Team reveals extraordinary plasticity of the glucocorticoid receptor

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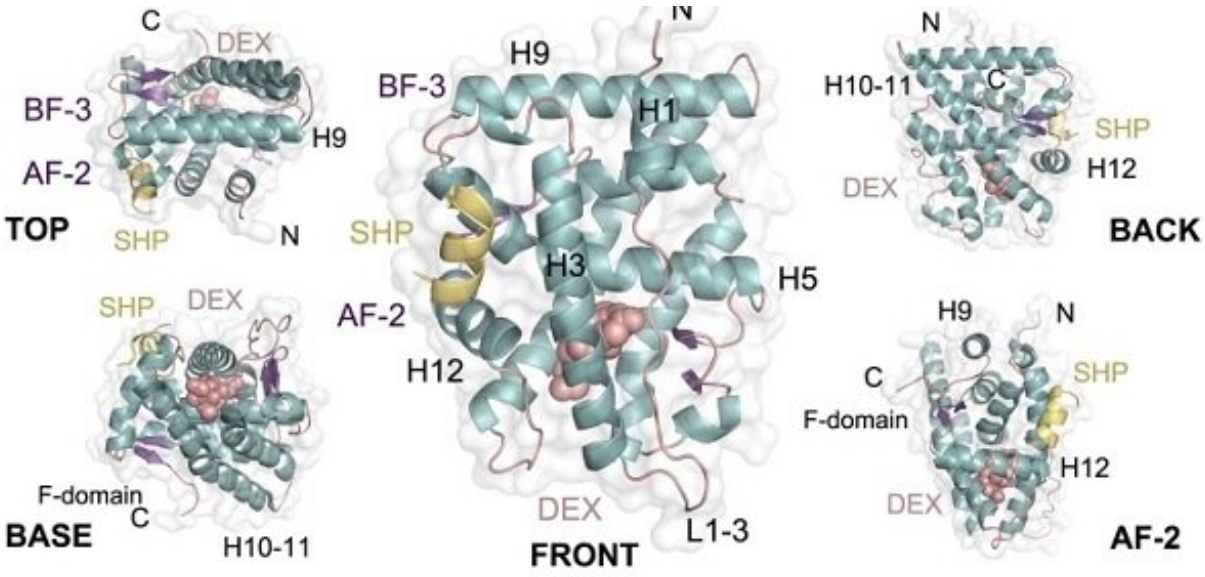

The discovery of the receptor's structural versatility could contribute to the design of more selective and less toxic drugs for patients. Credit: University of Barcelona

Glucocorticoids—such as cortisone—are among the most widely used anti-inflammatory drugs, and are used to treat asthma, psoriasis, organ transplantation and even COVID-19. Regarding their pharmacological action, the activity of the glucocorticoid receptor (GR) is crucial.

The GR is a transcription factor that regulates vital processes in human

physiology. However, the detailed three-dimensional structure of this nuclear receptor—one of the most important therapeutic targets in the pharmaceutical industry—is still an enigma to the scientific community.

Now, a study published in the journal *Nucleic Acids Research* reveals for the first time that GR is a highly plastic protein with a highly versatile structure: its monomers (constituent molecules) are able to self-assemble in different ways to form dimers, tetramers and complexes with other proteins in the cell nucleus to control the expression of numerous genes.

The discovery of the previously unknown structural and functional versatility of the GR and its molecular self-assembly process (oligomerization) will contribute to the design of drugs that are more selective with the specific conformations of the receptor, as well as less toxic in order to avoid the serious side effects that classical corticosteroids generate in patients.

Avoiding side effects of glucocorticoids

The three-dimensional structure of the GR, which is essential for its physiological activity, has been questioned in the scientific literature. The first structure of the GR ligand-binding domain (GR-LBD) was published in 2002 in the journal *Cell*. According to this model, two GR-LBD molecules associate to form a dimer in a conformation never before described in nuclear receptors.

These findings opened a scientific debate—which still exists—on the conformation of the RBC and its oligomerization state in cells. Since pharmaceutical companies have been keen to develop drugs against the GR, most of the subsequent structural studies have focused on the interaction of the GR-LBD with therapeutic compounds. As a result, the analysis of the oligomerization state of RBC was neglected, generating a large amount of structural data that remained unexamined in detail.

Research on glucocorticoid action without side effects has been based exclusively on this partial model of the GR dimerization state. Traditionally, the GR, once activated by corticosteroids, was considered to have the ability to perform different functions in the cell depending on its oligomerization state: as a monomer, it repressed pro-inflammatory genes, while as a dimer it could induce the expression of anti-inflammatory genes.

This dogma was challenged when the NIH team in Bethesda showed that the GR could also act as a tetramer (four GR molecules connected together, perhaps a dimer of dimers) and have physiological activity, whereas the monomeric form of the receptor did not regulate any function.

However, the information that was known about the structure of the GR could not explain how the receptor forms these tetramers at the cellular level. "Our work analyzes the oligomerization potential of GR-LBD and shows how this receptor can form up to 20 different dimers. The results suggest that some of these dimers can associate to form functional tetramers when the receptor binds to DNA," says Eva Estébanez, from the Department of Biochemistry and Molecular Biomedicine of the Faculty of Biology.

The study also identified non-functional hexameric forms of GR mutants that have been described in patients who do not respond to corticosteroids (Chrousos syndrome or glucocorticoid resistance syndrome). "Therefore, our study associates for the first time the formation of non-functional oligomers of GR (or of any other nuclear receptor) to a rare human endocrinological disease of glucocorticoid resistance," says Estébanez.

An unknown structural plasticity in other nuclear receptors

To obtain the results, the team has applied a wide range of techniques, from X-ray crystallography with synchrotron radiation (ALBA-CELLS) to the method known as Number and Brightness, a leading microscopy technique that allows visualization of the oligomerization state of RBCs in living cells.

The study has allowed the researchers to explain, from a structural point of view, how GR dimers and tetramers can be formed, and how the ligand-binding domain is key to these multiple conformations. The analysis of all the structural data available for the GR—together with the new structures solved by the UB-IBUB group—has allowed them to determine a structural plasticity never seen before in other nuclear receptors.

"This versatility allows the RBC to form dimers with different conformations that can be modulated, to a certain extent, depending on the type of ligand that binds to the receptor, and this would explain the ability of the RBC to form tetramers," says researcher Alba Jiménez.

"Our results reinforce the data showing the formation of active tetramers when the receptor binds to DNA and consolidate the hypothesis that the mechanism of action of the GR in the regulation of transcription is much more complex and versatile," says expert Andrea Alegre.

This multidisciplinary approach has made it possible to transfer the results from observations derived from protein structure to processes occurring at the cellular level, a scientific progress with implications of interest in human physiology and the fight against certain diseases.

More information: Alba Jiménez-Panizo et al, The multivalency of the glucocorticoid receptor ligand-binding domain explains its manifold physiological activities, *Nucleic Acids Research* (2022). DOI: 10.1093/nar/gkac1119

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