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Cancer is the second-leading cause of death among all major ethnic groups, but the risk of developing cancer varies considerably by ethnicity. For example, African Americans have the highest colon cancer incidence and mortality rates among all racial groups in the United States, but the reason for that disparity - and many others - is not entirely clear. However, researchers at the University of Kansas Medical Center have recently uncovered a genetic change that could help explain why people of different ethnic backgrounds are susceptible to different cancers.

The gene of interest is COX-2, whose protein has a well-established role in promoting inflammation and pain.

"When it comes to inflammation, COX-2 is one of the first proteins on the scene. Anti-inflammatory drugs like aspirin and ibuprofen are designed to target and suppress its activity," says Dan Dixon, Ph.D., an associate professor and the fledgling Department of Cancer Biology's newest faculty member. "In addition, COX-2 has been linked to diseases like colon, prostate and esophageal cancers, but we still don't really understand why it's present in these tumors."

What Dixon and his research crew found may provide further illumination. There are just four bases, or biochemical units, that make up human DNA. These, abbreviated by the letters A, T, C and G, are strung together like beads on a necklace and contain the recipes from which proteins, our body's building blocks, are made. While much of this four-letter arrangement is identical across individuals,

tiny changes called single nucleotide polymorphisms (SNPs, pronounced "snips") often appear along the way - which simply means, as Dixon explains, that "not every gene is the same between you and me." Some SNPs are more common than others. Many affect a person's susceptibility to certain diseases and how well they respond to treatment.

As part of her doctoral research, Dixon's graduate student Ashleigh Moore, Ph.D., decided to closely analyze a particular SNP associated with abnormally high COX-2 protein levels in certain cancers. It's a seemingly minute change: in one region of the COX-2 gene, a single C occupies the spot where a T should be.

"There's something about the gene having this one C instead of T that allows COX-2 to be overexpressed, and we wanted to figure out why," Moore says.

Diving deeper into molecular biology, she and Dixon discovered that this switch from T to C affected the function of a microRNA called miR-542. Neither genes nor proteins, microRNAs are short strings of bases that - like Oscar the Grouch - have an affinity for trash.

How so? Proteins come from genes, but not directly. Intermediaries called transcripts have to be generated first. MicroRNAs bind to some transcripts, labeling them as trash: instead of being turned into proteins, the marked transcripts are destroyed. It's a routine exercise that keeps a lid on the levels of any one protein.

"Specifically, miR-542 acts as a controlling switch for the COX-2 protein and ensures that it isn't overproduced," Moore says. She found that this single base change from T to C disrupts the ability of miR-542 to attach to COX-2 transcripts. Essentially, miR-542 can no longer perform its main task - dragging COX-2 transcripts to the trash - which in turn allows for unfettered protein production. Moore and Dixon published their findings in the August 2012 issue of the journal *Oncogene*.

"Will this inability to turn off COX-2 protein production *cause* cancer?" Dixon says. "No. But might it be a promoting force in making cancer worse? Yes, according to the scientific literature."

Intriguingly, epidemiological studies have shown that the distribution of this particular SNP varies across ethnic groups: 38 percent in people of African descent, 11 percent in Caucasians and less than one percent in Asians. With Dixon and Moore's discovery that this SNP basically jams the accelerator in COX-2 protein production, a clearer picture is emerging not only as to why African Americans are at greater risk of developing colon cancer, but why out-of-whack COX-2 levels are the norm in this disease.

A potential application of this research - still hypothetical at this point - lies in the expanding area of targeted cancer therapies. "In the future, patients could find out if they have this particular SNP through, for example, a cheek swab for DNA," Dixon says. "Those with C instead of T would have

tumors with higher COX-2 protein levels, which means that they might be more likely to benefit from drugs that suppress COX-2." Unfortunately, he adds, current COX-2 inhibitors, including various anti-inflammatory drugs, are double-edged swords. They often cause severe cardiovascular and gastrointestinal side effects.

So Dixon would ultimately like to find a way to reverse the effect of the C to T base change that renders miR-542 incapable of doing its job. Along with collaborators at The University of Kansas Cancer Center, including Raymond Perez, M.D., and Ross Stein, Ph.D., he is beginning a study - newly funded by a KU Cancer Center pilot award - to discover drugs that selectively kill cancer cells harboring this genetic change.

"Too often, we're only aware that a certain SNP is associated with a disease, but we don't know how exactly that SNP is functioning to influence gene expression, or what to do about it," he says. "I believe it's important to show a cause-and-effect relationship. If we get some hits with this new study, we'll have fixed the problem and bypassed the known side effects of current COX-2 inhibitors."

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