How defects in 1 gene cause 3 distinct and devastating human diseases

May 29 2008

By studying heat-loving microbes, two research teams have gained new insight into how seemingly small differences in a single protein involved in DNA transcription and repair can lead to strikingly different genetic disorders in humans.

The two studies in the May 30th issue of *Cell*, a Cell Press publication, uncover the crystal structure and biochemical activity of an enzyme known as XPD helicase taken from Sulfolobus archaea, microbes distinct from bacteria that share many fundamental genes with humans. For reasons that had remained rather mysterious until now, point mutations in human XPD—sometimes at neighboring sites—can spell the difference between cancer-prone xeroderma pigmentosa, the aging disorder known as Cockayne syndrome and another aging disorder called trichothiodystrophy.

" If you consider the linear sequence of XPD and map the [disease-linked] point mutations onto it, there is nothing clear about why they would be causative for one of the three diseases or another," said Jill Fuss of The Scripps Research Institute. "By having these structures for XPD, we suddenly see how it is working."

"The protein from archaea is a simplified model, but that doesn't stop us learning a lot about the biology of the human enzyme," said Malcolm White of University of St Andrews, who led the other study. "Archaeal protein structures are often very close matches to the equivalent proteins from humans, even though they diverged from one another three billion

years ago. We can learn a lot about human health by looking deep into evolutionary time."

Archaea have particular similarities with humans and other eukaryotes in the way in which they process information, including DNA replication, transcription and repair, White explained. One of those common elements is XPD helicase, a component of a fundamental complex (known as TFIIH) with roles in initiating the transcription of genes into the templates for protein and in the repair of damaged DNA. In both instances, the helicase parts the two DNA strands at either the transcription start site or the site of DNA damage.

Defects in XPD are known to underlie xeroderma pigmentosa (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD). Although people with all three diseases share a sensitivity to the sun, they differ greatly in their predispositions to cancer or accelerated aging, explained John Tainer, who led the Scripps study. XP patients show several 1000-fold increase in skin cancer, whereas neither CS nor TTD patients show an increase in the cancer incidence despite their sun sensitivity. Furthermore, both CS and TTD are premature aging diseases plus developmental disorders, with CS patients being more severely affected and exhibiting severe mental retardation from birth.

Both teams now have evidence to explain what separates the diseases despite their similar molecular causes. They find that XP-causing mutations in XPD all fall in sites where the helicase binds ATP (the energy currency of the cell) or DNA. Those alterations leave the enzyme unable to function in DNA repair. However, the overall effect on the structure of the enzyme is minimal. As such, the enzyme still fills its position in the TFIIH complex, allowing transcription to proceed. That inability to repair defects, leaves those with XP prone to developing cancer as mutations arise and go uncorrected.

In the case of TTD, the defect is quite different, White said. TTD-linked mutations are found all over the protein at points important to its interactions with other proteins. Therefore, those mutations leave the protein floppy, destabilizing the entire TFIIH complex and causing defects in both transcription and repair.

“ It is thought that the transcription defects protect against cancer, but lead to an increase in cell death and therefore the rapid aging symptoms seen in TTD patients,” White said.

As for CS, Tainer’s group suggests it results when defects in XPD lock the protein into a rigid position. As a result, they said, the protein may stick in repair mode and cut out DNA at sites where it should be transcribing.

The new insights into XPD point to the importance of whole proteins, not just their “active sites.”

“ We’ve been able to characterize three activities together with the structure,” Tainer said. “We’ve shown how mutations in the binding site alone can cause cancer. Scientists often thought it was just the active sites that were important—that other changes wouldn’t matter. But we see that other changes can lead to very severe defects.”

The results also hold an important general lesson for the value of protein structure for understanding gene function. “The results of the Human Genome Project have revealed associations between sequence mutations and particular diseases or disease risks, but in many cases we don’t know why,” Tainer said. As in the case of XPD, the protein structures may hold the key.

Source: Cell Press