Motor enzyme protects genome through several mechanisms

February 11 2019

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A helicase, Pfh1, can thanks to several different mechanisms protect the genome from DNA obstacles and damages associated with cancer. This is shown in a new doctoral thesis at Umeå University, Sweden.

Approximately one per cent of each organism's genome encodes helicases. Helicases are mostly known as motor enzymes that can unwrap double-stranded DNA by use of energy.

In his doctoral thesis at the Department of Medical Chemistry and Biophysics, Jani Basha Mohammad focused on the evolutionary conserved Pif1 family helicases that are associated to breast cancer. Jani performed a detailed mechanistic study about how the yeast Schizosaccharomyces pombe Pif1 helicase, Pfh1, can maintain genome integrity. In S. pombe, Pfh1 is encoded by an essential gene and depletion of this gene leads to DNA damage.

DNA molecules are known to form a double-stranded DNA helix with two strands wrapping around each other. However, in his thesis Jani also studied another form of DNA which forms a four-stranded DNA in guanine-rich DNA regions, a so-called G4 structure. G4 structures are very stable structures, and need to be resolved by specialized helicases. If not unfolded, they can lead to DNA damage and genome instability, which is tightly connected to diseases such as cancer. Jani Basha Mohammad and his colleagues showed that Pfh1 is one of the specialized helicases that can unwind these structures, and thereby promoting genome integrity.

Other obstacles that can threaten genome integrity are tightly bound proteins to the genome and R-loops, a three-stranded RNA/DNA region. Jani Basha Mohammad showed that Pfh1 helicase also efficiently remove these obstacles from the genome. As these types of obstacles are found in humans as well, it is very likely that the human Pfh1 homolog, Pif1, also have similar properties. Apart from the above properties, Jani also found that Pfh1 can rewind DNA molecules, an enzymatic activity that may be important during DNA repair.

Jani Basha Mohammad further characterized different domains of the Pfh1 protein. One of these domains is mutated in human Pif1 and is carried by some breast cancer patients. This domain is evolutionary conserved, and he could show that the corresponding mutation in Pfh1 leads to a misregulated Pfh1. These misregulations may explain the

genome integrity defects that is found in the breast cancer families.

The data has shed light on how Pfh1 can promote genome integrity. These studies have been quite tricky to perform previously, since Pfh1 has been difficult to express and purify. Therefore, by optimizing the purification protocols Jani Basha Mohammad and his colleagues could finally perform these in-depth mechanistic studies.

Provided by Umea University