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Education

Recent advances in our understanding of the pathobiology of non-coding RNA

EDUCATION

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ABSTRACT

Summary

The central dogma of molecular biology recognised RNA as a mere intermediate between DNA sequence and proteins, the main protagonists of cellular functions. The shadow of a wrinkle in this concept appeared when the Human Genome Project revealed that protein-coding genes only account for 2% of our genome and the remaining 98% was originally dismissed as elusive "junk DNA."

Relevance

Recent advances in next-generation sequencing provided tantalising evidence that 70-90% of human genome is actively transcribed(1). Numerous studies started discerning the functional importance of long and short (>200 and <200 nucleotides, respectively) non-coding transcripts far beyond the initial textbook-engraved infrastructural and information-transmitting role of rRNA, tRNA and mRNA.

Take Home Messages

By "rediscovering the junk," this essay reviews a selection of recent disease-associated advances in the field of small non-coding RNAs before extending the discussion to long non-coding RNAs and finally to the overarching concepts of competing endogenous RNAs (ceRNAs) and 'social' RNA.

RNA interference (RNAi)

RNA interference is a process whereby micro RNA (miRNA) and small interfering RNA (siRNA) molecules inhibit target gene expression by acting on mRNA. The first miRNA to be identified, lin-4, was discovered as a short non-coding RNA required for repression of lin-14 gene and subsequent maturation of C. elegans larvae. (2) The sequence of lin-4 displayed complementarity to the 3' untranslated region (UTR) of lin-14 mRNA, (2) suggesting that lin-4 regulates lin-14 expression through an RNA-RNA interaction. The discovery of let-7 miRNA (3) and its conservation from worms to humans (4) first underscored the prevalence and functional importance of miRNA-dependent gene regulation. Although estimated to represent less than one percent of our genome, miRNAs have been proposed to regulate as many as 92% of human genes. (5)

What is the mechanism of gene regulation by miRNAs? The process of miRNA biogenesis typically starts with RNA polymerases transcribing miRNA genes into primary miRNAs, which fold to form hairpin-loop structures (Figure 1). These are recognised and cleaved by the Microprocessor complex to form precursor miRNAs (pre-miRNAs). Following nuclear export, pre-miRNAs are cleaved by a protein complex involving Dicer endonuclease and one of the resulting 21-23bp strands assembles with Argonaute proteins into an RNA-induced silencing complex (RISC). Using miRNA as a guide, RISC binds to complementary miRNA-response elements (MREs) in 3' untranslated region (UTR) of target mRNAs leading to mRNA cleavage or translational inhibition. While miRNAs are endogenous, siRNAs are exogenous RNA duplexes that enter the cell, are cleaved by Dicer and follow the same processing and functional path as miRNAs.

About 20 years since their discovery and landmark observations, miRNAs are recognised as regulators of most cellular processes, with their derangements reported in a host of human disease.

miRNAs in tumorigenesis

Tumorigenesis is generally associated with gain-of-function mutations or amplification of oncogenes and/or loss-of-function mutations in tumour suppressor genes (TSG). Oncomirs, i.e. miRNAs that promote cancer, typically repress TSGs. The polycistronic cluster miR-17-92 is located in a region of chromosome 13q and is frequently amplified in tumours. (6) The binding of oncprotein MYC to this cluster drives the expression of six miRNAs with reported roles in cell proliferation, apoptosis and angiogenesis. (7) Overexpression of this cluster in MYC-driven mouse model of lymphoma accelerated tumorigenesis by suppressing apoptosis, (8) identifying miR-17-92 as an oncomir normally acting downstream of MYC.

The first evidence for altered miRNA expression in cancer came from genome-wide studies in patients with B-cell chronic lymphocytic leukaemia (B-CLL), the most prevalent type of adult leukaemia. Using somatic cell hybridisation, 68% of B-CLL patients were found to carry a deletion in the gene cluster encoding miR-15 and miR-16 miRNAs. (9) Prolonged survival of B cells in B-CLL corresponded to increased expression of the anti-apoptotic protein Bcl-2 (among other targets), a process successfully reversed by forced expression of miR-15 and miR-16 into cultured B cells of B-CLL patients. (10) This demonstrated the tumour-suppressing function of miR-15 and miR-16, which was confirmed in mouse xenograft experiments: human prostatic tumour grafts transfected with miR-15 and mir-16 displayed increased regression compared to untransfected controls. (11) Hence, miRNAs can function as TSGs and their restoration bears therapeutic promise.

Human cancers typically show a global decrease in miRNA expression, (12) which could reflect the undifferentiated state of tumours or causally contribute to the transformed phenotype. To answer this question, Kumar and co-workers generated mouse and human lines deficient in miRNA processing proteins Drosha or DGCR8 (components of the microprocessor complex) and Dicer1. These lines displayed a substantial decrease in steady state miRNA levels, increased growth in soft agar cultures and more malignant behaviour when injected into nude mice compared to controls, (12) demonstrating that miRNA pathways tend to act as an overall brake on cancer growth rather than simply reflecting the undifferentiated state. Interestingly, overexpression of let-7 miRNA alone reversed the in vitro effects of Dicer1 knockdown (12), implying that let-7 may be the key TSGs among miRNAs. Let-7 miRNAs target the KRAS oncogene, (13) whose properties have to date thwarted all therapeutic efforts using small molecule inhibitors. Hence, overexpression of let-7 miRNA provides an alternative approach to target KRAS, which is frequently mutated in human cancer. (14)

miRNAs in immunity

One caveat in therapeutic application of miRNAs is that a single miRNA typically induces pleiotropic effects in cell types with different transcriptional profiles. While let-7 suppresses tumorigenesis in cancer cells, (13) it was demonstrated to play a diametrically opposite role in tumour-associated macrophages (TAMs). (15) TAMs typically exist as two populations: tumour-reactive (M1) macrophages attack tumour cells whereas tumour-tolerant (M2) macrophages supress anti-tumour immunity. Global ablation of miRNAs by deletion of Dicer1 in mice resulted in polarisation of M2 towards M1 population and boosted anti-tumour reactivity. (15) This process was rescued by forced expression of let-7 miRNA, (15) suggesting that the tumour-tolerant M2 phenotype is chiefly maintained by let-7 miRNA.

In adaptive immunity, tolerance mechanisms including regulatory T (Treg) cells prevent other T cells from reacting against self-proteins, thereby limiting autoimmune disease. Tregs exist in two

populations: natural nTregs differentiate in the thymus whereas induced iTregs are induced by IL-2 and TGFβ stimulation of naïve CD4 T cells in the periphery. nTregs and iTregs differ epigenetically (16) and iTregs were shown to lose Treg markers (and immunosuppressive function) and differentiate into exTreg cells (16) (Figure 2). The latter recognise self-antigens and can, instead of suppressing autoimmunity, actually attack self-antigens themselves. (17) This raises the question of what causes iTregs to become exTregs? Immunosuppressive Treg cells and immunoreactive TH17 cells have diametrically opposite functions, yet share many differentiation factors. In the presence of IL-1β (from activated monocytes) and IL-2, iTregs downregulate the canonical Treg transcription factor Foxp3 (i.e. become exTregs) and start producing pro-inflammatory IL-17, thus functionally resembling TH17 cells. (18) Interestingly, the transition from iTreg cells to TH17-like exTreg cells has been shown to involve miRNAs. Peripheral CD4 T cells from humans with systemic lupus erythematosus and Crohn's disease as well as autoimmune mouse models demonstrated downregulation of miR-125a, which stabilises both the commitment and regulatory capacity of Treg cells. (19) Mice deficient in miR-125a spontaneously developed autoimmune disease, which was successfully reversed using synthetic miR-125a analogues. (19) Hence, miR-125a serves as a transcriptional regulator of Treg cells whose forced re-expression can re-wire aberrant Treg cells back to normal physiological function and prevent autoimmunity.

tRNA fragments in transgenerational epigenetic inheritance

Besides the conventional role of tRNAs in translation, striking new evidence suggests an active role of tRNA fragments (tRFs) in transgenerational inheritance independent of changes in DNA sequence. Using in vitro fertilisation, offspring of males consuming a low-protein diet exhibited significant hepatic up-regulation of squalene epoxidase (involved in cholesterol biosynthesis) compared to controls, implying that paternal diet can affect offspring metabolism via information located in sperm. (20) Deep sequencing of small RNAs in sperm of low-protein diet versus control males demonstrated the former to have increased abundance of tRFs, whose injection into normal zygotes recapitulated the metabolic phenotype of tRF donors. (21) Locked nucleic acid (LNA) oligonucleotides blocking tRFs derived from the 5' end of glycine tRNA resulted in dramatic up-regulation of about 70 genes, (22) demonstrating that tRFs can profoundly influence the transcriptional profile of the zygote. Hence, sperm tRFs present a paternal epigenetic factor mediating transgenerational inheritance of diet-induced metabolic disorders.

Long non-coding RNAs

While short non-coding RNAs mainly affect mRNA stability and translation, the functional repertoire of long non-coding (lnc) RNAs is considerably more versatile. This includes chromatin binding and epigenetic regulation, protein scaffolding and "sponging" of miRNAs as discussed below.

Selective targeting of mitochondrial metabolism in melanoma through the lncRNA SAMMSON

The survival of several tumours requires oxidative phosphorylation, which stimulated the development of metabolism-targeting anti-cancer agents. Single nucleotide polymorphism (SNP) array data revealed that focal amplifications of chromosome 3p characteristic of melanoma invariably encompass a newly annotated lncRNA gene SAMMSON, which was found to be selectively expressed in more than 90% of human primary and metastatic skin melanomas as demonstrated by RNA sequencing. (23) Prognosis and clinical success of current anti-melanoma therapies is associated with mutational status of BRAF, NRAS and TP53 of the tumour while chronic treatment with novel BRAF inhibitors, e.g. vemurafenib, invariably leads to drug resistance. (24) Promisingly, silencing SAMMSON using antisense oligonucleotides reduced proliferation of all melanoma cultures independently of BRAF, NRAS and p53 status and preserved sensitivity to BRAF inhibitors. (23) RNA pull down and mass spectroscopy identified a SAMMSON-associated protein, p32, known for its role in maintenance of mitochondrial membrane potential and oxidative phosphorylation. (25) Antisense nucleic acid-induced silencing of SAMMSON decreased mitochondrial membrane potential and triggered apoptosis, and the effect was rescued by reintroduction of p32. (23) Hence, SAMMSON silencing inhibits the survival of melanoma at least partly by disrupting p32-mediated mitochondrial functions.

How does impaired mitochondrial function hinder cell proliferation? Collapsed mitochondrial membrane potential impairs the import of cytoplasmic proteins into mitochondria, which leads to toxic accumulation of mitochondrial precursors in the cytosol, stalling of the cell cycle and/or apoptosis. (26) The relevance of this mechanism was confirmed by exposure of human melanoma cells to inhibitors of translation, which abolished the lethal effect of SAMMSON silencing. (23) Importantly, intravenous treatment with SAMMSON-silencing antisense nucleic acids significantly suppressed the growth of human melanoma tumours injected into mice, (23) identifying SAMMSON as an attractive therapeutic target for the disruption of mitochondrial metabolism selectively in melanoma.

Competing endogenous RNA (ceRNA)

Specific miRNA molecules can be repressed experimentally using chemically modified antisense oligonucleotides or artificial miRNA sponges. The latter are synthetic RNA constructs harbouring multiple miRNA-binding elements (MREs). The competition for shared miRNAs between decoy MREs of the sponge and functional MREs of natural miRNA target transcripts titrates the amount of functional miRNA within the cell. Growing

understanding of human transcriptome led to postulating the existence of natural RNA sponges, whereby all (co-localised) RNA transcripts that contain MREs can communicate with and regulate each other by competing for shared miRNAs, thus acting as competing endogenous RNAs (ceRNAs) (27). In this way, protein-coding mRNAs may possess an additional non-coding function as ceRNAs. Though ceRNA research is still in infancy, the ceRNA role of lncRNAs, (28) mRNAs (29) and circular RNAs (30) has already been reported. For example, the non-coding PTENP1 pseudogene has been reported to regulate the levels of its cognate gene, the tumour suppressor PTEN, by competing for shared miRNAs. (31) PTENP1 pseudogene is frequently lost in human cancers, (31) which results for uncontrolled repression of PTEN protein by miRNAs. Intriguingly, comparison of cultured human transformed versus untransformed cells revealed that the former express mRNAs with shorter 3' UTR regions. (32) While reducing their regulation by miRNA, this property also diminishes their ceRNA role. The functional consequence of this, if any, still remains to be elucidated.

RNA trafficking and the controversy of 'social' RNA

Exosomes are plasma-membrane-derived vesicles that transfer proteins, mRNAs, miRNAs and other ncRNAs between cells. Returning to the study of sperm tRNA fragments (tRFs) in transgenerational inheritance: deep sequencing of sperm cells at different locations along the epididymis demonstrated that all sperm cells contained comparable amounts of tRNAs, yet the abundance of tRFs increased distally along the epididymis. (22) This suggests that tRFs are not the product of tRNA degradation within the sperm. Instead, deep sequencing showed the sperm tRFs to be derived from exosome-like vesicles released by epididymis termed epididymosomes, (22) suggesting that functional ncRNAs can participate in intracellular communication.

miRNAs are trafficked around the body in high-density lipoprotein (HDL) particles. (33) The HDL-miRNA profile of healthy human subjects was found to be significantly different from patients with familial hypercholesterolemia and the two types of HDL induced different transcriptional profiles in cultured human hepatocytes as demonstrated by miRNA microarrays. (33) This demonstrated that HDL-transported miRNAs are functional, differ in disease states and can alter the transcriptome of target tissues.

Lastly and most controversially, the 'social' RNA hypothesis posits that the RNA world extends beyond the boundaries of an organism. (34) Within numerous limitations, RNA-containing complexes in the environment could influence gene expression profiles between animals of the same species as well as across species. Using miRNA microarray profiling of HDL-miRNA complexes, healthy human subjects in regular contact with different domesticated animals were demonstrated to possess different HDL-miRNA profiles that clustered based on the type of animal they were in contact with. (35) Furthermore, the differentially abundant miRNA species were shown to differentially regulate the pro-inflammatory NFκB pathway in cultured human macrophages, (35) contentiously suggesting that the type of animal one regularly contacts could influence one's susceptibility to inflammation.

Conclusion

With comparable numbers of protein coding genes spanning the evolutionary tree from simple worms to humans, complexity is now believed to reside largely in the non-coding part of the genome previously dismissed as junk DNA or transcriptional noise. Unravelling the intricacies of this vast RNA underworld has already revealed numerous pathophysiological mechanisms, only a handful of which are presented here. To date, the role of some newly defined ncRNA classes, e.g. agotrons, (36) extra-coding RNAs (37) and enhancer RNAs (38) remains poorly characterised, which, together with the likely prospect of more ncRNA species still to be defined, heralds a profuse expansion of the newly (re)discovered layer of gene regulation and potential therapeutic applications.

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Figures

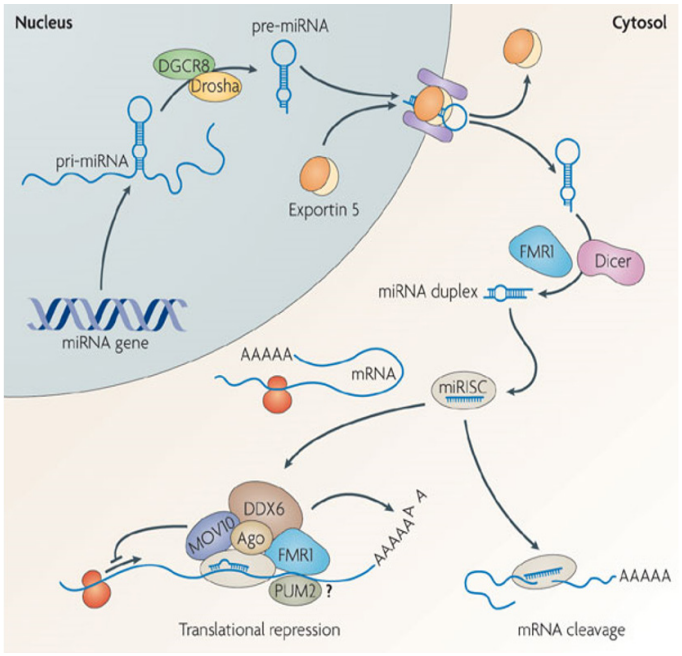

Figure 1: miRNA biogenesis and mode of action(39).

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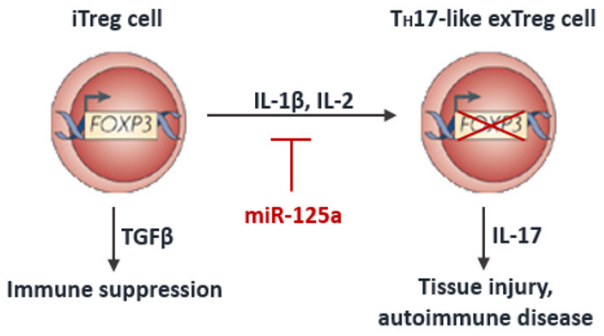

Figure 2: miR-125a stabilises iTreg cells and prevents their transition into pro-inflammatory TH17-like exTreg cells (adapted from(40)).

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