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## Editorial

### Resistance to Glucocorticoids: Another Piece of the Jigsaw<sup>☆</sup>

#### Resistencia a glucocorticoides: una pieza más para el puzzle

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Currently, the development of new drugs is based on previous research in physiopathological disease mechanisms, whose understanding in cellular and molecular biology is aimed at potential therapeutic targets. In the so-called “discovery phase” (in the terminology of the pharmaceutical industry), an extensive battery of molecules are scrutinized in order to analyze their capacity for antagonizing a particular receptor, block the activity of certain enzymes implicated in a specific signaling pathway, etc. Only a limited selection of said candidate drug molecules continue on to later developmental stages, where their effects are thoroughly studied along a trajectory that selectively opens the door to clinical development of the potential medication. It is a therapeutic development strategy in which the mechanism for action of the potential drug, designed and therefore known, is directed over a strong physiopathological base.

Only recent technology has facilitated this type of anterograde approach, where the understanding of a functional mechanism or disease leads to its pharmacological manipulation. Not long ago, however, therapeutic solutions had for the most part an empirical origin, and the beneficial properties (and undesired effects) of a composition were discovered without understanding its mechanism of action. A many number of medications with this type of origin, from acetylsalicylic acid to theophylline, are still being used today, even though their mechanisms of action have been understood (although incompletely) much later than their therapeutic use.

In this “retrograde” process (therapeutic application before learning about mechanisms of action), glucocorticoids are paradigmatic. Following the first clinical uses of cortisone in the 1940's<sup>1,2</sup> and during a very long stretch of history until our time, glucocorticoids have been the most effective anti-inflammatory treatment available for a large spectrum of immunologically-based affections, be they either autoimmune or allergic, from rheumatoid arthritis and inflammatory intestinal disease to atopic rhinitis and asthma. Within their recent role as part of our therapeutic arsenal, glucocorticoids have been extensively diversified, both

pharmacologically as well as in their administration procedures, and significant advances have been made in understanding their mechanisms of action.

Nevertheless, glucocorticoids present an additional puzzle beyond their complex mechanism of action: the mechanisms of resistance to glucocorticoids, whose behavior and variability are hardly comprehended. To begin with, different diseases with an inflammatory basis constitute in their general behavior different categories of response or resistance. Inhaled glucocorticoids are the cornerstone in the treatment of asthma, which is controlled with low dosages in an important percentage of patients. Chronic obstructive pulmonary disease, cystic fibrosis and interstitial lung fibrosis, however, are highly resistant. As an additional complication, there may be resistance to glucocorticoids in certain individuals with diseases that are responsive *per se*. Approximately 10% of patients with asthma and 30% of patients with rheumatoid arthritis show limited response against high doses of glucocorticoids.<sup>3</sup> Beyond the mechanisms of therapeutic action, the study of the mechanisms of resistance is consequentially a field of high current interest due to its potential to reveal new ways for controlling non-responsive patients, or even in non-responsive diseases.

After the binding of the glucocorticoids to their intracytoplasmic receptor, there is a translocation of the complex made up of the glucocorticoid molecule and the activated receptor to the interior of the cell nucleus. There, through its interaction with specific DNA sequences and other co-factors, it activates the transcription of genes that codify immunoregulatory mediators and repress the expression of proinflammatory genes. Likewise, glucocorticoids have the capacity to facilitate the degradation of RNA messengers of certain inflammatory mediators in the cytoplasm. As a whole, these mechanisms and the subsequent cascading effects lead to known therapeutic actions.

Regarding the mechanisms of glucocorticoid resistance, the data that are currently available suggest that there is no main pathway or critical “switch”. Instead, said mechanisms are diverse, act on different points of the therapeutic action pathways, and probably combine variably. The current data compiled from different studies present us this panorama of complexity. But they likewise indicate that there are identifiable mechanisms of glucocorticoid resistance

<sup>☆</sup> In memory of Dr. Manel Barbanj, director and vital driving force behind the Centro de Investigación de Medicamentos (CIM) at Santa Creu and Sant Pau.  
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as well as those left to be discovered, and therefore potential pharmacological intervention goals transferable to clinical benefits.

In this issue of *Archivos de Bronconeumología*, Embid et al.<sup>4</sup> have researched one of the possible targets of the resistance mechanisms, which is the nuclear translocation of the glucocorticoid receptor activated as an essential step for its action. In order to do so, they used an interesting strategy for accessing cultivable living human tissue in the context of a disease with characteristic resistance to glucocorticoid treatment: nasal polyposis. Taking advantage of the association between asthma, hypersensitivity to aspirin and nasal polyposis, Embid et al. were able to generate upper airway cell cultures in a study population including asthmatics with different characteristics, in addition to a control subject group with indication for corrective nasal surgery.

When they analyzed in fibroblasts the nuclear translocation capacity of the glucocorticoid receptors against dexamethasone or budesonide, the authors found no differences between the asthma patients classified by severity category in accordance with the *Global Initiative for Asthma Management* (GINA)<sup>5</sup> or between asthmatics and control subjects. Nor did they find differences between asthmatics with or without hypersensitivity to aspirin. The mild asthmatics showed a non-statistically significant tendency towards an accelerated translocation of the glucocorticoid receptor against budesonide (and, interestingly, not against dexamethasone) compared with the control subjects and the subjects with moderate-severe asthma; these last two groups were practically superimposable.

Considering the possibility that a lack of statistical power may have impeded detecting this result as significant, it is an interesting finding for generating hypotheses in a new direction. It reflects a potential mechanism actively favoring the response to glucocorticoids at the receptor translocation level in mild asthmatics, more than a resistance in asthmatics with higher levels of severity, with a very exact approximation to the line of the control subjects. These data deserve special attention due to the fact that limited previous research in the clinical field about nuclear translocation of the glucocorticoid receptor in asthmatics of varying severity was either done exclusively with dexamethasone<sup>6,7</sup> or in the absence of a control group.<sup>7</sup> Embid et al. likewise reported the original finding of a decrease in the translocation of the glucocorticoid receptor in atopic patients compared with non-atopics. This result is consistent with a decrease in the affinity of the receptor observed in atopic subjects by other authors<sup>8</sup> and offers the particular relevance of being a finding directly obtained in inflammatory lesions of the airway.

As a whole, the article by Embid et al. contributes to a significant advance in the understanding of the role of the nuclear translocation of the glucocorticoid receptor in the therapeutic response of the airway. On one hand, the result of the translocation against budesonide suggests a possible direction to follow in subsequent research that, if the pattern of the data presented here is confirmed, could originate a new concept of mechanisms that actively facilitate the response to specific glucocorticoids. Can refractoriness to glucocorticoids be entirely explained by resistance mechanisms, or are there mechanisms that facilitate the response to glucocorticoids like a regulatory branch in certain phases or forms of immune response? Is there diversity in the behavior between different synthetic glucocorticoids in this aspect? On the other hand, the new finding of a difference in translocation response between atopic and non-atopic asthmatics provides a potential tool in a current context that is actively researching the way to subclassify asthmatics by phenotypes, predicting therapeutic management and response.<sup>9</sup> The continuance of this type of research on mechanisms of sensitivity or resistance to glucocorticoids can provide important advances with clinical translation.

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