

New anti-inflammatory drugs might help avoid side effects of steroids

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A new class of anti-inflammatory drugs may one day serve as an alternative to steroid medications and possibly help avoid the serious side effects of steroids, based on research findings at the Salk Institute for Biological Studies.

The scientists, led by Inder M. Verma, a professor in Salk's Laboratory of Genetics and Ronald M. Evans, the director of Salk's Gene Expression laboratory, discovered that a protein that defends the body against cancer also plays a key role in the anti-inflammatory action of [steroids](#). Targeting this protein might lead to new drugs that could replace or augment [steroid treatment](#).

"Steroids are the most potent anti-inflammatories available, but they can cause serious [side effects](#)," says Verma, Salk's American Cancer Society Professor of Molecular Biology. "We may have found a way to get around these limitations by reducing inflammation without steroids. Our findings also suggest that certain cancer patients don't respond to steroid treatment, so they might be taking the drugs needlessly."

In a paper on the research, published earlier this month in the *Proceedings of the National Academy of Science*, Verma, Evans and their colleagues report that p53, a protein best known for suppressing cancer tumors, is also key to the anti-inflammatory action of glucocorticoids, a class of [steroid drugs](#).

Glucocorticoids play a role in the [human immune system](#), and glucocorticoid drugs are often used to treat disorders where the immune system is overactive, such as allergies, asthma and [rheumatoid arthritis](#). They are also used to treat inflammation caused by cancer tumors.

Glucocorticoid drugs work by suppressing the production of cytokines, immune system signaling molecules that help initiate the body's first response to threats from infection by bacteria and

viruses.

Normally, cytokines tell the body to increase blood flow and sensitize nerves, among other reactions, which helps fight off the invading microbes. In the case of [autoimmune diseases](#) and [cancer tumors](#), the cytokines are released inappropriately, causing inflammation that serves no immune function. Steroids help counter this inflammation.

However, Evans, a Howard Hughes Medical Institute Investigator, points out that steroids can produce serious side effects, including [immune system](#) suppression, high blood sugar, muscle weakness and glaucoma that limit their use.

"To reduce these complications we wanted to know whether there are missing links in the steroid chain of suppression that can help us reduce some of the side effects," Evans says. "To figure out the chain of events, at the molecular level, we teamed with Verma and together uncovered the hidden link that may lead to [new drugs](#) targets."

The scientists found a potential new target by genetically modifying a strain of mice to silence the gene that produces the p53 tumor suppressor protein. As a result, glucocorticoids were ineffective at countering the inflammation response in the mice, meaning that p53 is key gear in the cellular mechanism that allows the steroids to suppress inflammation.

Due to p53's role in suppressing cancer, scientists have already identified a number of other proteins capable of altering its activity. Based on their findings, the researchers think these proteins also might be effective as anti-inflammatory drugs that operate by stimulating p53 activity. This could offer the possibility of powerful anti-inflammatories without the nasty side effects of steroids.

Their results also suggest that some cancer patients, who have a genetic mutation in their

tumors that results in abnormal p53 activity, might be suffer through the side effects of steroids for no reason.

"If p53 is required for glucocorticoids to work, yet their tumor cells aren't producing p53 normally, they may be receiving steroid treatment and dealing with the ramifications with no therapeutic benefit," says Verma. "Maybe we shouldn't give them steroids, or, even better, maybe we can find a new drug that will replace steroids."

Provided by Salk Institute

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