Chronic inflammation can trigger cancers via newly discovered mechanism

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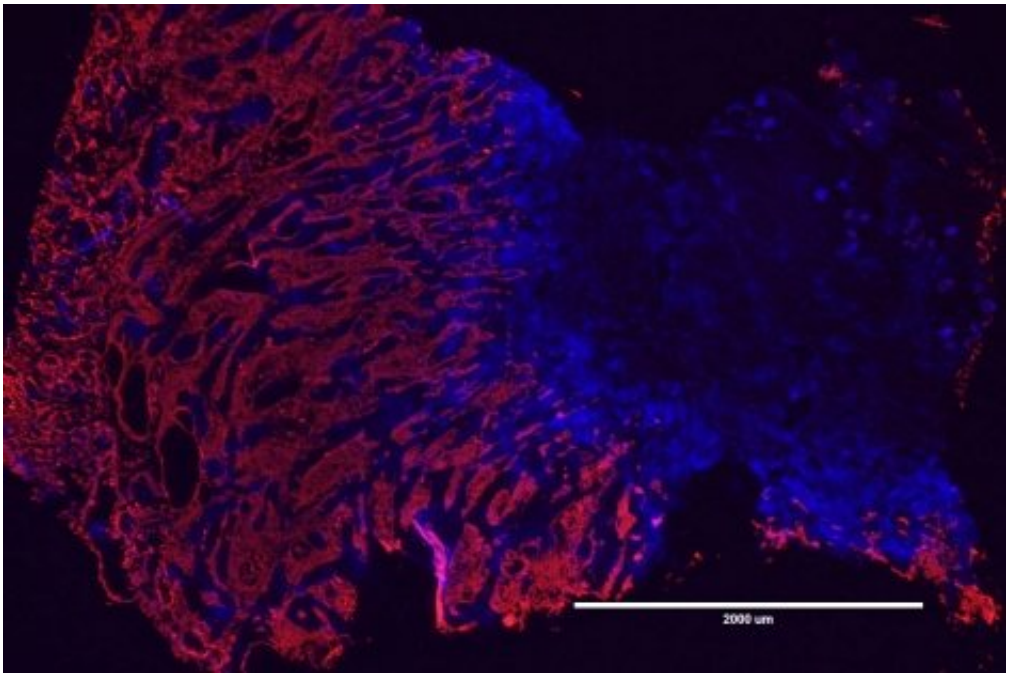

A microscopic view of an invasive squamous cell cancer that stemmed from a rare skin disorder called recessive dystrophic epidermolysis bullosa (RDEB), or Butterfly Syndrome. Credit: Andrew South

It is well known that extended exposure to the sun's UV rays can cause DNA mutations that lead to skin cancer. Now new research reveals that inflammation from chronic skin injury can trigger cancer-causing mutations as well by a totally distinct mechanism.

The researchers – led by scientists at UC San Francisco and Thomas Jefferson University in Philadelphia, in collaboration with Santa Cruz-based Nantomics LLC – say that better understanding this previously invisible driver of tumor formation could lead to a new class of therapies for a variety of cancers.

"We're describing for the first time a mechanism that instigates tissue damage-driven cancers," said study senior author Andrew South, Ph.D., an associate professor in the Department of Dermatology and Cutaneous Biology at Jefferson.

Previous studies of patients with head and neck cancers have suggested a link between tissue inflammation and cancer, but the specific mechanism behind this connection has remained elusive.

In their new study, published August 22, 2018, in *Science Translational Medicine*, South and UCSF Health dermatologist and geneticist Raymond Cho, MD, Ph.D., the study's first author, studied the cells of children with a rare skin disorder called recessive dystrophic epidermolysis bullosa (RDEB). Patients with RDEB, sometimes called "butterfly children" because their skin's extreme fragility calls to mind a butterfly's wings, lack the connective protein collagen, which makes their skin prone to blistering and scarring at the slightest touch. In addition to severe pain and potential disfigurement, patients also frequently develop aggressive squamous cell cancers early in life in frequently injured areas.

"RDEB is a terribly painful condition, but cancer is what causes premature mortality in these patients," said Cho, who is an associate professor of dermatology at UCSF and member of the UCSF Helen Diller Comprehensive Cancer Center. "The reason these patients get cancer is not well understood, but we realized that it had to be directly linked to chronic tissue damage, because the fragility of the skin is at the

root of everything in this disease."

Because RDEB is so rare – about five cases occur in every ten million live births in the U.S. – Cho and South needed to assemble a consortium of researchers from around the world to collect a sufficient number of tissue samples from children with the disease for the new study, including samples of cancerous, inflamed and normal tissue. Rather than focus on a few cancer-linked genes, the researchers sequenced the entire protein-coding part of the genome in these samples, which enabled them to detect subtle patterns of DNA mutation across the genome in inflamed and cancerous tissue that were clearly distinct from the types of mutational signatures caused by UV radiation.

The researchers showed that this pattern of mutation is caused by a protein called APOBEC, which normally plays a role in adding diversity to cellular proteins and is also thought to help defend against viruses. In RDEB patients, APOBEC appears to become overly active as a consequence of chronic tissue inflammation, causing it to introduce mutations across the genome, some of which eventually lead to cancer.

Using a computational approach developed in the Cho lab at UCSF, the researchers ruled out problems with DNA repair, which is a common driver of increased levels of mutation in many cancers. Patterns of mutation density throughout the genome of RDEB tissue samples indicated that normal DNA repair mechanisms were functioning properly, confirming that the cancer-causing mutations seen in RDEB patients were a result of inflammation and dysfunctional APOBEC alone.

The notion that inflammation and cancer are somehow linked has been gaining traction both in the medical world and in the general public, according to Cho, who hopes the new findings will help make further investigations of this relationship – in skin cancers, head and neck

cancers and other conditions – more concrete.

"In many ways, cancers are akin to wounds that never heal," Cho said. "Here we're showing a new mechanism for how inflammation from chronic tissue damage can actually lead to cancer. This could present the medical community with new opportunities to develop preventive measures against inflammation-driven cancers, as we have done successfully with cancers caused by UV exposure."

More information: Raymond J. Cho et al. APOBEC mutation drives early-onset squamous cell carcinomas in recessive dystrophic epidermolysis bullosa, *Science Translational Medicine* (2018). DOI: 10.1126/scitranslmed.aas9668

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