Molecular anchor links the 2 inheritable diseases Fanconi anemia and Bloom's syndrome

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A new study establishes a molecular link that bridges two rare inherited disorders and explains why these diseases result in genetic instability. The research, published by Cell Press in the December 24th issue of the journal *Molecular Cell*, may lead to a better understanding of the complex mechanisms that enable cells to repair damaged DNA.

Fanconi Anemia (FA) and Bloom's Syndrome (BS) are unique rare genetic disorders that have some key characteristics in common. Both FA and BS are associated with disrupted DNA repair mechanisms and an elevated predisposition for cancer. The genetic mutations that cause FA and BS have been identified and, importantly, the genetic mutations associated with both FA and BS affect large molecular complexes composed of several proteins (the FA and BS core complexes) that mediate key DNA repair processes.

"There is strong clinical and biochemical evidence suggesting that FA and BS proteins may act in a common DNA repair pathway," explains study author Dr. Stephen C. West from the London Research Institute. "However, the specific interactions are poorly understood." Dr. West and co-author, Dr. Andrew J. Deans, examined the FA gene FANCM because it has been shown to directly bind to DNA and has been shown to have specificity for substrates that are similar to those linked with the BS core complex.

The researchers identified two regions in the FANCM protein that enabled it to physically link the FA core complex and the BS complex. FA and BS complexes bound independently to FANCM, but not with each other in the absence of FANCM. The researchers went on to show that a disruption of the interaction between the two core complexes and FANCM led to similar chromosomal repair defects representative of both BA and FA cells.

"We have shown for the first time that FANCM acts as a molecular scaffold that functions in a variety of repair reactions and serves as a bridge between FA and BS. The biological and clinical implications of this link are likely to be important in relation to the phenotypes associated with these genetic disorders," explains Dr. West. "Further understanding how these interactions and reactions are regulated should provide a more complete understanding of the molecular basis of FA and BS."

Deans et al.: “FANCM Connects the Genome Instability Disorders Bloom’s Syndrome and Fanconi Anemia.” Publishing in Molecular Cell 36, 943-953, December 24, 2009. DOI 10.1016/j.molcel.2009.12.006 www.molecule.org.

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