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EDUCATIONAL SECTION

Small RNAs: a new class of genome regulators and their significance

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The discovery of new functions for RNA and a new category of RNA molecules offers significant insights into the regulation of the genome. This may have considerable implications for the understanding and manipulation of cancer biology.

INTRODUCTION

Small RNAs have made a large impact. For many years, we have recognised three principal functions for ribose nucleic acid in the transcription of genomic DNA into the proteins, which give form to life. These are messenger RNA (mRNA), ribosomal RNA (mRNA) and transfer RNA (tRNA). Another heterogenous form of RNA has been associated with the nuclear chromatin proteins, which contribute structure to chromosomes (hnRNA), but its function has been uncertain. It has also become apparent that the human genome codes for much more RNA than is necessary to code for protein alone. The sum of all the transcribable RNA produced by the genome is the *transcriptome*.

The complete sequencing of the genomic DNA of a number of species has highlighted the need for greater understanding of the organised processes which control the switching on and off of each and every gene at all stages in the life of cells and organisms. Efforts are now under way to catalogue the total range of protein product of cells, the proteome. It had been believed that proteins and peptides effected regulatory control of the expression of genes. In cancer research, much interest has focussed on the protein product of dysfunctional genes, the oncogenes and their oncoproteins, for the regulation of the malignant phenotype. The mechanisms by which proteins might effect feedback control of the genome were nevertheless obscure.

Since 1993, focus has moved to a category of RNAs of progressively disclosed function, which measure between 20 and 300 nucleotides in length, and which now appear to be the key to the understanding of the regulation and control of genes.[1–5]

The small RNAs include a class of molecules only 21–28 nucleotides long, and other categories between 200 and 300 nucleotides long. They are known variously as small nuclear RNA (snRNA), small nucleolar RNA (snoRNA) and interfering RNA (RNAi). RNA classes with 'interference' functions include small interfering RNA (siRNA) and microRNA (miRNA), of which more than 100 different types have been identified. snRNAs are often found in complexes with proteins as small nuclear ribonucleoprotein particles (SnRNP). An example of their role in the regulation of RNA polymerase enzyme activity has been described in detail.[6]

THE FUNCTION OF SNRNAS

The nematode roundworm *C elegans* has been a powerful tool for the study of genomic regulation. Its genome has been sequenced, and the life of each and every cell produced during its development has been documented and correlated with gene expression and mutation. *C elegans* genes such as *lin-4* and *let-7* code for small RNAs which regulate directly the expression of other genes

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during developmental transitions, and they are thus known as timekeeper genes. These genes are well conserved across animal species, and it would thus appear that such RNA regulated mechanisms are important in embryogenesis and the emergence of form and function. The existence of large complexes of such closely related genes regulating development, the Hox genes, in all species including man, also points to a common ancestry for all symmetrical organisms.[1]

The range of regulatory functions now attributable to snRNAs is considerable,[5] in that:

- snRNAs can suppress the expression of genes in both plant and animal cells;
- folded, double stranded PNAs effect powerful negative feedback on RNA producing genes;
- the enzyme *Dicer* subdivides such small double stranded RNA (dsRNA) into miRNA and siRNA, which inhibit translation of conventional mRNA into protein;
- snRNAs degrade mRNAs, probably by binding directly to them, and hence stopping protein production;
- RNAi is a powerful and relatively simple tool for producing gene 'knockouts' in experimental models such as the mouse;
- snRNA permits permanent changes to genome function, known as *epigenetic* phenomena, without otherwise damaging or physically altering the genome;
- snRNAs can alter temporarily or permanently the physical structure of chromatin, including deletion, and thus modify the capacity for gene expression;
- snRNA can alter the expression of genes by selective blocking of one or more of the exons, the protein defining components of mRNA, a number of which contribute to the construction of most proteins and which are separated from each other by sections of seemingly inert RNA;
- snRNA may block the defective expression of genes, and protect the genome from viral and invading nucleic acids, thus acting as a housekeeper or 'immune system' for the genome.[7]

The potential role for snRNAs and dysfunctional snRNAs in the genomic instability of cancer has been considered but no evidence or actual examples have yet been produced. However, a number of authors have indicated how the use of high capacity analytical tools such as microarrays, which we have previously introduced,[8] can be used to measure very large numbers of RNA species in the transcriptome simultaneously, and thus to develop a classification of tumours based upon their RNA expression profiles, which may include the snRNA profiles, rather than upon their histopathological features.[9–12]

CONCLUSIONS

We are privileged to witness a phase of history wherein the molecular architecture of life and the product of three billion years of evolution is being unravelled in a few decades of headlong genomic discovery. The small RNA story ploughs a new furrow of innovative research into the controls of the mechanisms of life and disease. It has a long way to run before it translates into practical consequences for cancer patients, but a large gap in our understanding of the framework of life is now being filled.

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