RNA Guanine-tract Recognition and Encaging by hnRNP F quasi-RRM2

I. Introduction

Our DNA defines who we are, encoding for proteins that carry out specific functions in our cells. Human DNA encodes for over 100,000 proteins, and yet, recent studies have shown that humans have only approximately 25,000 protein-encoding genes. Research has shown that a single gene can produce multiple protein products through a process called alternative splicing. Splicing affects over 90 percent of our genome allowing humans to be as intricate as we are. The process of alternative splicing is highly regulated by a group of splicing proteins called heterogeneous nuclear ribonucleoproteins (hnRNPs). hnRNP F is such a protein. hnRNP F binds RNA in a unique way compared to other hnRNPs, and new research suggests that too much hnRNP H, a close homologue of hnRNP F, plays a role in promoting brain cancer. Understanding how hnRNP F binds G-rich RNA to cause alternative splicing may lead to the development of therapies for genetic diseases.

II. Gene Expression

Proteins are made when DNA is transcribed and RNA is translated. Alternative splicing allows more than one protein to be made from one gene, as shown above. The spliceosome removes introns and the remaining exons are ligated to form mRNA. Exons are the segments of RNA used to make mRNA while introns are often ‘junk’ RNA that gets degraded. Two different mRNAs result in two different proteins and this contributes to protein diversity. In this stylized example, Protein 1 has a helix contributed by exon 4, where as Protein 2 does not. The proteins, made from the same gene, would be functionally distinct.

III. The Spliceosome

Splicing is performed by a molecular machine called the spliceosome. The spliceosome recognizes 5’ and 3’ splice sites (ss), removes introns from pre-mRNA, and joins exons together to form the mature mRNA. mRNA is then translated to form a protein.

IV. Alternative Splicing

Alternative splicing is important for generating protein diversity. One fact that remains clear though, is that alternative splicing is highly regulated by a group of splicing proteins called heterogeneous nuclear ribonucleoproteins (hnRNPs). hnRNP F binds RNA in a unique way compared to other hnRNPs and interacts with tri-GA-G tracts in pre-mRNA. Using 3D printing technology, the Valders SMART team (Students Modeling A Research Topic) modeled hnRNP F binding via arginine 116, phenylalanine 120, and tyrosine 180. Understanding how hnRNP F interacts with RNA in alternative splicing may lead to the development of therapies for genetic diseases.

V. hnRNP F Recognizes Guanine (G) Tract Sequences in pre-mRNA and Influences the Spliceosomes Alternative Splicing Decisions

In alternative splicing, precursor messenger RNA is processed to produce many different messenger RNAs. The expression of these different RNAs from one gene makes possible the enormous protein diversity found in humans. Alternative splicing affects over 90 percent of our genome, allowing humans to be as complex as we are. hnRNP F is a protein that binds to tri-GA-G sequences in pre-mRNA and facilitates alternative splicing. This protein has a RRM (RNA recognition motif) that provides the first example of binding specific RNA guanines (G3) through amino acids in three loops. Classical RRM2s bind RNA through their beta-surface sheets. New research also suggests that over expression of hnRNP F, a protein with a similar structure and function, can manifest as a certain type of brain cancer. Understanding how hnRNP F binds RNA and function in alternative splicing could lead to potential therapies for disease.

VI. hnRNP F RRM2 Prevents RNA structure

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VII. Biological Significance

Enormous protein diversity results from alternative splicing. Mammals are much more complex than nematodes and fruit flies (as shown below), yet the genomes of these organisms differ by less than 2 fold (about 25,000, 20,000 and 14,000 genes, respectively). The extent to which alternative splicing contributes to the complexity of eukaryotic organisms is a question that remains unanswered, but a strong correlation exists between complexity and intron number and alternative splicing. One fact that remains clear though, is that alternative splicing is important for generating protein diversity.

References: