GENERAL SCIENCE NOTES

INTRONS: NEW COMPLEXITY IN THE SYNTHESIS OF HIGHER ORGANISM RNA

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In studies with lower organisms such as bacteria and their viruses, it has been found that when an RNA molecule is made (transcription) it is copied directly from the DNA template (the genetic information source) on a basic unit basis, nucleotide for nucleotide. The final product has the same continuous sequence of bases as the complementary strand of DNA from which it was copied. Within the last year new and unexpected information about gene organization has been obtained in studies with plants, animals, and animal viruses.

The first of these results came from an analysis of the rabbit beta-globin (BG) system[1] (BG is a portion of hemoglobin). BG-DNA was obtained in two different ways. One, the BG-messenger RNA was purified and copied with an enzyme which makes DNA using RNA as its template. Two, BG-DNA was isolated from rabbit DNA using the techniques of recombinant DNA analysis in which restriction enzyme fragments of rabbit DNA were grown in bacterial cells. Those bacteria containing the BG genes were selected and replicated further to yield large amounts of BG-DNA. When the sequence of these BG-DNAs was compared it was found that the BG-DNA derived from DNA had approximately 600 nucleotides in the middle of the sequence that were not present in the BG-DNA derived from messenger RNA.

Further study has demonstrated that DNA insertions (introns) within genes may be the rule rather than the exception. They have been detected in the messages for mouse BG,[2] chick ovalbumin,[3] immunoglobulin[4] and in SV40 and polyoma animal viruses. Genes which yield structural RNAs with no known protein product, such as yeast transfer RNA and *Drosophilia* ribosomal RNA,[5] have been shown to be synthesized from DNAs containing large or small internal regions which are absent from the final RNA molecule. In those cases which have been examined the

primary RNA transcript contains the intronic sequence. Subsequently, the RNA is processed to cut out the unused portion(s) and the ends rejoined.

Synthesis of these spliced RNAs seems to involve copying the whole DNA sequence followed by cutting out the unused portion(s) and joining the ends back together again. Very little is known about this type of RNA processing. The 5200 nucleotides of the SV40 virus DNA may be used to make 30-50 different messenger RNAs of several hundred nucleotides each by using different combinations of cuttings and splicings. A single messenger RNA may contain as many as three gaps when its sequence is compared with the original viral DNA. In the case of SV40, with its very tiny genome, perhaps RNA splicing provides a mechanism of compact storage of genetic information. In animal cells, however, there is more DNA than can be functionally accounted for so that compactness of information storage would not seem to be necessary. The intronic sequences may be involved in the structural organization of the RNA molecule that occurs as the molecule loops and folds during synthesis. This secondary structure may help determine the RNA half-life or the RNA ribosomal binding constant. Thus it may be an important regulatory aspect of protein synthesis. The problems of how the introns are recognized, how they are cut, and how the ends of the preserved molecules are rejoined are just being studied.

As usual, there are those who find in this new complexity of cell regulation a mechanism for increased evolutionary efficiency.[6,7] Errors in the splicing process, they suggest, could provide new proteins for test by natural selection. Actually, arguments of this type are less than compelling. They are based upon the questionable premise that random changes in a complex system can improve it. In fact, the more complex a system, the more profound are the effects of such changes in the system and the greater the difficulty of finding changes which improve it and are accommodated by all levels of the system in a coordinate and functional manner. In a designed system, on the other hand, the problem of complex controls is one of designer ingenuity, because the system is required to function only in its final form and not in a gradual series of simpler subsets going back in time to no system at all.

The creation hypothesis includes a designer of infinite capability. As we have penetrated His design at the molecular level we have found that which also exists at higher levels of organization — a union of

elegant simplicity with prodigious complexity and variety; a biological universe that still holds many surprises for its investigators.

ENDNOTES

1. Jeffreys AJ, Flavell RA. 1977. The rabbit b-globin gene contains a large insert in the coding sequence. Cell 12:1097-1108.
2. Tilghman SM, Curtis PJ, Tiemeier DC, Leder P, Weissmann C. 1978. The intervening sequence of a mouse b-globin gene is transcribed within the 15S b-globin mRNA precursor. Proceedings of the National Academy of Sciences (USA) 75:1309-1313.
3. Weinstock R, Sweet R, Weiss M, Cedar H, Axel R. 1978. Intragenic DNA spacers interrupt the ovalbumin gene. Proceedings of the National Academy of Sciences (USA) 75:1299-1303.
4. Tonegawa S, Maxam AM, Tizard R, Bernard O, Gilbert W. 1978. Sequence of a mouse germ-line gene for a variable region of an immunoglobulin light chain. Proceedings of the National Academy of Sciences (USA) 75:1485-1489.
5. Glover DM, Hogness DS. 1977. A novel arrangement of the 18S and 28S sequences in a repeating unit of Drosophila melanogaster rDNA. Cell 10:167-176.
6. Gilbert W. 1978. Why genes in pieces? Nature 271:501.
7. Doolittle WF. 1978. Genes in pieces: were they ever together? Nature 272:581-582.