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The Fragile Helix: Damage, Repair, Disease, and Cell Death

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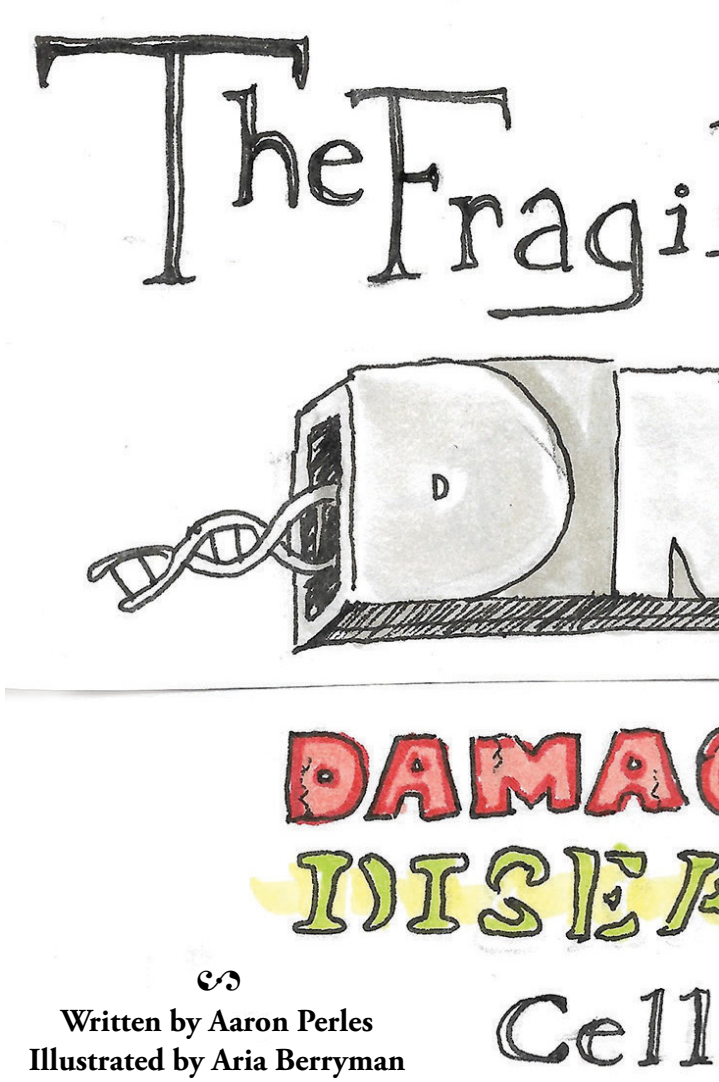

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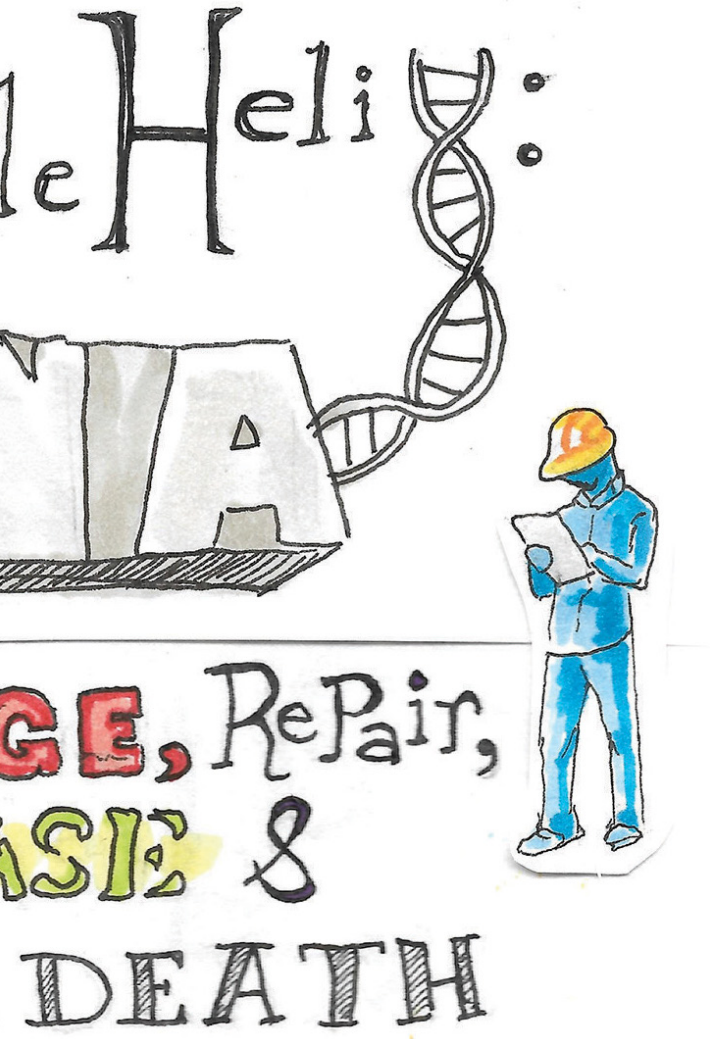
In 2009, the fad of "planking" took the Internet by storm. Images abounded of people lying flat, face-down upon surfaces of all kinds: soft grass, metal statues, escalator railings, and even airport baggage claim carousels. However, those of an especially athletic bent took a challenging approach to the fad, placing themselves on tiny surfaces high above the ground. Think lamp posts, flagpoles, and basketball backboards—structures that support only the abdomen and leave the rest of the body suspended in mid-air, held up solely by the sheer strength of the person doing the planking. To hold this position for even a few minutes requires an incredible amount of core strength. Now, imagine trying to hold this position yourself—for an hour. After five minutes, the vigor has drained out of you, and your muscles have become weak and depleted of oxygen. Unable to hold out any longer, they give out, and you topple from your perch, lying exhausted and broken on the ground.

Now imagine this feat of strength and balance happening at a microscopic scale. Imagine something akin to "planking" inside your cells, where some biomolecule extends itself without support almost beyond its limits. In truth, this kind of phenomenon is a fairly regular occurrence in the DNA double helix. Your DNA experiences small amounts of instability every single day when it replicates itself: the two strands of the double helix unwind, and, for a brief moment, they exist as single, unsupported strands of genetic material. Only once the cell synthesizes two new double helices from the separated strands does the DNA return to its normal, stable state.

As is all too common, however, malfunctions in this biological machine arise. Impediments to DNA replication exacerbate the instability normally resolved during replication. The DNA double helix is shaped like a ladder: two long strands of sugars and phosphates make up the frame of the ladder, while paired nitrogen groups, called *bases*, make up the "rungs" that connect the frame. It is the nitrogenous bases that encode the proteins that comprise every single facet of your body. However, the nitrogenous bases sometimes get damaged. Mutations replace correct bases with incorrect ones, and damaging agents like oxidative stress or ultraviolet radiation cause bases to become chemically corrupted and non-functional. Because the cell is instructed to not replicate corrupt or mutated bases, the double helix stops unwinding at the site of damage while the damage is repaired. The cell has a highly effective mechanism for DNA damage repair, called the nucleotide-excision repair pathway. First, a series of proteins, including RPA and γH2AX, are recruited to stabilize the suspended single-stranded DNA. Then the cell cuts the corrupted base out of the helix and replaces it with a functional nitrogen group so that the unwinding and replication of the DNA can continue as normal.

This mechanism maintains seamless, non-erroneous DNA replication in the cells, but what happens when something goes wrong in the nucleotide-excision repair pathway? What happens when the repair proteins don't come to stabilize the single-stranded DNA while it waits for the corrupted base to be excised? Well, what happens is the molecular equivalent of planking on top of a flagpole. Without the necessary repair proteins, the single-stranded DNA is left alone, unstable without its complementary strand, and completely lacking the support of the repair proteins to hold it steady. Call to mind again the person planking on the flagpole, about to collapse after expending all of their stamina. Imagine that two more flagpoles had sprouted up out of the ground, supporting the person's legs and torso; with this kind of support spanning the length of the body, the person is no longer burdened with the need for excessive core strength to hold themself up. This is the role the repair proteins play for the single-stranded DNA. But, because flagpoles do not magically materialize out of nowhere, the person will inevitably collapse. Without the support of the repair proteins, the DNA gives way under the weight of its own instability, and the entire helix splits in two at the site of damage.

This phenomenon is called a *double-stranded break*, and for the cell that experiences such a break, there can be dire consequences. Because a double-stranded break cleaves an entire segment of the DNA from the replicating double-helix, the cell can lose a staggering amount



of genetic information. Many of these losses can be fairly benign, as significant sections of the human genome are non-coding. But when the double-stranded break occurs in a crucial area of the genome, the results are devastating. For example, cleaving a tumor-suppressor gene increases one's risk of developing cancer. A remarkable amount of research has been conducted on the DNA damage repair genes *BRCA1* and *BRCA2*,

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mutations in which have been shown to be significant risk factors for hereditary breast cancer. Another disease associated with faulty DNA damage repair is Werner's Syndrome, in which double-stranded breaks cause impeded growth and premature aging.

If a person's cells lack the machinery necessary to repair DNA damage, then double-stranded breaks, and all the consequences that come with them, may be inevitable. But with this grey cloud comes a surprising, and somewhat ironic, silver lining: the very same cellular predisposition towards double-stranded breaks is also the key to curing the diseases they cause. If one's cells have a heightened proclivity towards losing genetic information, then we can manipulate the corrupt damage repair process, exacerbate the amount of genetic loss, and eventually kill the diseased cells. This has become the primary method of developing chemotherapeutics for diseases associated with faulty DNA damage repair, with the first major breakthrough occurring in 2005. Researchers at the University of Nebraska Medical Center found that inhibiting the enzyme PARP, a key protein in the damage repair pathway, increased cells' sensitivity to DNA damage. Genetic information was lost in droves through double-stranded breaks, and, no longer genetically viable, the cells initiated their pre-programmed death response called apoptosis. On the other hand, we can also deliberately induce cells to proceed with DNA replication despite the helix's damaged or mutated bases, stripping the cell of its time to facilitate a proper damage repair and causing a buildup of enough genetic damage to trigger apoptosis. In the face of deleterious biological mishaps, one of our best strategies is to use the cell's own weapons against itself.

It is rather incredible that so much of our health hinges upon these tiny clusters of sugars, phosphates, and nitrogen. It is rather inconceivable that one small malfunction in these molecules can send our bodies spiraling into harrowing disease. It is rather astounding that this unspeakably essential helix can weaken and shatter, undetectable to our immediate senses. Despite all of this, however, it is also rather wonderful that the same damaged helix, if prodded enough, can become its own worst enemy, destroy itself, and relieve its host of all the ails it had caused—for such a fragile helix it is. ●

For more information, check out "Targeting DNA double-strand break signaling and repair" from *Swiss Medical Weekly* in 2013.