Editorial
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Individualized Treatment for Allergic Rhinitis

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Glucocorticoid resistance in allergic airway diseases, such as allergic rhinitis and asthma, or in chronic rhinosinusitis has recently been the most challenging field, and this might be the reason for endotyping in these diseases. As described in the current article, neutrophils seem to be related to the development of glucocorticoid resistance. In asthma, glucocorticoid resistance is associated with increased numbers of neutrophils in the peripheral blood and bronchoalveolar lavage fluid (BALF).[1,2] Also, in chronic rhinosinusitis, increased neutrophil infiltration is known to be associated with steroid refractoriness.[3] While its action on lymphocytes, thymocytes or eosinophils is to increase the apoptosis and thus leading to anti-inflammatory action,[4] glucocorticoid is known to prevent neutrophil apoptosis.[5] Since the functional longevity of neutrophils in inflamed sites is generally controlled by apoptosis,[6] neutrophil-rich condition would sustain inflammatory activity when treated with glucocorticoid.

One common theory is the dominant negative glucocorticoid receptor β isoform (GRβ) which is expressed at a higher level than GRα in neutrophils.[7] In contrast to GRα, which is known as a classic receptor of glucocorticoid and interacts with pro-inflammatory transcription factors, such as NF-κB, mediating anti-inflammatory response,[8] GRβ is an isoform that has no transcriptional activity and is known to interfere with GRα by forming a heterodimer and thus repressing pro-apoptotic genes.[9]

The role of IL-17 in asthma and allergic rhinitis had recently been elucidated for the recruitment of neutrophils. IL-17A mainly secreted from Th17 cells leads to the activation of the signaling cascade, finally resulting in the secretion of chemokines CXCL1, CXCL2, and CXCL8, recruiting neutrophils.[10,11] This IL-17 is known to be related to the severity of allergic rhinitis.[12] Thus, taken together, increased IL-17 in the inflammatory airway disease leading to neutrophil recruitment seems to be the key feature of glucocorticoid resistance in these diseases.

However, the development of steroid resistance is not so simple. To understand the steroid resistance, we should first know the complexity of the molecular mechanism of the glucocorticoid receptor (GR). In the absence of the hormone, the GR predominantly resides in the cell cytoplasm, and it is combined with other proteins, including chaperons and forms a large multi-protein complex. When the hormone is bound, conformational changes occur and the multi-protein complex is dissociated. Ligand-bound GR is then translocated into the nucleus and thus acts as a regulator for downstream gene expression.[7] This is the genomic action of the GR, however, there are some non-genomic actions of the GR as well. In non-genomic action, the multi-protein complex dissociates after ligand binding to GR, and the proteins liberated participate in secondary signaling cascade. For example, when liberated from the GR complex, c-Src activates multiple kinase cascades that lead to the phosphorylation of annexin 1, inhibition of cytosolic phospholipase A2 activity, and impaired release of arachidonic acid.[13]

There are many isoforms of the GR. Isoforms of the GR are known to result from alternative splicing, translational isoforms, and translational modifications.[7] These isoforms are known to have different biological activities and to be differently regulated, so that the composition of these isoforms may differ according to the cell type and tissue. For example, GRβ is abundant in certain types of cells such as neutrophil and epithelial cell.[14,15] Glucocorticoid resistance seems to be mediated by a variety of pathways which influence different activities of the isoform composition. Moreover, regulation of the non-genomic interactions is another mechanism of this resistance. The superordinate concept of regulation of this complexity is based on the action of increased inflammatory cytokines in chronic inflammatory diseases such as asthma, sepsis, and oth-

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er rheumatologic diseases.[16]

Since the isoformic GR composition and the action of theGR are known to be different among different types of cells or tissues (different environment), the influence of chronic inflammatory condition may be even more complex.

Previous studies have linked *Chlamydia pneumoniae* and *Haemophilus influenzae* infections to glucocorticoid-resistant asthma. These infections induce strong neutrophilic inflammation and potent Th1/ Th17 responses, thus leading to glucocorticoid resistance. In the animal model of glucocorticoid-resistant asthma, treatment with amoxicillin did not show improvements in Th2 inflammation, but it restored the glucocorticoid sensitivity. On the contrary, when treated with clarithromycin alone, inflammation has been suppressed by both antimicrobial and anti-inflammatory effects through its action on TNF-α and IL-17.[17] Thus, macrolides have been proposed as a new therapeutic option for glucocorticoid-resistant asthma[18] and chronic rhinosinusitis,[19] as they possess anti-inflammatory properties.

In addition, sensitivity of MUC5AC to topical corticosteroid is low if the IL-17A level in patients with allergic rhinitis is high,[20] and macrolide is known to have an inhibitory effect on MUC5AC secretion,[21] which may in part explain a significant decrease in nasal secretion in neutrophil-dominant allergic rhinitis.

In the current issue of Allergy, Asthma and Immunology Research, Chen et al, have individualized the treatment of allergic rhinitis patients according to their nasal cytology. In this study, allergic rhinitis patients with locally predominant neutrophils had a better response to treatment with oral clarithromycin compared to intranasal corticosteroid spray and oral antihistamine. It suggested the importance of nasal cytology for subtyping and individualized treatment.[22]

Taken together, one of the candidate markers for glucocorticoid resistance is the presence of neutrophil in allergic inflammatory disease. Proposed mechanisms underlying glucocorticoid resistance include the expression of GRβ in neutrophils and increased IL-17 cytokine level, resulting in neutrophil recruitment. However, the regulation of the GR is so complex that other possible mechanisms leading to glucocorticoid resistance should be considered. Another mechanism underlying glucocorticoid resistance is the increased infection due to the immunosuppressive action of glucocorticoid, which increases the overall inflammation. As clarithromycin has both anti-bacterial and anti-inflammatory effects through TNF-α and IL-17, it can be used as an alternative drug for glucocorticoid-resistant patients. In addition, clarithromycin has an additive MUC5AC-lowering effect, thus alleviating rhinitis symptoms.

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