New advance in RNA studies holds out hope for cancer drug development

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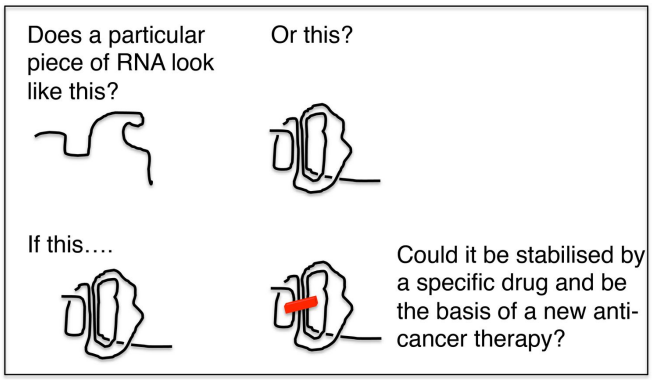

Formation of quadruplexes by RNA might allow new ways to control gene expression. Credit: University of Leicester

An international research team led by the University of Leicester has made a breakthrough advance that could pave a new route for the development of anti-cancer drugs.

The advance is announced today (7 November) in an online publication in *Nature Chemical Biology*. The Leicester team members say they are delighted by their finding which could lead to new anti-cancer drugs thanks to "wonderful interdisciplinary collaboration involving biochemists and chemists from England, Scotland, France and USA."

Professor Ian Eperon and Dr Cyril Dominguez from the University of Leicester's Institute of Structural and Chemical Biology led the team that developed a new method to analyse the RNA step in expressing our genetic code.

Dr Dominguez, of the Department of Molecular and Cell Biology, said: "Our research aims at understanding how four-stranded RNA structures called G-quadruplexes affect cellular processes such as RNA splicing. In this research, we describe a novel method that, for the first time, allows us to show that G-quadruplexes form in long RNAs and in conditions where the splicing reaction can take place."

G-quadruplexes are specific structures formed when a piece of DNA or RNA folds into a four-stranded structure. DNA G-quadruplexes have been shown to be associated with diseases such as cancer and many small molecules called G-quadruplex binders have been developed as putative novel anti-cancer drugs, the best example being Quarfloxin that reached a phase II clinical trial. RNA G-quadruplexes are also believed to play important roles in cancers but to date there are no straightforward methods to prove that they exist in cells. If they form and do control RNA splicing, then the design of molecules that bind them would be a new route for the development of anti-cancer drugs.

During the process of gene expression, DNA is transcribed to RNA molecules that are in turn translated to produce proteins. RNA splicing is an essential step in producing the finished messenger RNA and the RNA copied from one gene can be spliced in different ways. This is how the 20,000 human genes can produce around 130,000 proteins.

This process is highly regulated and defects in its regulation are a common cause of many diseases, including spinal muscular atrophy and some cancers.

Professor Eperon said: "Our novel method, FOLDeR, will allow RNA scientists to investigate the existence of G-quadruplexes in physiological condition allowing a better understanding of their role in cellular processes. It is particularly interesting that the RNA we have been studying is one that plays an important role in some cancers. When the RNA is spliced using one set of sites, it produces a protein favouring cell survival. This is a

problem for cancer treatments, many of which work by damaging growing cells in the hope that they will then die. However, when an alternative set of sites is used, the RNA produces a protein that encourages cell death. We have shown that G-quadruplexes form near the alternative sites, and our hope is that we can target these to shift splicing towards the pro-death pattern."

This is a major step forward in the G-quadruplex research field. In a follow-up paper, the team will report their work on drugs that exploit this structure.

Dr Dominguez added: "We are delighted that a prestigious journal such as *Nature Chemical Biology* recognize the importance of our work. This has been a wonderful interdisciplinary collaboration involving biochemists and chemists from England, Scotland, France and USA.

"This publication is crucial for us to obtain further funding and carry on with this topic. Our next step is to investigate the effect of G-quadruplex binders on RNA splicing and use this knowledge to design novel drugs with a high degree of specificity for cancer cells."

More information: Carika Weldon et al, Identification of G-quadruplexes in long functional RNAs using 7-deazaguanine RNA, *Nature Chemical Biology* (2016). DOI: 10.1038/nchembio.2228

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