Collisions of protein machines cause DNA replication derailment

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Scientists have published results that will forever change the way researchers view the interplay between gene expression, DNA replication and the prevention of DNA damage.

DNA damage, if not kept in check, can lead to many problems including cancers. Researchers, funded by the Biotechnology and Biological Sciences Research Council (BBSRC) and the Wellcome Trust and working at The University of Nottingham, have shown that the process of replication is even riskier than originally thought. This new information is published today (24 February) in the journal *Nature*.

Lead researcher Panos Soultanas, a Professor of Biological Chemistry from The University of Nottingham School of Chemistry said "Consider DNA as a bi-directional rail track with two types of train: a big fast one like an eight-carriage cross country train and a small slow one like a two-carriage regional train. As it travels, the big train – the DNA replisome – is responsible for copying the DNA e.g. when a cell is preparing to divide. And the small train – the RNA polymerase – makes its journey to deal with the expression of genes contained within the DNA sequence."

Just like trains, collisions between proteins moving along a strand of DNA can be catastrophic and this is one reason why areas of DNA that are being used a lot are particularly prone to damage. Until now it was thought that only head-on collisions between the DNA replisome (the big, fast, cross country train) and the RNA polymerase (the small, slow, regional train) could lead to serious DNA damage. This research shows

that collisions between big and small trains running in the same direction can be just as dangerous and hence the problem in areas of high use is exacerbated.

Professor Soultanas said "Until now we thought that if the fast and slow protein-trains meet going in the same direction along the track then the faster DNA replication train just slows down and follows along behind the slower gene expression train until it has finished its job and moved out of the way. Our new research shows that this isn't the case at all and in fact they do collide quite often causing what, in this analogy, we could only describe as a major derailment!"

When the DNA replisome falls off the DNA there are other proteins – called "restart replication proteins" – that come in to help get it back on track. Although this ensures that DNA replication can continue, it can potentially increase the risk of mistakes occurring during the copying process, particularly if such restart replication proteins are malfunctioning. In some cases these mistakes can lead to problems e.g. if the mistake causes a genetic malfunction that can lead to a cancer developing.

Describing what happens to the DNA replisome in areas of DNA where there are many RNA Polymerases working on genes that are in high use, Professor Soultanas said: "We are now realizing that when there are a lot of slow moving trains close together on the track, the fast moving train is faced with a huge obstacle and any failure to safely negotiate these areas could easily result in significant errors. Therefore, replication restart mechanisms are of vital importance to ensure accurate copying of the genetic material"

Professor Douglas Kell, Chief Executive, BBSRC said "This is exciting news and an excellent achievement. Biological sciences as a discipline is unique because there are a collection of key ideas, tools, techniques and

processes that are applied across an enormous range of topics. The interplay between gene expression, DNA replication and the prevention of DNA damage is an example of just such a tenet of biology and so this result has the potential to touch on research right across BBSRC's portfolio and beyond."

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