Molecular Genetic Engineers in Junk DNA?

DR. MAE-WAN HO / The Institute of Science in Society 25jun03

Much of the fluidity of the genome is due to mobile genetic elements that respond to physiological and environmental signals to recraft genes and genomes, creating new patterns of gene expression, new proteins and new evolutionary opportunities. But this fluidity also leaves the genome vulnerable to many environmental insults. Dr. Mae-Wan Ho reports.

Perhaps only 1% of the human genome codes for genes, and that's what the human genome map contains. The rest is mainly repetitive DNA, commonly known as 'junk DNA'.

However, evidence has been emerging that lurking within junk DNA are armies of transposons (mobile genetic elements) that play an indispensable role in 'natural genetic engineering' the genome. They make up nearly half of the human genome, and serve as 'recombination hotspots' for cutting and splicing, and hence reshuffling the genome. They are also a source of ready to use motifs for gene expression, as well as new protein-coding sequences.

These important transposons are scattered throughout the genome. There are two main categories: Long Interspersed Elements (LINEs) about 6.7 kilobasepairs in length and Short Interspersed Elements (SINEs) of several hundred basepairs. The most abundant SINEs are Alu elements, of which 1.4 million copies exist, comprising 10% of the human genome, and are apparently only found in primates.

Most LINEs are dormant, except for LINE1. But both LINE 1 and other LINEs are abundant in areas of the genome where the bases A and T predominate, which do not

have many genes. Alu elements, however, are more common in 'GC-rich'regions that are also gene-rich. This is quite baffling as Alu itself cannot move, but depends on enzymes encoded by LINE1 in order to insert itself. Alu elements, like LINE1 are retrotransposons that move and multiply by being transcribed into RNA, then reverse transcribed into DNA copies that jump into new sites.

New research is suggesting that Alu elements may help create new proteins from existing ones. The reasons the human genome contains so few genes – the latest count is just under 25 000, is that more than half the genes are interrupted and subject to alternative splicing.

In other words, the coding sequence of the gene is broken up into segments (exons) interrupted by non-coding segments (introns) that are spliced out from the RNA transcript before it is translated into protein. But there are alternative splicing pathways that join different exons together, with the result that many different proteins can be made from a single gene.

It appears that about 5% of alternatively spliced internal exons in the human genome originate in an Alu sequence. It suggests that Alu elements can actually jump into genes and, instead of destroying that gene, actually contributes a new coding sequence to it. There are two ways in which this could be done, either by jumping into an existing gene so that the gene gains a new exon and increases its repertoire of possible proteins by alternative splicing, or else, the gene can become duplicated first, with one copy remaining intact, while the other is crafted by the Alu element. Currently, it is estimated that 238 000 Alu elements are located within introns of protein-coding genes and each one can actually or potentially become an exon.

Gil Ast, head of a group in Tel Aviv University, Israel, which has made some of the most significant discoveries about Alu, is understandably pleased. "We believe that

Alus allowed the shuffling of genetic information that may have led to the evolution of primates," said Ast. "They may contribute to a lot of disorders we don't even know about yet. But they have also created genetic diversity."

Alternative splicing is quite precisely regulated, and all other things being equal, depends on the spacing of potential splice sites consisting of the dinucleotide, AG, as well as neighbouring nucleotides. A single base change can destroy alternative splicing, and this can cause a disease, as in the case of Alport syndrome.

Also, gaining an exon is not always a good thing. There are numerous 'insertion mutations' associated with the inappropriate insertion of transposons into genes. And even Alu sequences that are already in introns can cause problems. More than a decade ago, it was discovered that a point mutation in an Alu element residing in the third intron of the ornithine aminotransferase gene activated a cryptic splice site, and led to part of the Alu element becoming incorporated into the coding sequence. Unfortunately, it carried a stop codon, which cut the protein short, leading to ornithine aminotransferase deficiency.

There is increasing evidence that physical and chemical stresses to the cell, such as heat shock, chemical poisons and viral infections, tend to activate Alu elements. The resultant gene reshuffling may be responsible for a variety of chronic diseases (see "Dynamic genomics", this series).

Sources:

"Junk DNA" Creates Novel Proteins by Nancy Touchette, Science May 30, 2003.

"Geneticists play the numbers game in vain" Helen Pearson, Nature 2003, 423, 576.

Makalowski W. Not junk after all. Science 2003, 300, 1246-7.

Lev-Maor G, Sorek R, Shomron N and Ast G. The birth of an alternatively spliced exon: 3' splice-site selection in Alu exons. Science 2003, 300, 1288-91.

"How the sequence got the way it is" by John Whitfield, Nature, 12 February 2001.