New mapping technique helps scientists run circles around cancer by revealing roots of esophagus and stomach cancers

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Rampant inflammation has long been linked to cancer but exactly how it pushes healthy cells to transform into malignant ones has remained a

mystery.

Now, scientists at Van Andel Institute have found one culprit behind this connection: oxidative stress, a process that disrupts the genetic code by damaging DNA. The findings, published in *Science Advances*, provide crucial new insights into the roles of inflammation and oxidative stress in certain cancers and offers new opportunities for potential prevention strategies.

"Our findings provide an important piece of evidence for how inflammation and oxidative stress can cause cancer," said Gerd Pfeifer, Ph.D., a professor in VAI's Department of Epigenetics and the study's senior author. "The body has a good defense system that repairs DNA damage and reduces oxidative stress, but nothing is failsafe. The more we know about the precise links between inflammation and cancer, the better equipped we are to design more effective prevention strategies."

Inflammation is a normal part of the body's natural immune defenses. When presented with a threat, such as an infection or injury, the body rallies resources in the form of inflammation to combat the problem and promote healing.

Part of this process is the production of reactive oxygen species (ROS), unstable molecules that play important roles in normal cellular function and communication. Occasionally, something goes awry that causes the inflammatory response to continue longer than it is needed. The results can be damaging, including a buildup of excess ROS that can elevate oxidative stress.

Using a new technique developed by his lab called circle damage sequencing, Pfeifer and his colleagues mapped two types of DNA damage caused by oxidative stress. They then compared their results to mutation signatures of cancer genomes housed in the COSMIC

Database, the world's largest database of somatic cancer mutations. They found a match—the damage patterns identified by the team matched the mutation signatures found in cancers of the upper gastrointestinal (GI) tract, such as esophageal cancer and stomach cancer.

Upper GI cancers frequently are preceded by inflammatory precursor conditions. For example, infection with the bacterium Heliobacter pylori can damage the lining of the stomach, causing inflammation and ulcers. In the esophagus, severe acid reflux can lead to a condition called Barrett's esophagus, in which the lining of the esophagus becomes inflamed. In both cases, long-term inflammation is associated with increased cancer risk.

Thanks to the team's findings, the reason for this elevated risk is now clear. DNA comprises four chemical bases that exist in pairs—adenine (A) and thymine (T), and cytosine (C) and guanine (G). Different sequences of these pairs encode all the instructions for life. The team's findings reveal that in upper GI cancers, the oxidative stress caused by inflammation damages specific parts of the DNA, causing Gs to be replaced with oxidized Gs. These errors prevent DNA from being copied accurately—a key hallmark of cancer.

"Our DNA is our genetic instruction manual. When the letters get scrambled, the instructions can't be carried out properly and the result can be cancer," Pfeifer said. "There has been a lot of debate over the years about exactly how inflammation and oxidative stress contribute to disease, but we didn't have the right tools to study the link. Our new circle damage sequencing technique is allowing us to take a fresh look at old problems. I'm hopeful it will be a gamechanger."

Circle damage sequencing allows scientists to "break" DNA at each point where damage occurs. They coax the DNA into circles, which are replicated thousands of times using a technology called polymerase chain

reaction (PCR). Once they have enough DNA, they use next generation sequencing to identify which DNA bases are present at the breaks. Last year, Pfeifer's lab used circle damage sequencing to determine that the mutations that give rise to melanoma result from a chemical conversion in DNA damaged by sunlight—not just a DNA copying error as previously believed.

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