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Researchers find a likely cause of inflammatory myofibroblastic tumors

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Inflammatory myofibroblastic tumors (IMTs)—masses of immune cells— are benign, but poorly understood. Current IMT treatments often have side effects and surgery is sometimes not an option due to the tumor's proximity to vital organs. A better understanding of how IMTs form could spur the development of more effective therapeutics. Researchers at University of California San Diego School of Medicine have now found that a likely cause of IMT is deficiency in nonsense-mediated RNA decay (NMD), a system cells use to control which genes are activated.

The study is published June 27 by the *Journal of Clinical Investigation*.

"This finding is significant because virtually nothing was previously known about the underlying mechanisms of IMT," said senior author Miles Wilkinson, PhD, professor of reproductive medicine in the UC San Diego School of Medicine. "Until now, it was essentially a syndrome without a cause."

It's normal for immune cells to home to the site of an infection or injury, but their convergence should be temporary. In IMT, immune cells form an abnormal solid mass that doesn't usually go away on its own. IMT can occur in any tissue or organ in the body.

In this collaborative study, Wilkinson and Yanjun Lu, PhD, at the Tongji University in China, and their research teams compared human lung IMT samples and normal lung tissue samples from the same patients.

They found mutations in the master NMD gene—*UPF1*—in 80 percent of the IMT samples. No mutations were found in the normal lung samples.

"It is extremely unlikely that a gene would be so frequently mutated by chance alone," Wilkinson said. "Furthermore, almost all the mutations were clustered in a single region of the *UPF1* gene. Together, these data raise the strong possibility that *UPF1* mutation are at least one contributing factor to IMT."

NMD acts on messenger RNAs (mRNAs), which carry the blueprints encoded by the genome. Without mRNAs, our cells could not make the enzymes and other proteins essential for life. One of NMD's roles is to degrade errant mRNAs that encode bad proteins. NMD's other role—the one that may be more relevant in IMT—is to degrade normal mRNAs in specific cell types and situations when they are not needed.

The Lu and Wilkinson teams found that NMD is deficient in IMT, which leads to increased levels of RNAs normally degraded by NMD. One of the normal mRNAs that should be degraded but isn't in IMT encodes a protein that activates NFkB, the lead molecule in a biological system that drives inflammation. When NFkB is activated, immune cells are activated—they proliferate and produce communication chemicals that call up even more immune cells.

The researchers determined that these pro-NFkB mRNAs were elevated in an IMT sample, as compared to corresponding normal lung tissue. So were the immune homing signals that are produced as a result of NFkB activation. Antibody molecules normally found in allergic individuals—called IgE—were also produced in IMT.

"In this study we've connected many of the dots to explain why IMTs form—*UPF1* is mutated, NMD is inhibited and so NFkB runs out of

control," Wilkinson said. "And now that we know what likely causes IMT, we can look for ways to stop it, for example by identifying drugs that stimulate the NMD pathway."

Provided by University of California - San Diego