Symposium 2. Advances in asthma management

Development of new asthma drugs

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Bronchial asthma is recognized as a heterogeneous clinical syndrome consisting of various disease phenotypes. Each asthma phenotype may have distinct observable molecular, cellular, morphological, functional, and clinical features, all of which can be possibly integrated into specific biological mechanisms, called as endotypes. Considering these backgrounds, the improvement of the characterization of the patients is required to achieve appropriate therapeutic responses for asthma. It is expected that the determination of phenotype and endotype leads to more effective precision medicine.

However, to date, pharmacologic treatments for asthma are predominantly nonspecific anti-inflammatory agents such as corticosteroid and bronchodilators including $\beta 2$ agonists, which are effective in the majority of patients with asthma. However, therapeutic responses to these agents vary. Severe asthma is characterized by uncontrolled symptoms and recurrent exacerbation with excessive chronic airway inflammation despite adequate and even maximum treatment with these current medications. Although multiple factors can cause poor responses and underlying pathogenic differences are being revealed explaining the various therapeutic responses including steroid insensitivity, effective therapeutic modalities for severe asthma are still remained as a major unmet need. Moreover, new members of pharmacological therapeutics and more effective drug-delivery devices (i.e., inhaled device) have been designed but the proportion of severe asthmatic patients remains stable.

Recently, many clustering analyses have demonstrated that more specific subpopulations of severe asthmatic patients exist and they are associated with different molecular mechanisms contributing to their own pathogenesis sometimes respectively or cooperatively. As for these findings, in 2006 our research team has reported for the first time that PI3K-δ isoform plays an important pathogenic role in OVA-induced allergic asthma and nowadays, it is believed that phosphoinositide 3-kinases (PI3Ks)-δ contributes to the steroid resistance of severe respiratory diseases and more specifically that oxidative stress directly induces PI3K-δ-dependent Akt activation. In fact PI3Ks play critical roles in inflammation, promoting cell polarization, migration, adhesion, and invasion. Class I PI3Ks are activated by tyrosine kinases and is

implicated in a wide range of cellular functions, including induction of Th2-related immune responses. They are cytosolic heterodimers consisting of a catalytic p110 subunit (designated as α, β, γ, or δ) and a particular regulatory subunit (designated as p85, p55, p50, or p101). These proteins are a family of lipid signaling kinases that generate lipid-based second messenger, phosphatidylinositol-3,4,5-trisphosphate (PIP3) and subsequently phosphorylate effector proteins such as Akt. In mammals, the class I PI3K isoforms are present in all cell types in which expression of the p110α and p110β isoforms are ubiquitous while expression of p110γ and p110δ is restricted in some cells such as leukocytes. The restricted expression profile of PI3K-δ makes it an attractive drug target for various inflammatory conditions such as asthma.

In addition, our recent studies have revealed that severe asthma is associated with functions of subcellular organelles such as mitochondria and endoplasmic reticulum (ER). In the pathogeneses, the subcellular organelles seem to have new and different roles from their classic ones and the new roles are implicated in various inflammatory/immune responses actively. Moreover, PI3K-δ signaling is appeared to relate with the out of control of functions in these subcellular organelles and immunes responses in the pathogenesis of severe asthma. In fact, very recently we have revealed that the role of ER stress in various types of severe asthma and pulmonary inflammation, in which ER stress induces the inflammatory responses through the

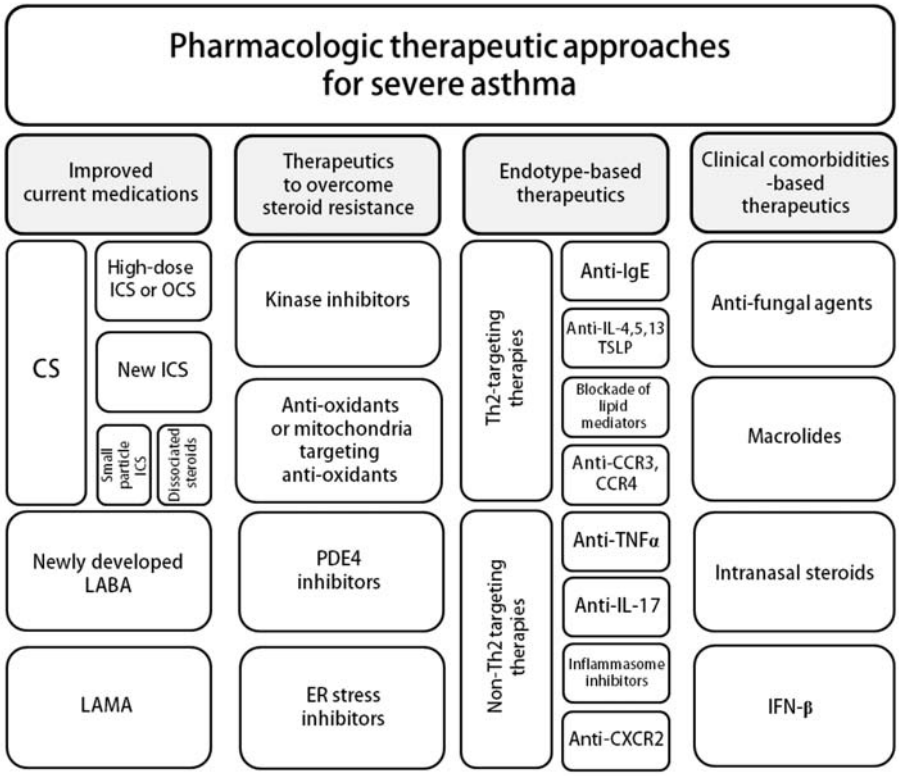

Figure 1. Summary of pharmacologic therapeutics for severe asthma. *Adopted from Severe Asthma: Toward Personalized Patient Management* (*Book*)[1]

interplay with PI3K-δ, NF-κB or HIF-1α signaling. Based on these observations, we suggest a hypothesis that the link can exist between subcellular organelles and PI3K-δ signaling in various types of severe asthma in which PI3K-δ isoform plays differential roles in each type of severe asthma. In addition, the therapeutic approach via controlling PI3K-δ isoform is very promising as a precision medicine for severe asthma.

In this lecture, recent advances in pharmacologic treatment of severe asthma will be introduced including improved current medications, potent non-specific anti-inflammatory agents, endotype-targeted treatments, specific treatment for comorbidities and potential therapeutic candidates focusing on the modulation of PI3K signaling as well as subcellular organelles associated with immune responses (Figure 1).

Reference

1. Lee YC, Kim SR, Cho SH. Severe asthma: Toward Personalized Patient Management. 1st ed. Springer. 2018 Edition