TITLE

“DNA G-Quadruplexes: ‘knot’ that simple!”

GENERAL INTRODUCTION

Known as the ‘molecule of life’, DNA is found in every cell in our body, providing a set of instructions for the function and organization throughout our bodies. These instructions are encoded by only four structural variations, abbreviated to A, C, G and T. While the helix shape of DNA is best known to science students around the world, many other shapes of DNA exist as well. Double-helical DNA combines each letter in pairs with one another to create two twisted strands. However, different types of DNA exist, with unique physical characteristics. One of these types, known as ‘G-quadruplex’ DNA, forms knot-like structures out of regions made up mostly of Gs, out of a single strand of DNA. G-quadruplex DNA has been fascinating scientists across diverse disciplines, since their presence or absence can ‘turn on’ or ‘turn off’ the instructions in DNA in settings related to diseases. However, little is known about which sections of DNA are able to form G-quadruplexes, the conditions under which they form, or which of several types of ‘knot’ they do form.

INTRODUCTION TO STUDY

The group of Webba da Silva has been studying how to predict and control the formation of G-quadruplexes by observing their formation in laboratory settings. Early work focused on defining the range of possible knot types, known as ‘topologies’. Most recently, the group focused on how basic structural elements such as the core (made of all Gs) and the parts outside the core, known as ‘loops’, influence the final outcome in G-quadruplex formation. Since many factors can be involved in the final shape of a DNA molecule, the researchers focused on just a few G-quadruplex topologies. Within these shapes, they experimented with different arrangements of letters. In some cases, they changed the number of Gs in the core to see how this affected its size. In other instances, they changed the number or arrangement in loops to determine if this had an impact on which shape of G-quadruplex would form, or if one would form at all.

METHODOLOGY

After designing and preparing over 30 different DNA molecules, the success or failure of each in forming a G-quadruplex was assessed using a technique called Nuclear Magnetic Resonance (NMR) spectroscopy. In its most basic form, this method allowed the team to determine if a G-quadruplex had formed by showing the connections between Gs in the core. Once several G-quadruplexes had been identified, the most interesting were selected to investigate in further detail. Advanced NMR experiments were used to determine the relationship between each atom in the G-quadruplex, and from this build an experimentally-validated model of the topology formed.

RESULTS

The research team found new connections between the sequence of letters and their likelihood of making a G-quadruplex. One of the most surprising observations was an interdependent relationship between the size of the core is to the number letters in the loops. When the core was larger and more rigid, smaller loops were better. The size of each loop also was observed to affect the most successful size of other loops. From all of the observations, the team was able to define a set of ‘rules’ for describing which features of a short span of DNA are most important for controlling the ability to make a G-quadruplex.

CONCLUSIONS

From these results, the research team was able to conclude that factors involved in formation of G-quadruplexes are very complicated indeed. In particular, the core and loops cannot be considered as acting independently from each other. The rules for formation that were established included specific subsets of shapes formed by the non-core residues, all of which behaved differently from each other. Consequently, the rules defined are only applicable to a strict set of circumstances due to the many inter-relationships identified.

GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

However, this complexity also served to confirm that the biological function of these DNA knots must be highly specific to each set of instructions. The many different shapes possible, and their sensitivity to the arrangement of the letters in the DNA code, demonstrate that different G-quadruplexes are likely to have different functions in human body, depending on which set of instructions they are attached to. This is promising for other scientists who aim to use G-quadruplexes as a tool to alter the control over harmful or faulty DNA instructions found in some diseases.