Enhancers and DNA damage – unexpected connections?

Wendy Bickmore

MRC Human Genetics Unit, Institute of Genetics and Molecular, University of Edinburgh, UK

Most of the human genome (>90%) does not contain protein-coding genes and there are vast tracts of inter-genic space. Much of that genomic space contains enhancers that regulate the expression of genes in time and space. Remarkably, enhancers can be found as far away as 1 megabase from the target gene whose expression they control.

It is hard to envisage how distant enhancers function if one only considers the genome as a linear DNA sequence. Rather, three-dimensional chromatin folding in the nucleus must play a fundamental role in enhancer-promoter communication. I will describe our work using different experimental approaches to investigate and manipulate the three-dimensional folding of the mammalian genome at genetically defined long-range regulatory elements. Our data indicate un unexpected involvement of DNA repair factors in long-range enhancer function.

In addition, I will discuss a human developmental disorder – Cornelia de Lange syndrome – which is often considered as a disorder of compromised cohesin function leading to the malfunction of long-range enhancers. I will present evidence that some cases of this genetic disease unexpectedly result in in appropriate DNA repair pathway choice. Our data are causing us to consider the links between transcriptional regulation and DNA damage/repair.