

# Steroid hormone receptor prefers working alone to shut off immune system genes

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Researchers at Emory University School of Medicine have obtained a detailed molecular picture that shows how glucocorticoid hormones shut off key immune system genes.

The finding could help guide drug discovery efforts aimed at finding new anti-inflammatory drugs with fewer side effects.

The results are published in the journal *Nature Structural & Molecular Biology*.

Synthetic glucocorticoid hormones – for example, prednisone and dexamethasone—are widely used to treat conditions such as allergies, asthma, autoimmune diseases and cancer. They mimic the action of the natural hormone cortisol, which is involved in the response to stress and in regulating metabolism and the immune system. For this reason, synthetic glucocorticoids have a variety of severe side effects such as increased blood sugar and reduced bone density.

Both cortisol and synthetic hormones act by binding the glucocorticoid receptor, a protein that binds DNA and turns some [genes](#) on and others off. The hormone is required for the glucocorticoid receptor (GR) to enter the nucleus, giving it access to DNA.

For GR-targeting therapeutics, the desired anti-inflammatory effects are thought to come mainly from turning off inflammatory and immune system genes, while the side effects result from turning on genes

involved in processes such as metabolism and bone growth.

The mechanism driving GR anti-inflammatory action has been debated, since no GR binding site identified near these anti-inflammatory genes. Thus, GRs immunosuppression was thought to occur indirectly, whereby GR blocks the ability of other critical DNA-binding proteins to stimulate gene expression. Last year French scientists discovered that the GR turns some [immune system](#) genes off directly by recognizing a distinct DNA sequence used only in gene repression.

Eric Ortlund, PhD, Emory assistant professor of biochemistry, and first author William Hudson, a Molecular and Systems Pharmacology graduate student, used X-rays to probe crystals of GR bound to a stretch of DNA where it acts "repressively" to shut down the transcription of immune genes.

When the GR turns genes on, two GR molecules grasp each other while binding to DNA. However, the mode of binding to DNA at repressive sequences had remained unknown. Their analysis demonstrated that GR binds to repressive sites in pairs, but with two monomeric GR molecules located on opposite sides of the DNA helix.

"This unexpected geometry was still a surprise because GR has never been crystallized as a monomer bound to DNA, though previous studies proposed that GR monomers repress genes as opposed to GR dimers, which activate genes," says Ortlund.

In addition, the two GR molecules bind to different DNA sequences within the repressive DNA element, Hudson and Ortlund found. They also analyzed how mutations affected the ability of GR to bind repressive sites, showing that binding of the first GR molecule inhibits the binding of a second GR molecule. This "negative cooperativity" may play a role in ensuring that only GR monomers bind to DNA.

The study suggests that a drug preventing GR from interacting with other GR molecules while still allowing them to bind DNA and turn genes off may have anti-inflammatory effects with fewer side effects. One such plant-based compound, "compound A," has been under investigation by several laboratories.

"Our structural data could help scientists design synthetic hormones that separate these two aspects of GR function, potentially leading to improved steroid hormones for diseases ranging from asthma to autoimmune disorders," says Ortlund.

Provided by Emory University

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