The concept of asthma disease has been around since 400 BC (Asthma & Allergy 2018) and yet, there is no cure for it. It was not until the 20th century when asthma was specifcally classifed as an infammatory disorder, but its severity was underestimated. Currently, the chronic infammation and malfunctioning airway classify the disease as a major noncommunicable disease that afects both children and adults (WHO, 2022). Worldwide, in 2019 asthma afected 262 million people; 455,000 had died. Unfortunately, the condition continues to burden many children and adults (WHO, 2022).

Specifcally in the United States, data collected by the NHIS in 2022 revealed that 26 million people sufer from asthma (Gof, 2023). Of this, 21 million were adults. There needs to be progress made in this feld of study as scientists continue to battle the ongoing challenge of defning asthma. That is why asthma research supported by a well-fnanced foundation should be prioritized. In doing so, innovative methods can be produced to identify, classify, and diagnose asthma at an earlier stage. Early, accurate diagnosis nurtures optimal disease management, precision medicine and reduced asthma-attributable health burdens.

Asthma is a heterogeneous disease and so its severity and risk factors range between people. However, each day, 10 people in the U.S. die from asthma (Gof, 2023). Most deaths are likely Black and/or females. Moreover, those who are at higher risk for developing asthma include Black and female populations. In fact, around 9.7% adult-females have asthma (Gof, 2023). And Black children are two times as likely to suffer from asthma than white children. In the U.S, Black people are also three times more likely to die from asthma. And despite the advancements in the diagnosis and care of asthma, a large population continues to sufer. To reduce these rates, it is important to further asthma research. While patterns of diagnosis including age, gender and race are important to characterize asthma, asthma cannot be understood without study

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guished by infammation, mucus buildup and bronchoconstriction (CDC, 2017). People afcted with asthma typically display multiple symptoms simultaneously. These include shortness of breath, dry short coughs, chest tightness and pain, and wheezing (CDC, 2017). More chronic cases of asthma result in sleep disturbance and a drop in the peak fow meter. Symptoms for the onset of an asthma attack include failure of quick-relief medicines, immobilizing chest tightness, severe breath shortness and hunched shoulders. The failure to treat these asthma symptoms results in increased disease severity and pain.

Yet treatment cannot be obtained without at least understanding some of the cellular mechanisms behind asthma. There are several classifcations of asthma. Type 1 asthma, known as “brittle asthma,” is difculties in daily breathing, whereas type 2, which is the primary focus in most research, is characterized by excessive T helper cells. There is also allergic or nonallergic asthma. Regardless, each case of asthma induces pathological changes in the cells and their functions. Several mechanisms to examine as potential cellular targets are the role of the homeobox homolog, Six1 promoting exacerbations and miRNAs mediating efects on Six1. As well as the upregulation and/

of Six1 in asthma and that it played a key role in pathogenesis. In that study researchers utilized an ovalbumin-induced mice model and analyzed findings through immunohistochemistry and western blotting to evaluate the expression level of Six1. Further, it was revealed that Six1 disrupted regular lung tissue and was significantly overexpressed in asthma patients when compared to the negative control. Additionally, Six1 effect on various leukocytes was also examined; cell numbers for each immune cell were highly increased in the upregulated Six1 expressing OVA mice, compared to the control. Knockdown of Six1 showed decreased numbers. This study confirmed the presence of Six1 in asthma and its effects on several immune cells. However, the exact relationship between Six1 and airway remodeling is still being investigated.

Airway remodeling is a main mechanism involved in irregular lung and bronchus asthma effects. Specifically, it is a pathological change in severe asthma and constitutes extracellular and cellular changes in the airways. This prognosis has contributed to fibroblast activation, airway smooth muscle (ASM) proliferation and epithelial cell apoptosis (Hough et al., 2020). One of its main components, epithelial-mesenchymal transition (EMT), may have direct linkage to Six1 and fibrosis. Furthermore, Wang et al. (2021) discovered Six1 promotes EMT in bronchial epithelial cells. Results indicated that Six1 promoted EMT through the TGFB1/Smad pathway. This pathway is important in mediating fibrosis. Smad is a downstream regulator and when exposed to a ligand, Smad protein nuclear localization is stimulated and regulates targeted gene expression. For asthma patients, activation of this pathway promotes fibrosis and ultimately stimulates airway remodeling as a response.

Within this study, in cells overexpressing Six1, researchers were able to determine through rt-PCR and western blotting that both TGFB1 and Smad were significantly overexpressed compared to the negative control. However, when Six1 was inhibited, TGFB1 and Smad protein expression decreased. This study indicated that Six1 expression contributes to airway remodeling. More specifically, the relationship between Six1 and TGFB1/Smad revealed extensive fibrosis and EMT enhancement. Six1 overexpression in asthma promotes negative effects on cell morphology, pathology, and expression. Potential effective treatments should focus on inhibiting Six1 in asthma patients.

Asthma is also associated with increased IgE production within the lungs. Therefore, researchers have also aimed to focus on more biologic components to treat, such as inflammatory response. Inflammation is a key characteristic of asthma and is triggered by interleukin-4 (IL-4) and IL-13. Mediated by receptors, IL-4 and IL-13 play a pivotal role in severe asthma. IL-4 is heavily involved in T helper 2 (Th2) lymphocyte cell differentiation, while IL-13 works alongside IL-4 to promote IgE synthesis, fibroblast proliferation and elicit ASM response (Pelaia et al., 2022). Both interleukins share common signaling pathways as when selective parts of IL-4 are blocked, IL-13 has potential to also be blocked. In severe asthma, these cytokines primarily work to amplify bronchial inflammation, persistence, and remodeling. When overexpressed, their presence is indicated by heightened IgE levels in lung samples.

The interleukin-4 pathway is mediated by its receptor IL-4R signaling system. This system includes two receptors, type 1, and type 2. However, type 2 IL-4R is more associated with interleukin 13 as it comprises an IL-4Ra chain paired with IL-13Ra1 and can be activated by IL-13. Type 1 IL-4R cannot be activated by interleukin 13 (Karo et al., 2018). In general, initiation of the signal transduction requires receptor-associated kinase phosphorylation. IL-4 does not naturally contain endogenous kinase activity and so in asthma, its activation is due to Jak2 and/or tyrosine kinase 2 (Tyk2) (Ladjemi et al., 2018). When engaged with IL-4 or IL-13, Jak phosphorylates and dimerizes STAT6. Subsequently, translocation of STAT6 occurs and induces the transcription of IL-4 and IL-13 thus promoting IL4 and/or IL-13 responses.

In severe asthma, this mediated response induces differentiation of B cells into IgE secreting plasma cells and raises the level of IgE antibodies in the blood. With repeated exposure and secretion, IgE cross-linking occurs on mast cells and induces histamine secretion and chemokines that cause inflammatory cells, importantly eosinophils, transmigration (Karo et al., 2018). This increase associated with acute exacerbations. It was once thought of only afect