



Editorial: Genome Invading RNA-Networks

Luis P. Villarreal¹ and Guenther Witzany^{2*}

¹ Center for Virus Research, University of California, Irvine, Irvine, CA, United States, ² Telos-Philosophische Praxis, Buermoos, Austria

Keywords: RNA Networks, genetic identities, regulatory RNAs, infectious agents, Natural Genetic Content Operators

Editorial on the Research Topic

Genome Invading RNA-Networks

It has been long accepted that newly acquired biological information is mostly derived from random, error-based events (Eigen, 1971). However, the serial nature of acquiring such random events makes it very difficult to account for the origin or modification of regulatory networks. There is now abundant empirical evidence establishing the crucial role of non-coding DNA (acting through the expression of RNA with its complex biology) to create regulatory control (Mattick, 2003; Atkins et al., 2011). Along with the parallel comeback of regulatory RNA in virology, RNA is now at center stage in how we think about complex organisms (Koonin et al., 2006; Atkins et al., 2011).

Regulatory RNAs derive from infectious events and can co-operate, build communities, generate nucleotide sequences de novo and insert/delete themselves into host genetic content (Villarreal, 2005; Koonin, 2009). In this sense genome invading RNA-networks determine host genetic identities (self-recognition) throughout all kingdoms including the virosphere (Britten, 2004; Marraffini and Sontheimer, 2010; Villarreal, 2011a). But inclusion of a transmissible viral RNA biology differs fundamentally from conventional thinking in that it represents a vertical domain of life providing vast amounts of linked information not derived from direct ancestors (Villarreal, 2014). Interestingly single RNA stem loops react as physico-chemical entities exclusively, whereas with the network-cooperation of various RNA stem-loops in a module-like manner biological selection emerges (Manrubia and Briones, 2007; Vaidya, 2012; Higgs and Lehman, 2015). Additionally co-operating RNAs outcompete selfish genetic parasites (Hayden and Lehman, 2006; Vaidya et al., 2012).

Thus, we can argue, that for DNA based organisms, the introduction of infective collectives of RNA groups are a central driving force of evolution. Such RNA groups are co-adapted from persistent infectious agents and now serve as regulatory tools in nearly all cellular processes (Witzany, 2016) as documented in several retrovirus derived mobile genetic elements (Brosius, 1999; Villarreal, 2011b; Chuong et al., 2016). Additionally, the resulting productive RNA-networks constantly produce new sequence space (i.e., complex regulation) which not only further serve as adaptation tools for their cell-based host organisms but also provides crucial roles in evolutionary novelty (Villarreal, 2011b). This RNA productivity results out of the empirical fact that a single RNA sequence can fold into different and unrelated secondary structures with different functions in a (environmentally determined) context-dependending way (Schultes and Bartel, 2000).

Infection derived RNAs serve as the agents of regulatory networks in the cellular transcriptome (Feschotte, 2008; Briones et al., 2009; Koonin, 2009; Villarreal and Witzany, 2010). Without transcription from the genetic storage medium of DNA into the living world of such RNA agents, no relevant genetic process in the cellular transcriptome can be initiated (Volf, 2006). RNAs,

OPEN ACCESS

Edited by:

David Gilmer,
Université de Strasbourg, France

Reviewed by:

Cristina Romero-López,
Institute of Parasitology and
Biomedicine "López-Neyra" (CSIC),
Spain

Roland Marquet,
Architecture et Réactivité de l'ARN,
France

*Correspondence:

Guenther Witzany
witzany@sbg.at

Specialty section:

This article was submitted to
Virology,
a section of the journal
Frontiers in Microbiology

Received: 11 February 2018

Accepted: 14 March 2018

Published: 27 March 2018

Citation:

Villarreal LP and Witzany G (2018)
Editorial: Genome Invading
RNA-Networks.
Front. Microbiol. 9:581.
doi: 10.3389/fmicb.2018.00581

with their inherent repeat syntax, format the expression of coding sequences and organize the coherent line-up of timely coordinated steps of replication (Shapiro and von Sternberg, 2005). The transport of genetic information to the progeny cells is also coordinated by these agents (Spadafora, 2017). Furthermore, they are crucial for the cooperation between networks of RNA-stem loops to constitute important nucleoprotein complexes such as ribosome, spliceosome, and editosome (Witzany, 2011). Therefore, such RNA groups are essential for complex order of genome constructions (Witzany, 2014).

Additionally of interest is that infectious non-coding RNAs insert preferentially in non-coding DNA areas, whereas coding DNA usually is not the target (Bushman, 2003; Mitchell et al., 2004; Bartel, 2009). In this perspective the non-coding DNA is the preferred habitat to settle down by infectious RNAs, e.g., y-chromosome in human genomes (Shapiro, 2002; Villarreal, 2009; Lambowitz and Zimmerly, 2011). This may indicate that the preferred change in evolutionary processes occurs in regulatory sections and not in the information storage coding for proteins, the main source for “mutations” in previous theoretical concepts of evolution (Villarreal and Witzany, 2013).

Frontiers Research Topic Genome Invading RNA-Networks highlights various RNA networks being active in host genomes.

Sablok et al. discussed classification, identification and roles of tRNA derived smallRNAs across plants and their potential involvement in abiotic and biotic stresses. Wang et al. investigated how retrotransposon insertion polymorphisms can impact human health and disease. Moelling et al. demonstrated that RNase H-like activities of retroviruses, TEs, and phages, have built up innate and adaptive immune systems throughout all domains of life. Liu et al. summarize recent advances in understanding the roles of miRNAs involved in the plant defense against viruses and viral counter-defense. Malicki et al. review three retrotransposon classes that might represent a domestication of the selfish elements. Habibi and Salmani exemplified direct action of RNA networks in shaping the genome. Pecman et al. compared two different approaches for detection and discovery of plant viruses and viroids. Nagata et al. found that sequence changes in the RNase H domain and the reverse transcriptase connection domain are responsible for subtype classification. Zinad et al. suggest that natural antisense transcripts interfere with their corresponding sense transcript to elicit concordant and discordant regulation. Ottesen et al. describe how the abundance of Alu-like sequences may contribute toward Survival Motor Neuron gene pathogenesis. Ariza-Mateos and Gómez show how RNA viruses mimic key factors of the host cell. Spadafora found that spermatozoa act as collectors of somatic information and as delivering vectors

to the next generation. Frías-Lasserre et al. demonstrate how current epigenetic advances on non-coding RNAs has changed the perspective on evolutionary relevant variations. Scolaro et al. demonstrate that evolutive processes for viruses are now interpreted as coordinated phenomenon that leads to global non-random remodeling of the population. Seligmann and Raoult found that ribosomal RNA stem-loop hairpins resemble those formed by viruses and short parasitic repeats infesting bacterial genomes. Fu et al. provide deep insights into the molecular mechanisms of influenza virus infection.

More and more empirical evidence establishes the crucial role of natural genetic content editors such as viruses and RNA-networks to create genetic novelty, complex regulatory control, epigenetics, genetic identity, immunity, inheritance vectors, new sequence space, evolution of complex organisms and evolutionary transitions (Villarreal and Witzany, 2015; Chuong et al., 2016, Spadafora, this issue).

Genetic identities of RNA-networks such as e.g., group I introns, group II introns, viroids, RNA viruses, retrotransposons, LTRs, non-LTRs, SINEs, LINEs, Alus invade and even persist in host genomes (Villarreal, 2009). Also mixed networks of RNA- and DNA viruses derived parts that integrate into host genomes have been found (Stedman, 2015), not forgetting persistent retroviral infections and the essential roles of reverse transcriptases and related RNase H endonucleases (Moelling and Broecker, 2015).

Highly dynamic RNA-Protein networks such as ribosome, editosome and spliceosome together with several context-dependent sequence modifying interactions, such as pseudo-knotting, frame-shifting, loop-kissing, by-passing translation generate a large variety of RNA regulatory functions out of a given DNA content (Cao et al., 2014; Denzler et al., 2014; Peselis and Serganov, 2014; Samatova et al., 2014; Keam and Hutvagner, 2015; Atkins et al., 2016).

There are reasonable expectations that this new empirically based perspective on the evolution of genetic novelty and biological information will have more explanatory power in the future than the “error-replication” narrative of the last century.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

Atkins, J. F., Gesteland, R. F., and Cech, T. R. (eds.). (2011). *RNA Worlds. From Life's Origin to Diversity in Gene Regulation*. New York, NY: Cold Spring Harbor Laboratory Press.

Atkins, J. F., Loughran, G., Bhatt, P. R., Firth, A. E., and Baranov, P. V. (2016). Ribosomal frameshifting and transcriptional slippage: from genetic steganography and cryptography to adventitious use. *Nucleic Acids Res.* 44, 7007–7078. doi: 10.1093/nar/gkw530

- Briones, C., Stich, M., and Manrubia, S. C. (2009). The dawn of the RNA world: toward functional complexity through ligation of random RNA oligomers. *RNA* 15, 743–749. doi: 10.1261/rna.1488609
- Britten, R. J. (2004). Coding sequences of functioning human genes derived entirely from mobile element sequences. *Proc. Natl. Acad. Sci. U.S.A.* 101, 16825–16830. doi: 10.1073/pnas.0406985101
- Brosius, J. (1999). RNAs from all categories generate retrosequences that may be exapted as novel genes or regulatory elements. *Gene* 238, 115–134. doi: 10.1016/S0378-1119(99)00227-9
- Bushman, F. D. (2003). Targeting survival: Integration site selection by retroviruses and LTR-retrotransposons. *Cell* 115, 135–138. doi: 10.1016/S0092-8674(03)00760-8
- Bartel, D. P. (2009). MicroRNAs: target recognition and regulatory functions. *Cell* 136, 215–233. doi: 10.1016/j.cell.2009.01.002
- Cao, S., Xu, X., and Chen, S. J. (2014). Predicting structure and stability for RNA complexes with intermolecular loop-loop base-pairing. *RNA* 20, 835–845. doi: 10.1261/rna.043976.113
- Chuong, E. B., Elde, N. C., and Feschotte, C. (2016). Regulatory evolution of innate immunity through co-option of endogenous retroviruses. *Science* 351, 1083–1087. doi: 10.1126/science.aad5497
- Denzler, R., Agarwal, V., Stefano, J., Bartel, D., and Stoffel, M. (2014). Assessing the ceRNA hypothesis with quantitative measurements of miRNA and target abundance. *Mol. Cell* 54, 766–776. doi: 10.1016/j.molcel.2014.03.045
- Eigen, M. (1971). Selforganization of matter and the evolution of biological macromolecules. *Naturwissenschaften* 58, 465–523. doi: 10.1007/BF00623322
- Feschotte, C. (2008). Transposable elements and the evolution of regulatory networks. *Nat. Rev. Genet.* 9, 397–405. doi: 10.1038/nrg2337
- Hayden, E. J., and Lehman, N. (2006). Self-assembly of a group I intron from inactive oligonucleotide fragments. *Chem. Biol.* 13, 909–918. doi: 10.1016/j.chembiol.2006.06.014
- Higgs, P. G., and Lehman, N. (2015). The RNA World: molecular cooperation at the origins of life. *Nat. Rev. Genet.* 16, 7–17. doi: 10.1038/nrg3841
- Keam, S. P., and Hutvagner, G. (2015). tRNA-Derived Fragments (tRFs): Emerging New Roles for an Ancient RNA in the Regulation of Gene Expression. *Life* 5, 1638–1651. doi: 10.3390/life5041638
- Koonin, E. V. (2009). On the origin of cells and viruses: primordial virus world scenario. *Ann. N.Y. Acad. Sci.* 1178, 47–64. doi: 10.1111/j.1749-6632.2009.04992.x
- Koonin, E. V., Senkevich, T. G., and Dolja, V. V. (2006). The ancient Virus World and evolution of cells. *Biol. Direct.* 19, 1–29. doi: 10.1186/1745-6150-1-1
- Lambowitz, A. M., and Zimmerly, S. (2011). Group II introns: Mobile ribozymes that invade DNA. *Cold Spring Harb. Perspect. Biol.* 3:a003616 doi: 10.1101/cshperspect.a003616
- Manrubia, S. C., and Briones, C. (2007). Modular evolution and increase of functional complexity in replicating RNA molecules. *RNA* 13, 97–107. doi: 10.1261/rna.203006
- Marraffini, L. A., and Sontheimer, E. J. (2010). Self versus non-self discrimination during CRISPR RNA-directed immunity. *Nature* 463, 568–571. doi: 10.1038/nature08703
- Mattick, J. S. (2003). Challenging the dogma: the hidden layer of non-protein-coding RNAs in complex organisms. *Bioessays* 25, 930–939. doi: 10.1002/bies.10332
- Mitchell, R. S., Beitzel, B. F., Schroder, A. R., Shinn, P., Chen, H., Berry, C. C., et al. (2004). Retroviral DNA integration: ASLV, HIV, and MLV show distinct target site preferences. *PLoS Biol.* 2:e234. doi: 10.1371/journal.pbio.0020234
- Moelling, K., and Broecker, F. (2015). The reverse transcriptase-RNase H: from viruses to antiviral defense. *Ann. N.Y. Acad. Sci.* 1341, 126–135. doi: 10.1111/nyas.12668
- Peselis, A., and Serganov, A. (2014). Structure and function of pseudoknots involved in gene expression control. *Wiley Interdiscip. Rev. RNA* 5, 803–822. doi: 10.1002/wrna.1247
- Samatova, E., Konevega, A. L., Wills, N. M., Atkins, J. F., and Rodnina, M. V. (2014). High-efficiency translational bypassing of non-coding nucleotides specified by mRNA structure and nascent peptide. *Nat. Commun.* 5, 4459. doi: 10.1038/ncomms5459
- Schultes, E. A., and Bartel, D. P. (2000). One sequence, two ribozymes: Implications for the emergence of new ribozyme folds. *Science* 289, 448–452. doi: 10.1126/science.289.5478.448
- Shapiro, J. A. (2002). Repetitive DNA, genome system architecture and genome reorganization. *Res. Microbiol.* 153, 447–453. doi: 10.1016/S0923-2508(02)01344-X
- Shapiro, J. A., and von Sternberg, R. (2005). Why repetitive DNA is essential to genome function. *Biol. Rev. Camb. Philos. Soc.* 80, 227–250. doi: 10.1017/S1464793104006657
- Spadafora, C. (2017). The “evolutionary field” hypothesis. Non-Mendelian transgenerational inheritance mediates diversification and evolution. *Prog. Biophys. Mol. Biol.* 134, 27–37. doi: 10.1016/j.pbiomolbio.2017.12.001
- Stedman, K. M. (2015). Deep Recombination: RNA and ssDNA Virus Genes in DNA Virus and Host Genomes. *Annu. Rev. Virol.* 2, 203–217. doi: 10.1146/annurev-virology-100114-055127
- Vaidya, N. (2012). *Spontaneous Cooperative Assembly of Replicative Catalytic RNA Systems*. Dissertations and Theses. Portland state University
- Vaidya, N., Manapat, M. L., Chen, I. A., Xulvi-Brunet, R., Hayden, E. J., and Lehman, N. (2012). Spontaneous network formation among cooperative RNA replicators. *Nature* 491, 72–77. doi: 10.1038/nature11549
- Villarreal, L. P. (2005). *Viruses and the Evolution of Life*. Washington, DC: ASM Press.
- Villarreal, L. P. (2009). *Origin of Group Identity. Viruses, Addiction and Cooperation*. New York, NY: Springer.
- Villarreal, L. P. (2011a). Viruses and host evolution: virus-mediated self identity. *Adv. Exp. Med. Biol.* 738, 185–217. doi: 10.1007/978-1-4614-1680-7_12
- Villarreal, L. P. (2011b). Viral ancestors of antiviral systems. *Viruses* 3, 1933–1958. doi: 10.3390/v3101933
- Villarreal, L. P. (2014). Force for ancient and recent life: viral and stem-loop RNA consortia promote life. *Ann. N.Y. Acad. Sci.* 1341, 25–34. doi: 10.1111/nyas.12565
- Villarreal, L. P., and Witzany, G. (2010). Viruses are essential agents within the roots and stem of the tree of life. *J. Theor. Biol.* 262, 698–710. doi: 10.1016/j.jtbi.2009.10.014
- Villarreal, L. P., and Witzany, G. (2013). Rethinking quasispecies theory: from fittest type to cooperative consortia. *World J. Biol. Chem.* 4, 79–90. doi: 10.4331/wjbc.v4.i4.79
- Villarreal, L. P., and Witzany, G. (2015). When competing viruses unify: evolution, conservation, and plasticity of genetic identities. *J. Mol. Evol.* 80, 305–318. doi: 10.1007/s00239-015-9683-y
- Volf, J. N. (2006). Turning junk into gold: domestication of transposable elements and the creation of new genes in eukaryotes. *Bioessays* 28, 913–922. doi: 10.1002/bies.20452
- Witzany, G. (2011). The agents of natural genome editing. *J. Mol. Cell. Biol.* 3, 181–189. doi: 10.1093/jmcb/mjr005
- Witzany, G. (2014). RNA sociology: group behavioral motifs of RNA consortia. *Life (Basel)*. 4, 800–818. doi: 10.3390/life4040800
- Witzany, G. (2016). Crucial steps to life: From chemical reactions to code using agents. *Biosystems* 140, 49–57. doi: 10.1016/j.biosystems.2015.12.007

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Villarreal and Witzany. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.