizobium* and *Sinorhizobium* spp. (Provorov, Onishchuk, Yurgel, and Simarov, 2014).

Importantly, symbiogenesis as an integrative evolution based on merging the partners' genomes, provides a mechanism to overcome the gene deficiency, which restricts the ability of organisms to adapt the changeable environment. During the symbiogenic evolution, gene number increased from 2000–12 000 in free-living prokaryotes up to 6500–75 000 in eukaryotes. However, this increase did not solve the problem of gene deficiency because: (i) eukaryotic genomes are mostly “closed” for regular replenishment with new genes; (ii) genes for some vital functions (e.g., N₂ fixation) are absent in these genomes. Although a range of HGT events in eukaryotes have been detected, its evolutionary consequences are limited: analysis of 497 species revealed only 1138 genes that could appear in nuclear chromosomes *via* HGT (Katz, 2015). This is why, eukaryotes expand their adaptive potential greatly acquiring the symbiogenomes and hologenomes as open genetic systems, which can be replenished with new genes during the hosts' evolution, and even during its ontogeny (Table 2). The use of symbionts' adaptive potential by host is implemented *via* functional integration of partners' genomes based on the joint signal and metabolic circuits.

In prokaryotes, the gene deficiency is replenished by pangenomes, in which new genes recruited *via* HGT are included in the accessory parts. In hologenomes, accessory parts are represented by associated microbial communities, while the hosts' nuclear-cytoplasmic genetic systems representing a closed type (Table 2) constitute the core parts of hologenomes.

Natural selection, altruism and pangensis: factors of symbiogenesis

The loss of biological and genetic individuality in symbiotic organisms cannot be explained by the commonly accepted concepts of adaptive evolution directed by natural (individual) selection. This restriction was outlined by Ch. Darwin (1872) who suggested that natural selection does not support organisms with the features that are useful for an associated partner, but are useless or even harmful for their owners. Developing these ideas, J. Maynard Smith (1989) suggested that the benefit or harm, which an evolving organism exhibits towards its symbiotic partner represent the side effects of individual adaptations. However, A. de Bari (1879), B. Kozo-Polyansky (1924), Th. Dobzhansky (1970) and L. Margulis (1996) suggested that natural selection represents a major factor in the evolution of inter-species communities.

The population genetic research of symbiotic microorganisms demonstrated that mechanisms involved in their evolution differ from the individual (Darwinian) selection. It is known that selective pressures operating in evolution of antagonistic symbionts (parasites) are usually represented by frequency-dependent selection (FDS) (Jones and Dangl, 2006). This factor is also involved in the evolution of beneficial symbionts: FDS operating along with disruptive selection may favor the rhizobia genotypes with high N₂-fixing activity (Andronov et al., 2015; Onishchuk, Vorobyov, and Provorov, 2017). Markedly, the majority of rhizobia do not use this activity outside symbiosis, and mechanisms involved directly in its evolution are to be clarified.

Simulation of rhizobia evolution demonstrated that the highly active N₂ fixers are supported in their populations by inter-deme selection, the units for which are represented by the bacteria groups located in different

plant individuals or in different nodules of the same plant (Provorov, Tikhonovich, and Vorobyov, 2018). This selection is associated with the mode of host infection which may be mixed (through ruptures of epidermis) or clonal (through deformed root hairs) (Sprent, 2001). In latter case, reproduction of N₂-fixing rhizobia genotypes can occur due to their preferential: (i) uptake by plants from soil populations; (ii) multiplication inside nodules.

Up to now, the second mechanism based on positive feedbacks between symbionts and hosts have been confirmed. It turned out that in N-free atmosphere (80% Ar + 20% O₂) which blocks nitrogenase activity, nodules receive much less C-compounds than in the presence of N₂ (Denison and Kiers, 2004). These data suggest that the host ensures preferential reproduction of N₂-fixing bacterial genotypes due to their intensive carbon supply.

The experimental and mathematical models demonstrated that irreversible bacteroid differentiation occurring in nodules of many legumes can be represented as altruism expressed by rhizobia towards the plants and supported by the host-induced kin selection. Specifically, extinction of bacteroids associated with the renovation of N₂-fixing nodule zone is compensated by reproduction of the undifferentiated bacterial cells which are isogenic to bacteroids and assimilate the host-provided C compounds (Provorov, Tikhonovich, and Vorobyov, 2018). Importantly, the irreversible bacteroid differentiation is under dual control of both partners (Tikhonovich et al., 2015), suggesting that hosts operate as mediators in transfer of altruistic impacts within the plant-associated microbial populations. This mediation is compensated by the nitrogen flow from rhizobia to plants, showing that in the nodular N₂-fixing symbioses, the interspecies altruism is involved (Provorov, 2021).

Altruistic differentiation of N₂-fixing symbiotic microbes is represented not only by rhizobia bacteroids but also by multiple heterocysts of *Nostoc punctiforme* (Kumar, Mella-Herrera, and Golden, 2010) and by non-reproducible cellular forms of *Azoarcus* endophytes (Hurek, Handley, Reinhold-Hurek, and Piche, 2002). Importantly, rhizobia and symbiotic cyanobacteria possess the complicated genomes characterized by increased sizes and by multicomponent architectures representing the progressive evolution of bacteria. An additional example of altruistic strategy is represented by ruminal symbionts which undergo a genetically controlled apoptosis providing proteins to the animal hosts (Harun and Sali, 2019). Moreover, altruistic strategy is expressed at the late stages of symbiosis evolution: when micro-symbionts acquired the obligatory dependence on hosts, “forced altruism” is established, which is beneficial for and is genetically controlled by both partners (Darlington, 1978).

The organizing role of hosts in evolution of their micropartners may be due to selection for an increased symbiotic activity in the host populations. In legume-rhizobia

system, this selection results in differentiation of cellular compartments (infection threads, symbiosomes) harboring the endosymbiotic rhizobia and providing the active expression of host-beneficial traits (Sprent, 2001). Thus, the targets of symbiosis-specific selection pressures are represented by holobionts since their increased fitness is favorable for both partners. Transition from facultative to obligatory interactions occurs due to vertical transmission of symbionts during host reproduction (Zakharov and Shaikevich, 2021) which leads to the transformation of SOGS into a system of inheritance resulting in an increased integrity of holobionts.

Importantly, evolution of facultative symbionts into the obligatory, vertically transmitted ones should be considered as pangenes, i.e., inheritance of adaptive traits acquired during hosts’ ontogeny (Provorov, Tikhonovich, and Vorobyov, 2018). Under laboratory conditions, this evolution can be accelerated: treatment of aphids, from which the *Buchnera* symbionts (producers of essential amino acids) were expelled, by free-living *Serratia* genotypes led to their hosting in the vacant intracellular niches and to a vertical transmission as of newly acquired symbionts (Koga, Tsuchida, and Fukatsu, 2003).

Cellular genome as a product of symbiogenesis

Being originated from research on the hybrid origin of eukaryotic cell, Symbiogenetics extends this research greatly by addressing the intracellular symbiotic bacteria as models to reconstruct the emergence of prokaryotic cell and of its genome. These reconstructions should be based on the assumption that during organellogenesis which involves a reductive evolution of bacterial symbionts, genes for the DNA-based template processes (replication, transcription, reparation, recombination) are less stable and were lost earlier than genes for the RNA-based translation process (Provorov, Tikhonovich, and Vorobyov, 2016). This difference suggests that an ancestral prokaryotic cell perhaps had RNA-genome which was replaced by DNA-genome, e.g., according to the viral nucleogenesis scenario (Claviere, 2006).

Importantly, a range of organelles (mitosomes, many hydrogenosomes, some plastids) are devoid of genomes but retain the basic vital functions — metabolism and reproduction using the gene products (proteins, RNAs) imported from the host cells (Smith and Keeling, 2015). Many of these products are encoded by genes which were previously allocated from organelles to the nuclear chromosomes. These data suggest that the ancestral cell-like organisms were devoid of own genomes and implemented their housekeeping functions using the external sources of genetic information. Experimental evidence suggests that incorporation of RNA or DNA molecules into the artificially generated “giant

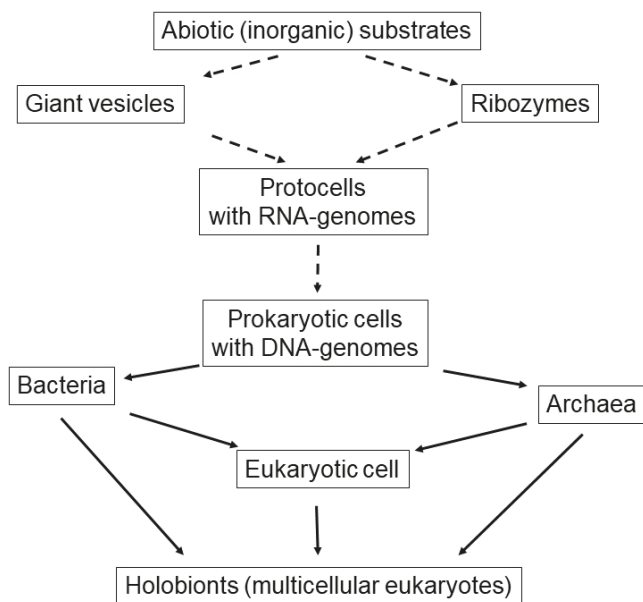


Figure. Generalized scenario of cellular evolution based on integrative processes

Dotted arrows represent the hypothetical evolutionary processes, solid arrows — the empirically supported processes. The integrative evolutionary stages are introduced in Section “Cellular genome as a product of symbiogenesis”.

vesicles” — coacervate droplets surrounded by bilipid membranes results in the genome-containing protocells which display increased reproduction rates as compared to their genome-free precursors (Oberholzer, Wick, Luisi, and Biebricher, 1995; Kurihara et al., 2011).

Proceeding from these assumptions, we suggest a generalized scenario of cellular evolution including several integrative stages (Figure): (i) incorporation of RNA-based auto-replicating macromolecular complexes (e.g., ribozymes) into cell-like “giant vesicles” resulted in protocells with RNA genomes; (ii) emergence of eukaryotic cells due to the integration of bacteria and archaea diverged from a common ancestor of these prokaryotic organisms (in which the RNA-genomes had been replaced by DNA-genome); as a result of this evolution, endosymbiotic bacteria were converted into permanent organelles maintained in all cells of a multicellular host; (iii) emergence of holobionts based on multi-cellular eukaryotes which are capable of hosting numerous microbial cohabitants including intracellular symbionts to be considered as temporary organelles (maintained only in some host cells).

The proposed scenario assumes that symbiogenesis is not restricted to the emergence of multi-genomic eukaryotic cell: it involved also the evolution of ancestral prokaryotic cells from the genome-free cell-like precursors which hosted the nuclear acid molecules. This assumption goes back to the hypothesis of C. Mereschkowsky (1909) who proposed a symbiotic origin of nuclear chromosomes from the free-living bacteria.

From gene interactions to genomic integration: a conclusion

In this overview, we introduce Symbiogenetics as a biological discipline which opens the new prospects for genetic and evolutionary research. Using a broad range of models including the highly specific two-partite symbioses and the multi-partite biocenotic communities, this discipline develops a holistic approach to study the variability and heredity phenomena coupled with a broad spectrum of integrative processes — from gene interactions to genomic integration.

Universality of genetic material organization and expression in all cellular organisms which is probably based on monophyletic origin of life underlies the integrative evolution considered by Symbiogenetics. It assumes that evolution of cellular organisms is essentially symbiotic: it started from integration of “giant vesicles” with RNA or DNA molecules and resulted in the holobionts — multicellular eukaryotes harboring diverse microbial communities ensuring a broad spectrum of adaptive functions for hosts.

The proposed evolutionary scenario (Figure) assuming that the genome origin is exogenic with respect to the cell structure and metabolism rises up a range of exciting questions for the further research. For example, it is necessary to reveal how the externally emerged system of heredity acquired the control over housekeeping functions of a host protocell that arose independently of its genome. The other debatable problem is the emergence of membrane compartments in eukaryotic cells including the nucleus and endoplasmic reticulum. It looks probable that these compartments are of symbiotic origin being originated from the vesicles produced by mitochondrial membranes which have a bacterial origin (Brueckner and Martin, 2020).

For the further progress of Symbiogenetics, development of relevant models is required including the intracellular symbionts (Zakharov and Shaikevich, 2021; Goryacheva and Andrianov, 2021) which represent the temporary cellular organelles to be addressed as the precursors of permanent organelles. The other important models of Symbiogenetics are aimed to study the gene transfer from prokaryotes to eukaryotes (Matveeva, 2021) which give insights into the evolution of structurally integrated SOGS as of the basic products of symbiogenesis.

Analysis of the ecological factors of symbiogenesis has shown that many of them go far beyond the synthetic theory of evolution and involve, in addition to natural selection, a number of “non-Darwinian” mechanisms, including interspecies altruism and the inheritance of acquired traits (pangenes). In the evolution of symbiosis, these factors are combined with various selective and stochastic processes, which are induced in micro-part-

ners by hosts implementing the role of “breeders” and, perhaps of “genetic engineers” creating the beneficial symbionts. Further analysis of these factors will suggest the algorithms for symbiotic engineering aimed at constructing the superorganismal systems for agricultural, biomedical and environment-protecting purposes.

References

- Andronov, E. E., Igolkina, A. A., Kimeklis, A. K., Vorobyov, N. I., and Provorov, N. A. 2015. Characteristics of natural selection in populations of nodule bacteria (*Rhizobium leguminosarum*) interacting with different host plants. *Russian Journal of Genetics* 51:949–956. <https://doi.org/10.1134/S1022795415100026>
- Benzer, S. 1957. The elementary units of heredity; pp. 70–93 in W. D. McElroy and B. Glass (eds), *The Chemical Basis of Heredity*. Johns Hopkins Press, Baltimore, Maryland.
- Bingham, E. T., Groose, R. W., Woodfield, D. R., and Kidwell, K. K. 1994. Complementary gene interactions in alfalfa are greater in autotetraploids than diploids. *Crop Science* 34:823–829. <https://doi.org/10.2135/cropsci1994.0011183X003400040001x>
- Brueckner, J. and Martin, W. F. 2020. Bacterial genes outnumber archaeal genes in eukaryotic genomes. *Genome Biology and Evolution* 12:282–292. <https://doi.org/10.1093/gbe/evaa047>
- Claverie, J. M. 2006. Viruses take center stage in cellular evolution. *Genome Biology* 7:110–115. <https://doi.org/10.1186/gb-2006-7-6-110>
- Darlington, P. J. 1978. Altruism: its characteristics and evolution. *Proceedings of the National Academy of Sciences USA* 75:385–389. <https://doi.org/10.1073/pnas.75.1.385>
- Darwin, Ch. 1872. *The Origin of Species by Means of Natural Selection or the Preservation of Favored Races in the Struggle for Life*. 6th ed. 526 pp. John Murray, London.
- Denison, R. F. and Kiers, E. T. 2004. Lifestyle alternatives for rhizobia: mutualism, parasitism and foregoing symbiosis. *FEMS Microbiology Letters* 237:187–193. <https://doi.org/10.1016/j.femsle.2004.07.013>
- Dobzhansky, Th. 1970. *Genetics of the evolutionary process*. 315 pp. Columbia University Press, New York.
- Flor, H. H. 1946. Genetics of pathogenicity in *Melampsora lini*. *Journal of Agricultural Research* 73:335–357.
- Goryacheva, I. and Andrianov, B. 2021. Reproductive parasitism in insects. The interaction of host and bacteria. *Biological Communications* 66:17–27. <https://doi.org/10.21638/spbu03.2021.103>
- Harun, A. Y. and Sali, K. 2019. Factors affecting rumen microbial protein synthesis: A review. *Veterinary Medicine — Open Journal* 4:27–35. <https://doi.org/10.17140/VMOJ-4-133>
- Hurek, T., Handley, L. L., Reinhold-Hurek, B., and Piche, Y. 2002. *Azoarcus* grass endophytes contribute fixed nitrogen to the plant in an unculturable state. *Molecular Plant-Microbe Interactions* 15:233–242. <https://doi.org/10.1094/MPMI.2002.15.3.233>
- Igolkina, A. A., Bazykin, G. A., Chizhevskaya, E. P., Provorov, N. A., and Andronov, E. E. 2019. Matching population diversity of rhizobial *nodA* and legume *NFR5* genes in plant-microbe symbiosis. *Ecology and Evolution* 9:10377–10386. <https://doi.org/10.1002/ece3.5556>
- Inge-Vechtomov, S. G. 1983. *Introduction into Molecular Genetics*. 343 pp. Vysshaya shkola Publ. Moscow. (In Russian)
- Inge-Vechtomov, S. G. 2015. *Genetics in Retrospect*. 336 pp. N-L Publ. St. Petersburg (In Russian)
- Jones, J. D. and Dangl, J. L. 2006. The plant immune system. *Nature* 444(7117):323–329. <https://doi.org/10.1038/nature05286>
- Katz, L. A. 2015. Recent events dominate interdomain lateral gene transfers between prokaryotes and eukaryotes and, with the exception of endosymbiotic gene transfers, few ancient transfer events persist. *Philosophical Transactions of the Royal Society B* 370:20140324. <https://doi.org/10.1098/rstb.2014.0324>
- Koga, R., Tsuchida, T., and Fukatsu, T. 2003. Changing partners in an obligate symbiosis: a facultative endosymbiont can compensate for loss of the essential endosymbiont *Buchnera* in an aphid. *Proceedings of the Royal Society B* 270:2543–2550. <https://doi.org/10.1098/rspb.2003.2537>
- Kozo-Polyanski, B. M. 1924. *New Principle of Biology. Review of the Symbiogenesis Theory*. 124 pp. Puchina Publ. Moscow. (In Russian)
- Kumar, K., Mella-Herrera, R. A., and Golden, J. W. 2010. Cyanobacterial heterocysts. *Cold Spring Harbor Perspectives in Biology* 2:a000315. <https://doi.org/10.1101/cshperspect.a000315>
- Kurihara, K., Tamura, M., Shohda, K., Toyota, T., Suzuki, K., and Sugawara, T. 2011. Self-reproduction of supramolecular giant vesicles combined with the amplification of encapsulated DNA. *Nature Chemistry* 3:775–781. <https://doi.org/10.1038/nchem.1127>
- Lobashev, M. E. 1967. *Genetics*. 751 pp. Leningrad University Publ. Leningrad. (In Russian)
- Loegering, W. Q. 1978. Current concepts of inter-organismal genetics. *Annual Review of Phytopathology* 16:309–320. <https://doi.org/10.1146/annurev.py.16.090178.001521>
- Margulis, L. 1996. Archaeal-eubacterial mergers in the origin of Eukarya: phylogenetic classification of life. *Proceedings of the National Academy of Sciences USA* 93:1071–1076. <https://doi.org/10.1073/pnas.93.3.1071>
- Matveeva, T. 2021. New naturally transgenic plants: 2020 update. *Biological Communications* 66:36–46. <https://doi.org/10.21638/spbu03.2021.105>
- Mereschkowsky, C. 1909. Theory of two plasms as a basis of symbiogenesis, new concept on the origin of organisms. 102 pp. Tipografia Imperatorskogo universiteta Publ. Kazan. (In Russian)
- Mereschkowsky, C. 1910. Theorie der zwei Plasmaarten als Grundlage der Symbiogenesis, einer neuen Lehre von der Entstehung der Organismen. *Biol. Centralbl.* 30:278–288.
- Nutman, P. S. 1946. Genetic factors concerned in the symbiosis of clover and nodule bacteria. *Nature* 157:463–465. <https://doi.org/10.1038/157463a0>
- Oberholzer, T., Wick, R., Luisi, P. L., and Biebricher, C. K. 1995. Enzymatic RNA replication in self-reproducing vesicles: an approach to a minimal cell. *Biochemical and Biophysical Research Communications* 207:250–257. <https://doi.org/10.1006/bbrc.1995.1180>
- Oda, Y., Larimer, F. W., and Chain, P. S. 2008. Multiple genome sequences reveal adaptations of a phototrophic bacterium to sediment microenvironments. *Proceedings of the National Academy of Sciences USA* 105:18543–18548. <https://doi.org/10.1073/pnas.0809160105>
- Onishchuk, O. P., Vorobyov, N. I., and Provorov, N. A. 2017. Nodulation competitiveness of nodule bacteria: genetic control and adaptive impacts. *Applied Biochemistry and Microbiology* 53:117–124. <https://doi.org/10.1134/S0003683817020132>
- Phillips, P. C. 2008. Epistasis — the essential role of gene interactions in the structure and evolution of genetic systems. *Nature Reviews Genetics* 9:855–867. <https://doi.org/10.1038/nrg2452>

- Provorov, N. A. 2021. Genetic individuality and inter-species altruism: modelling of symbiogenesis using different types of symbiotic bacteria. *Biological Communications* 66:65–71. <https://doi.org/10.21638/spbu03.2021.108>
- Provorov, N. A., Onishchuk, O. P., Yurgel, S. N., and Simarov, B. V. 2014. Construction of highly-effective symbiotic bacteria: evolutionary models and genetic approaches. *Russian Journal of Genetics* 50:1125–1136. <https://doi.org/10.1134/S1022795414110118>
- Provorov, N. A., Tikhonovich, I. A., and Vorobyov, N. I. 2016. Symbiogenesis as a model for reconstructing the early stages of genome evolution. *Russian Journal of Genetics* 52:117–124. <https://doi.org/10.1134/S1022795416020101>
- Provorov, N. A., Tikhonovich, I. A., and Vorobyov, N. I. 2018. Symbiosis and Symbiogenesis. 464 pp. Inform-Navigator Publ. St. Petersburg. (In Russian)
- Rey, F. and Harwood, C. S. 2010. FixK, a global regulator of microaerobic growth, controls photosynthesis in *Rhodospseudomonas palustris*. *Molecular Microbiology* 75:1007–1020. <https://doi.org/10.1111/j.1365-2958.2009.07037.x>
- Rosenberg, E. and Zilber-Rosenberg, I. 2018. The hologenome concept of evolution after 10 years. *Microbiome* 6:78. <https://doi.org/10.1186/s40168-018-0457-9>
- Sagan, D. 2021. From Empedocles to Symbiogenesis: Lynn Margulis's revolutionary influence. on evolutionary biology. *BioSystems* 204:104386. <https://doi.org/10.1016/j.biosystems.2021.104386>
- Shatskaya, N. V., Bogdanova, V. S., Kosterin, O. E., Vasiliev, G. V., Kimeklis, A. K., Andronov, E. E., and Provorov, N. A. 2019. Plastid and mitochondrial genomes of *Vavilovia formosa* (Stev.) Fed. and phylogeny of related legume genera. *Vavilov Journal of Genetics and Breeding* 23(8):972–980. <https://doi.org/10.18699/VJ19.574>
- Smith, D. R. and Keeling, P. J. 2015. Mitochondrial and plastid genome architecture: Reoccurring themes, but significant differences at the extremes. *Proceedings of the National Academy of Sciences USA* 112:10177–10184. <https://doi.org/10.1073/pnas.1422049112>
- Smith, J. 1989. Generating novelty by symbiosis. *Nature* 341:284–285. <https://doi.org/10.1038/341284a0>
- Sprent, J. I. 2001. Nodulation in legumes. 105 pp. Cromwell Press Ltd., Kew Royal Botanical Gardens. London.
- Tikhonovich, I. A. and Provorov, N. A. 2009. From plant-microbe interactions to Symbiogenetics: a universal paradigm for the inter-species genetic integration. *Annals of Applied Biology* 154:341–350. <https://doi.org/10.1111/j.1744-7348.2008.00306.x>
- Tikhonovich, I. A. and Provorov, N. A. 2012. Development of symbiogenetics approaches for studying variation and heredity of superspecies systems. *Russian Journal of Genetics* 48:357–368. <https://doi.org/10.1134/S1022795412040126>
- Tikhonovich, I. A., Andronov, E. E., Borisov, A. Yu., Dolgikh, E. A., Zhernakov, A. I., Provorov, N. A., Rumyantseva, M. L., and Simarov, B. V. 2015. The principle of genome complementarity in the enhancement of plant adaptive capacities. *Russian Journal of Genetics* 51:831–846. <https://doi.org/10.1134/S1022795415090124>
- von Bertalanffy, L. 1968. General system theory: foundations, development, applications. 258 pp. George Braziller. New York.
- Zakharov, I. and Shaikevich, E. 2021. Hereditary symbionts and mitochondria: distribution in insect populations and quasi-linkage of genetic markers. *Biological Communications* 66:6–16. <https://doi.org/10.21638/spbu03.2021.102>
- Zilber-Rosenberg, I. and Rosenberg, E. 2008. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. *FEMS Microbiology Reviews* 32:723–735. <https://doi.org/10.1111/j.1574-6976.2008.00123.x>