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nature's flaws

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Nothing is perfect. And nature is no exception. This said, we should be grateful for nature's imperfections because, were it not for them, we would not be here. Without the changes that have been accumulating in genes over millions of years, we would not know the rich diversity of species that inhabit Earth today. Yet we all know that mutations can be lethal to an individual. Tinker with a crucial position in a gene and you can find yourself with a severe handicap. Extensive damage to a cell's genome can lead to all sorts of ailments, not the least cancer. This is why Nature imagined DNA repair mechanisms so as to limit the damage and prevent as many mutations as possible. One such mechanism is nucleotide excision repair, and at its heart: protein Xeroderma Pigmentosum A (XPA).

The Children of the Moon, by Catherine Arsaut ©

Courtesy of the artist

Along with other proteins, XPA forms a complex that specifically recognises damaged DNA – especially alterations caused by UV light – and then severs the part which contains the lesion. Once the spoilt nucleotides have been removed, they can be replaced by sound ones, restoring the DNA and the information it should have carried in the first place. The precise role of XPA in the whole process is still misunderstood. As the protein specifically recognizes DNA whose helix has been distorted because of mutated nucleotides, it was initially thought that XPA raised the alarm over DNA damage. Such is not the case however. The actual binding of XPA might signify that the DNA is indeed damaged and prompt the assembly of the rest of the nucleotide excision repair machinery. As an illustration, XPA's association with one of the DNA severing proteins might ensure the latter's correct positioning and thus guarantee accurate excision of the damage.

Whatever its exact function may be, it is clear that XPA is essential for DNA repair to happen in the first place. If the protein is unable to carry out its task, the whole repair process fails, leading to terrible consequences for an individual's health. Mutations in XPA, for instance, cause the disease that gave the protein its name: Xeroderma pigmentosum. Xeroderma pigmentosum was first described more than a century ago, in 1874, by Moriz Kaposi, a professor of dermatology in Vienna. But it was only in 1968 – almost a century later! – that James Cleaver, himself a professor of dermatology in San Francisco, linked the disease symptoms to defects in DNA repair.

Patients suffering from Xeroderma pigmentosum are extremely sensitive to sunlight and have to wear protective clothing as even brief exposure to UV light leads to severe sunburns. As a result, children who are affected stay indoors during most of the day and only go out at night, which is why they are sometimes known as "moon children". It is hardly surprising then that patients suffering from Xeroderma pigmentosum are also a thousand times more at risk of developing skin cancer

and, in some cases, the disease is associated with progressive neuronal degeneration...

Though XPA is essential for DNA repair, it also occupies a central position in regulating the whole process. Indeed, several mechanisms modulate the activity of nucleotide excision repair and they all do so by targeting XPA first. Take the circadian clock for example, the internal clock that adjusts the daily rhythm of many physiological processes. This particular clock affects the rate of DNA repair through its effect on XPA expression. In mouse brain, liver and skin, for instance, the level of XPA and consequently nucleotide excision repair activity varies throughout the day, with a maximum in the evening and a minimum in the morning. DNA repair can also be activated by getting XPA to move to the cell's nucleus. This tactic is chosen once DNA damage has been sensed and cellular processes are triggered off in order to deal with any; getting XPA to visit the nucleus as fast as possible is one. Turning off nucleotide excision repair when it is not needed anymore occurs through XPA as well. Indeed, once the damage has been repaired and XPA is not engaged in the DNA repair machinery anymore, the protein is chemically modified and subsequently destroyed.

So, to cut a long story short, control XPA and you control nucleotide excision repair. Naturally, the fact has not gone unnoticed amongst researchers, especially as it has implications for cancer treatment. Chemo-therapeutic drugs are designed to induce DNA damage. Hence, the efficiency and side effects of these drugs largely depend on nucleotide excision repair, i.e. on how XPA behaves. Resistance of cancer cells to chemotherapeutic drugs has been linked to XPA protein levels. Depleting XPA increases the cells sensitivity to the drugs. Researchers have identified regulators of XPA expression. Clinically silencing them would reduce XPA expression and hence improve the efficiency of chemotherapeutic drugs. Another current line of study is focusing on XPA transport to the nucleus. The mechanisms controlling this nuclear transport happen to be different in cancer cells because of a mutation in what is known as the p53 gene. Targeting the mechanism specific to p53 mutant cells could prevent XPA from entering the nucleus in cancer cells. As a result, DNA repair would not occur and the cancer cells would be more sensitive to chemotherapeutic drugs – hopefully with little or no consequence to healthy cells.

Over time, Nature has set up mechanisms to counter its imperfections. And scientists are setting up their own to counter diseases by understanding Nature's flaws in the first place. Gaining knowledge, on the molecular level, of mechanisms as intricate as DNA repair will provide the means to tamper with these processes in the hope of fixing the flaws Nature has overlooked.

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