Finding cortisone alternatives with fewer side effects

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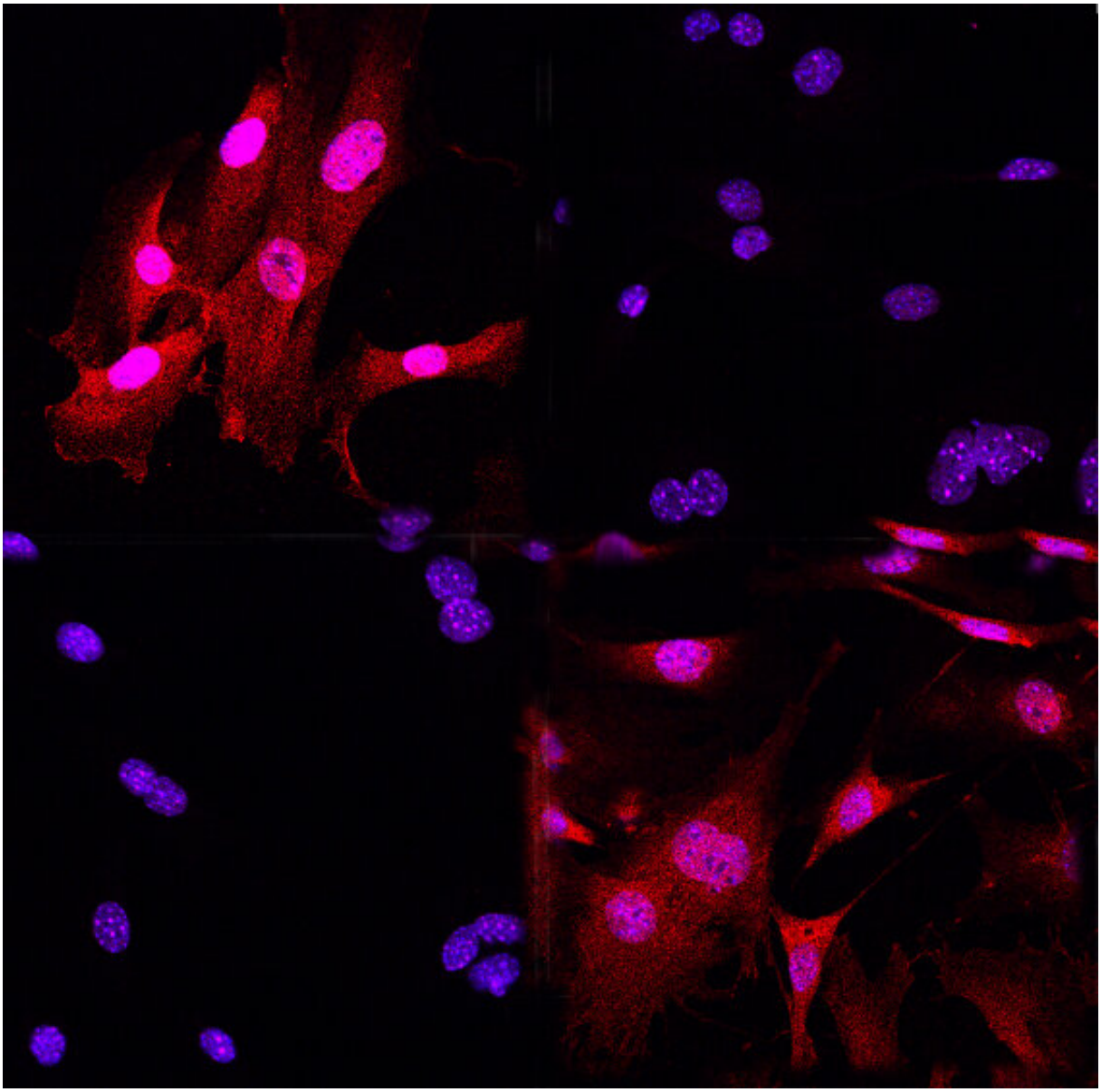

Immunofluorescent hue of the GR (glucocorticoid receptor, red) in mouse cells reacting to an inflammation signal - the cell nucleus is colored blue. You can see how - without steroids - the GR disperses in the cell's cytoplasm and how it is visible in the cell nucleus after the medication (dexamethasone) was administered (red and blue converge inside the round nucleus). Credit: Laura Escoter / TUM

Many people use cortisone of a regular basis. It is used for treating rheumatism, asthma, multiple sclerosis, or even COVID-19. Steroidal medication such as cortisone is highly effective but also possesses severe side effects. Henriette Uhlenhaut, professor at Technical University of Munich (TUM), and her team are examining the beneficial effects of cortisone in order to lay the groundwork for the development of similar drugs with fewer side effects.

The work group of Henriette Uhlenhaut, Professor for Metabolic Programming at TUM School of Life Sciences in Freising-Weihenstephan and researcher in the field of Molecular Endocrinology at Helmholtz Zentrum München is working with so-called glucocorticoids. These are steroidal hormones such as cortisone, which are released by the adrenal glands every day before waking up or whenever a person is subjected to stress. These steroids are bound to their glucocorticoid receptor and control not only our body's immune reaction but also our sugar and fat metabolism.

As glucocorticoid receptors are so efficient at disabling immune reactions, synthetic steroid medication is among the most prescribed drugs overall and it has been for decades.

The goal: Finding molecules with anti-inflammatory effects

"Unfortunately, this useful property leads to severe side effects as one hormone or drug causes different effects in other non-immune cells," explained the professor. Among these effects are the reduction of muscle mass or the deposition of fat.

"We still don't fully understand the effects of steroid compounds," said Uhlenhaut. With her team, she wants to discover the molecular mechanisms that steroids such as cortisone utilize to stop inflammatory reactions.

As soon as researchers know how cortisone works, so how it mutes inflammation genes in immune system cells, they can begin looking for molecules that possess the same anti-inflammatory properties as cortisone, but with fewer side effects.

Common theory refuted

Until recently, scientists believed that the steroids' anti-inflammatory effect was based on protein-to-protein interaction. It was assumed that the glucocorticoid receptor—in other words, the protein that binds these drugs or hormones—would connect to other inflammation inducing proteins without any DNA contact.

Using a new preclinical model, the team of researchers could now demonstrate that DNA binding is required for these drugs to have an effect; for years, scientists had assumed that this was not the case. Without the glucocorticoid receptor (the protein that binds these drugs or hormones) enabling DNA binding to chromosomes, chromatin or genes, there is no biological effect.

A milestone for drug development

"Now we know that DNA binding plays a major role, yet we have not

found a way to separate side effects from the desired effects," explained Prof. Uhlenhaut. Regarding COVID-19, researchers do not have a clear answer either as to why these kinds of treatments are successful. Further research in this area is required.

Until now, various approaches focused on protein-to-protein contact, which might explain why these have not been successful. As this basic approach can now be discarded, further research regarding drug development of cortisone alternatives can now focus on the DNA.

More information: Laura Escoter-Torres et al, Anti-inflammatory functions of the glucocorticoid receptor require DNA binding, *Nucleic Acids Research* (2020). DOI: 10.1093/nar/gkaa565

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