Researchers find structural basis for incidence of skin cancers in a genetic disorder

June 23 2010

Researchers from Mount Sinai School of Medicine have found why patients with a variant form of xeroderma pigmentosum (XPV), an inherited genetic disorder characterized by extreme sensitivity to the sun, are more susceptible to skin cancers than the general population. The data are published in the current issue of the journal *Nature*. Their finding sets the stage for research into therapies that would help protect people with XPV from developing skin cancers.

The research team determined that, in the general population, DNA polymerase eta, an enzyme able to overcome the barriers created by sun damage and ultraviolet rays and continue replicating DNA strands, is structured differently from any other polymerase. However, in people with XPV, since this enzyme is missing, they are unable to bypass this damage, causing the replication process to stall, resulting in mutations and extremely high susceptibility to skin cancer.

Researchers have never been able to fully determine a structural basis for why the enzyme can get around UV damage. After nearly a decade of research, the Mount Sinai team successfully developed a crystal model, or a three dimensional chemical derivation, of the enzyme. They determined that in the general population, DNA polymerase eta suppresses skin cancer because the active site, where chemical reactions required to replicate DNA take place, can adjust much better to UV damage than any other DNA polymerase.

"We have been unable to study how DNA polymerase eta can replicate through UV damage because we did not have a crystal structure of the enzyme to study," said Aneel K. Aggarwal, Ph.D, Professor, Structural and Chemical Biology, Mount Sinai School of Medicine. "Our team succeeded in developing this structure and determining what makes this enzyme unique."

In conjunction with Drs. Louise and Satya Prakash's group at the University of Texas Medical Branch in Galveston, Texas, Dr. Aggarwal's team generated crystals and analyzed them using X-rays. They determined that the active site of DNA polymerase eta is structured in such a way that it can easily accommodate the UV induced DNA lesions and replicate through them.

"Now that we know the structural basis for the suppression of skin cancers by this enzyme, one question for the future is if there's a way to restore its function in people with XPV and reduce their risk for cancer," said Dr. Aggarwal.

According to the National Center for Biotechnology Information of the National Institutes of Health, xeroderma pigmentosum is an inherited genetic disorder characterized by severe sun sensitivity resulting in blisters and precancerous freckles, benign tumors on the skin and eyes, blurry vision and eye pain from atrophic eye lids, and neurologic symptoms including cognitive decline.

Provided by The Mount Sinai Hospital