Do we eat gene regulators?

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In a recent study, plant microRNAs (miRNAs) have been found in the sera and tissues of various animals including humans. These miRNAs are acquired orally by food intake and can pass through the mammalian gastrointestinal tract into sera and organs. In vitro and in vivo studies have demonstrated that these plant microRNAs in food can regulate the expression of target genes in mammals. Correct regulation or dysregulation of miRNAs is linked to important gene expression patterns and diseases, such as cancer and atherosclerosis. Interestingly, plant miRNA function in mammalian cells is similar to the function of mammalian miRNAs; this gives rise to some notable questions.

If we look at the symbiotic relationship between higher eukaryotes and microbial agents, we find striking evidence that higher eukaryotes depend crucially on their microbial symbionts. As demonstrated by the hologenome project, the interactions between an animal population, the environment and intestinal microbiota within the gastrointestinal tract represents a rich niche-specific ecosphere with an abundance of microbes, ranging from bacteria to protozoa and viruses. The gastrointestinal tract of animals serves a similar function for animals to that of root ecospheres for plant organisms. This means that in the case of food intake of plant miRNAs that also act as regulatory miRNAs in the animal that has consumed the plant, the uptake may also confer some benefits on the helper agents (such as prokaryotic or viral symbiots). The acquisition of miRNAs and other non-coding RNAs, as a common method of horizontal gene transfer or viral infection events. Here, a completely different method is under investigation. Organisms that need to feed to maintain metabolism may take in miRNAs and other non-coding RNA species, through eating.

Recently, plant miRNAs have been found in various animals, including humans. These miRNAs are acquired orally by food intake and can pass through the mammalian GI tract into sera and organs. Epithelial cells in the small intestine can take up these miRNAs and package them into microvesicles, and hence act as a transport system into the circulatory system of host. In vitro and in vivo studies have demonstrated that these plant miRNAs in food can regulate the expression of target genes in mammals. The correct regulation of miRNAs is linked to important gene expression regulation, and diseases such as cancer and atherosclerosis. Due to several plant miRNAs acting as RNA interference (RNAi) molecules, which is possible due to a high degree of complementarity between miRNAs and target RNAs, miRNAs in mammals are perceived to also have a role in immune functions. Interestingly, plant miRNA function in mammalian cells is similar to mammalian miRNAs. Therefore, miRNAs represent a novel class of universal modulators in a cross-species, or even in a cross kingdom, manner. This raises several important questions:

- Are there other non-coding RNAs, with similar important roles in gene regulation, that are able to transfer horizontally through plant food intake, such as siRNAs, snoRNAs or Piwi RNAs, which are thought to be remnants of viral infection events?
Important Roles of microRNAs

miRNAs are small non-coding RNAs that regulate sequence specific gene expression. They identify and target the genes that they regulate, such as mammalian mRNAs.5,6 miRNAs are single-stranded RNAs of 19–25 nucleotides in length, and are generated from 70 nucleotide precursors miRNAs. The transcription of this pre-miRNA is processed by RNA polymerases pol II and pol III.10 Whereas pol II produces the mRNA, small nuclear RNAs of the spliceosome, pol III produce shorter non-coding RNAs, such as snRNAs, and a nuclear RNA that is part of the spliceosome.11 miRNAs control not only developmental timing, hematopoiesis, organogenesis, apoptosis and cell proliferation, but also fat metabolism in flies, neuronal patterning in nematodes and control leaf and flower development in plants.5 In plants, microRNAs target gene regulation and genes that are themselves regulators, especially the steps and sub-steps of developmental processes.12 Every metazoan cell type, at each developmental stage, has a distinct mRNA expression profile.5 Additionally, the acquisition ratio of microRNAs correlates with the evolution of complexity in vertebrates.13,15 The most characteristic differences between how miRNAs act in plants or animals are found in the stem loop. MicroRNAs, as well as small interfering RNAs derive from transposable elements which had an inherent regulatory competency over gene regulation. Both, siRNAs and miRNAs act in a coordinated manner, in that they share a division of labor in hierarchical steps of suppression and amplification.13 The defense mechanism of host genomes against transposable element invaders through siRNA, evolved into miRNAs with a new regulatory complexity and a new phenotype. First evolving as an immune function, it was later co-opted as a tool for the regulation of complex pathways in the host’s gene expression.5,16

miRNAs are acknowledged as key regulators of gene expression. This means that dysfunctions of these regulatory mechanisms may lead to dysregulation of genes, with a cascade of disease-causing consequences.5 In their original function miRNAs had an immune function against viruses and similar agents, and only later was their function adapted for the regulation of eukaryotic gene expression.15 Mammalian cells express a variety of miRNAs, and mRNA expression patterns can characterize different tissues. As seen with viruses, miRNAs also share tissue tropism. This indicates that the regulatory network of miRNAs, siRNAs together with foreign, as well as self-similar (persistent) viruses, is the reason for the interrelationship of (1) immune function against genetic parasites, and (2) coopted adaptation of complementary functions of siRNAs and miRNAs for regulatory host gene regulations.5,16

Eukaryotic cells use RNA silencing to defend genetic parasites. Using similar pathways they also regulate expression of their own genes.15 In common with their immune functions used against genetic parasites, miRNAs and siRNAs were formerly domesticated genetic parasites that now act against related invaders. This means that in prokaryotes and eukaryotes, immune function against genetic parasites are domesticated remnants of former viral infection events.15

Interestingly miRNAs target groups of genes within their repeat-rich coding regions.11 Repeat sequences derive from former retroviral infection events.17 This indicates regulatory roles for miRNAs on endogenous retroviruses, or on the remnants of retroviral infection events (e.g., env, gag, pol).

Conclusions

Through the recent discovery that plant microRNAs are found in mammalian sera and tissues, transferred via food intake, and may play similar regulatory roles with a cascade of disease-causing consequences.15 In their original function miRNAs had an immune function against viruses and similar agents, and only later was their function adapted for the regulation of eukaryotic gene expression. Mammalian cells express a variety of miRNAs, and mRNA expression patterns can characterize different tissues. As seen with viruses, miRNAs also share tissue tropism. This indicates that the regulatory network of miRNAs, siRNAs together with foreign, as well as self-similar (persistent) viruses, is the reason for the interrelationship of (1) immune function against genetic parasites, and (2) coopted adaptation of complementary functions of siRNAs and miRNAs for regulatory host gene regulations.5,16

1. Benes D, Benos P, Panuta L, Hortesi N. Food-based strategies to modulate the composition of the intestinal microbiota and their associated health effects. J Physical Pharmacol 2009; 60(Suppl 5-11); PMID: 21215419.
2. Bugli E, Gradilla M, Piarroux Tair, S, Franchetti C, Brigidi F. Aging of the human metaorganism: the intestinal microbiota and their associated health effects. Int J Mol Sci 2011; 12:3687-45; PMID:21547847.
3. Winder G. Nerve-immune RNS: postivory viral aposm or module task for cellular reach. Ares V Y and Sci 2003; 1178:249-67; PMID:19869404; http://dx.doi.org/10.1111/j.1749-6632.2009.04989.x
4. Zhang L, Hou D, Chen X, Li D, Zhu L, Zhang Y, et al. Exogenous plant MIR168a specifically targets mir168a in mammalian cells. Cell Res 2012; 22:107-26; PMID:22397396; http://dx.doi.org/10.1038/cr.2011.138
5. Cai Q, Gao C. MiRNA signatures in human cancers. Nat Rev Cancer 2006; 6:59-69; PMID:16489990; http://dx.doi.org/10.1038/nrc1799
6. He L, Hanouz J. MicroRNAs and RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5:520-31; PMID:15313576; http://dx.doi.org/10.1038/nrg1379
7. Badoual J. MicroRNAs target recognition and regulatory function. Curr Opin 2006; 16:211-25; PMID:16767256; http://dx.doi.org/10.1016/j.cub.2006.01.002
8. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009; 19:92-105; PMID:19193936; http://dx.doi.org/10.1101/gr.082701.108

9. Kim VN. MicroRNA biogenesis: coordinated cropping and damping. Nat Rev Mol Cell Biol 2005; 6:776-85; PMID:16010244; http://dx.doi.org/10.1038/nrm1664

10. Colleen BR. Viruses and microRNA. Nat Genet 2006; 38(suppl):S25-9; PMID:16796021; http://dx.doi.org/10.1038/nrg1793

11. Bartel DP. MicroRNAs: genomics, biogenesis, mechanisms, and function. Cell 2004; 116:281-97; PMID:15074446; http://dx.doi.org/10.1016/S0092-8674(04)00045-5

12. Heimberg AM, Sempere LF, Moy VN, Donoghue PCJ, Peterson KJ. MicroRNAs and the advent of vertebrate morphological complexity. Proc Natl Acad Sci U S A 2008; 105:2946-50; PMID:18287013; http://dx.doi.org/10.1073/pnas.0712259105

13. Shkumatava A, Stark A, Sive H, Bartel DP. Coherent but overlapping expression of microRNAs and their targets during vertebrate development. Genes Dev 2009; 23:466-81; PMID:19240133; http://dx.doi.org/10.1101/gad.1745709

14. Doench JG, Petersen CP, Sharp PA. siRNAs can function as miRNAs. Genes Dev 2003; 17:438-42; PMID:12600936; http://dx.doi.org/10.1101/gad.1064703

15. Piriyapongsa J, Jordan IK. Dual coding of siRNAs and miRNAs by plant transposable elements. RNA 2008; 14:814-21; PMID:18377716; http://dx.doi.org/10.1261/rna.917908

16. Scaria V, Hariharan M, Pillai B, Maiti S, Brahmachari SK. Host-virus genome interactions: major roles for microRNA. Cell Microbiol 2007; 9:2786-94; PMID:17949962; http://dx.doi.org/10.1111/j.1462-5822.2007.01050.x

17. Schnall-Levin M, Rissland OS, Johnston WK, Perrimon N, Bartel DP, Berger B. Unusually effective microRNA targeting within repeat-rich coding regions of mammalian mRNA. Genome Res 2011; 21:3595-601; PMID:21685129; http://dx.doi.org/10.1101/gr.122333.111

18. Sontheimer EJ, Carthew RW. Silence from within: endogenous siRNAs and miRNAs. Cell 2005; 122:9-12; PMID:16009127; http://dx.doi.org/10.1016/j.cell.2005.06.030

19. Vittemark LP. Viral antagonism of antiviral systems. Viruses 2011; 3:593-58; PMID:22009523; http://dx.doi.org/10.3390/v3030593

20. Schnall-Levin M, Brandl ON, Johnson WK, Peterson N, Bartel DP, Berger B. Usually effective microRNA targeting within repeat-rich coding regions of mammalian mRNA. Genome Res 2011; 21:3595-601; PMID:21685129; http://dx.doi.org/10.1101/gr.122333.111

21. von Sternberg R. On the role of repetitive DNA elements in the context of a unified genome-epigenetic system. Ann N Y Acad Sci 2002; 981:154-88; PMID:12547679; http://dx.doi.org/10.1111/j.1749-6632.2002.tb04917.x

22. Shapiro JA, von Sternberg R. Why repetitive DNA is essential to genome function. Red Bus Cam Pharm Soc 2005; 10:227-56; PMID:15921019; http://dx.doi.org/10.17157/46795008064637

23. Villarruel LP. Viruses and the Evolution of Life. ASM Press, 2005; Washington.