DNA encodes all the information needed to make every protein and enzyme in a living organism, acting as instructions for the basic building blocks in our body, including genes. But many of these genes are not needed all the time. So, our genetic machinery has developed the ability to effectively ‘switch’ different coding regions ‘on’ or ‘off’ – to either start or halt the expression of a gene. A process called transcription is the first stage of gene expression. DNA can regulate its transcription in lots of different ways, such as coiling around structural proteins or interacting with enzymes. Now, research by Dr Vanessa Meier-Stephenson, an Assistant Professor at the University of Alberta, Canada, examines novel ways to regulate some of these pathways. This involves DNA folding itself into intricate 3D structures called G4-quadruplexes. Meier-Stephenson’s findings could result in the development of new targeted treatments for conditions like cancer or chronic viral infections.

**Tangles in the helix**

Usually, the DNA molecule is a long sequence of the nucleotides (single units of the DNA code) adenine, thymine, cytosine, and guanine twisted into a perfect helix. However, in areas where the chain contains an abundance of the nucleotide guanosine, or G, those sections can fold the DNA molecule into a three-dimensional structure known as a G4-quadruplex (G4Q). The G4Q complex forms when four guanosines arrange themselves in sheets stacked on top of each other in various orientations. This causes the DNA strand to form bends and loops. The stability of the G4Q complex is affected by loop length, where longer loops tend to make the complexes more unstable. The shape and orientation of these loops influences which proteins and ions can interact with them. G4Qs have been associated with important regulatory regions, which is what makes them so interesting to genetics researchers.

The formation of G4Qs is not fully understood, but previous studies have demonstrated that their stabilisation and destabilisation in vitro can be influenced by temperature fluctuations. As these studies were done under artificial conditions outside a living cell, we don’t know for certain whether they reflect the natural G4Q development process. After all, there are many things within a living cell that can also interact with DNA, like the proteins which bind to and copy or translate the DNA code. Also, there could be other G4Q shapes that we have no way of seeing or measuring in the laboratory. Nevertheless, once formed, G4Qs are stable as a solitary DNA double helix. G4Q complexes have been shown to form ‘knots’ in the DNA, which change the way proteins interact with it or protect the ends of the DNA molecule from degradation. For example, they help stabilise the telomeres. Telomeres are regions at the end of the DNA strand that protect the DNA helix’s edges. Without the telomeres, proteins in the cell could result in the development of new targeted treatments for conditions like cancer or chronic viral infections.

**Structure, function, and binding proteins**

Over 700,000 sequences have been discovered within the human genome that are involved in regulating our DNA. They are found in regions of the DNA sequence requiring more intense regulation, such as a gene promotor. A promotor is a region of DNA at the beginning of a gene where the transcription proteins bind to begin expressing the gene. By manipulating this region of the DNA sequence, a regulatory mechanism can prevent proteins from binding to the DNA – and therefore ‘switch’ the gene off.

**G4Qs are as stable as a solitary DNA double helix and have been associated with important regulatory regions.**

Dr Vanessa Meier-Stephenson at the University of Alberta, Canada, is working to better understand the various functions of G4-quadruplexes and their binding proteins. This knowledge could help scientists develop drugs targeting cancer or chronic viruses.

Vanessa Meier-Stephenson

**How tangled knots of DNA help regulate and protect our genes**

- One of the ways in which DNA regulates and protects itself is by forming tangled knots called G4-quadruplexes.
- The exact function of these regions, and the proteins which interact with them, is still unknown.
- Dr Vanessa Meier-Stephenson at the University of Alberta, Canada, is working to better understand the various functions of G4-quadruplexes and their binding proteins.
- This knowledge could help scientists develop drugs targeting cancer or chronic viruses.
Exploring DNA regulatory mechanisms helps build on our knowledge of how DNA switches genes on and off.

mechanisms could inform future drug targets, for example, by disabling a protein known to switch on cancer-associated genes or other disease-causing processes.

G4Q and their associated binding proteins are critical to many cellular processes. Their varied binding orientations confer the selectivity and versatility required of these complex interactions. Studying this specific regulation and control of important processes, such as turning genes ‘on’ or ‘off’ in response to the environment, could inform future genetics research and potential drug targets. Significantly, Meier-Stephenson’s work could provide the basis for novel treatments for cancer, disease, or chronic viral infections.

Details

Dr Vanessa Meier-Stephenson is an Assistant Professor in the Departments of Medicine and Medical Microbiology and Immunology at the University of Alberta, Edmonton, Canada. Her lab is studying the unique structural features of G4Q-zinc finger protein interactions to determine what makes them selective and how this may be applied functionally.

References