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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 arteriosclerosis. Interestingly, plant miRNA function in mammalian cells is similar to the function of mammalian miRNAs; this gives rise to some notable questions.

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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.[1,2] 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 symbionts). The acquisition of miRNAs and other non-coding RNAs, is a common method of horizontal gene transfer or viral infection events.[3] 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 be found in various animals, including humans.[4] 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 arteriosclerosis.[5] 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.[4] Interestingly, plant miRNAs 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 snRNAs, snoRNAs or Piwi RNAs, which are thought to be remnants of viral infection events?

- The origins of plant miRNAs; are they remnants of viral infections or food-intake by soil bacteria, mycorrhiza or symbiotic co-evolutionary agents such as with insects?
- Is the food intake of miRNAs and possibly other non-coding RNAs a universal phenomenon throughout all kingdoms?
- Can we target beneficial gene regulatory processes through specified food intake, such as prebiotics?

Important Roles of microRNAs

miRNAs are small non-coding RNAs that regulate sequence specific gene expression.[6] They identify and target the genes that they regulate, such as mammalian mRNAs.[7,8] miRNAs are single-stranded RNAs of 19–25 nucleotides in length, and are generated from 70 nucleotide precursor miRNAs.[9] The transcription of this pre-miRNA is processed by RNA polymerases pol II and pol III.[10] Whereas pol II produces the mRNA, small nucleolar and small nuclear RNAs of the spliceosome, pol III produce shorter non-coding RNAs, such as tRNAs, some rRNAs, 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.[11] In plants, microRNAs target gene regulation and genes that are themselves regulators, especially the steps and substeps of developmental processes.[12] Every metazoan cell type, at each developmental stage, has a distinct miRNA expression profile.[11] Additionally, the acquisition ratio of microRNAs correlates with the evolution of complexity in vertebrates.[13,14]

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 competence 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.[15] 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.[16]

MicroRNAs as Tools in Virus-Host Interactions

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.[17]

Mammalian cells express a variety of miRNAs, and miRNA 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 symbiotic (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 microRNAs for regulatory host gene regulations.[18]

Eukaryotic cells use RNA silencing to defend genetic parasites. Using similar pathways they also regulate expression of their own genes.[19] 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 functions against genetic parasites are domesticated remnants of former viral infection events.[20]

Interestingly miRNAs target groups of genes within their repeat-rich coding regions.[21] Repeat sequences derive from former retroviral infection events.[22-24] 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 to those of mammalian derived microRNAs, the following question arises: Are microRNAs, and other non-coding RNAs also objects of other cross species, or cross kingdom transfers, such as between soil bacteria and their phages, mycorrhizal fungi, nematodes and insects? As we know that several families of non-coding RNAs are remnants of former viral infection events that now play important roles in host gene regulation as coopted adaptations, it will be important to clarify the relationship and interactions between viral infection derived miRNAs, and miRNAs that entered the host organism via food intake. We might then be able to direct future research activities at the regulation of beneficial gene expression by specified food intake, such as prebiotics.

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