and biomarker profiles. In general, Cluster 1 consists of patients with mild asthma not treated with steroids and well controlled with preserved lung function and a low-inflammatory phenotype; Cluster 2 is partially controlled, with mild airflow obstruction but severe airway hyperresponsiveness and a Th2 phenotype (brittle phenotype); Cluster 3 is partially controlled with mild airflow obstruction but reduced vital capacity, less bronchodilator reversibility, and a non-Th2 phenotype with neutrophilic inflammation (chronic obstructive pulmonary disease–like); and Cluster 4 is poorly controlled, with marked airflow obstruction, marked bronchodilator reversibility, and a mixed inflammatory phenotype. Overall, the ADEPT clusters were stable over 12 months and reproduced by identifying four analogous clusters in the U-BIOPRED asthma dataset, with distributions for most clustering and nonclustering variables similar to ADEPT.

Conclusions: We report four clinical clusters in ADEPT and confirmed these by external validation in U-BIOPRED. The ADEPT clusters have distinct clinical and molecular characteristics, are stable over 12 months, and present opportunities for the development of tailored therapeutics for asthma.

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Cistrome Analysis of Glucocorticoid Receptor Activity in Bronchial Epithelial Cells Defines Novel Mechanisms of Steroid Efficacy

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Glucocorticoids (GCs), which act by inducing the glucocorticoid receptor (GR) to regulate gene expression, are the primary therapy used to achieve long-term asthma control and are also used to treat asthma exacerbations, even among patients who exhibit relative baseline GC resistance. We hypothesized that analysis of the airway epithelial cistromes of GR, p65 (a component of the inflammatory nuclear factor [NF]-κB transcription factor complex), and RNA polymerase II (RNAP2) would provide new mechanistic insights into how GCs function in asthma. We performed chromatin immunoprecipitation and high-content sequencing (ChIP-seq) to determine genome-wide occupancy of GR, p65, and RNAP2 in BEAS-2B cells treated with vehicle, dexamethasone (dex, a potent GR agonist), tumor necrosis factor (TNF, which rapidly induces NF-κB activity), and a combination of dex and TNF. We identified thousands of genomic regions that are occupied by GR, p65 and RNAP2 in Beas-2B cells. GR and p65 co-occupancy resulted in surprisingly varied effects on RNAP2 occupancy at associated genes. GR was able to either antagonize or enhance the primary effects of TNF on RNAP2 occupancy and gene expression in a target-specific fashion. Through identifying genes in which RNAP2 occupancy was increased by both dex and TNF individually, with combinatorial treatment preserving or further enhancing RNAP2 levels, we defined novel, induced, antiinflammatory effectors of GCs in the airway, including TNFAIP3 and TNIP1. Taken together, our data strongly refute the long-standing model in which antagonism of NF-κB by GCs in the airway has been primarily attributed to GR tethering with NF-κB and reducing its activity. Instead, coinduction of shared antiinflammatory targets of GR and NF-κB is now also implicated in mediating beneficial effects of GCs in asthma. These data have important implications for current models of steroid-resistant airway disease.

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Severe Asthma in Pediatric Patients Pathophysiology and Unmet Needs

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Recent statistics have shown that asthma deaths and hospitalizations are decreasing, but there are unmet challenges in the management of severe asthma in children. Current asthma management is focused on achieving asthma control through an effort to minimize asthma impairment via specifically addressing factors that affect day-to-day symptoms, and minimizing the risk of future asthma-related events, such as asthma exacerbations, disease progression, and adverse effects to medications. New targeted medications have been developed for which therapeutic responses have been correlated with specific biomarkers; for example, sputum or blood eosinophil count with anti–IL-5 therapy and serum periostin with anti–IL-13 therapy. These drugs hold great promise, but will likely be expensive alternatives to traditional asthma therapy. There is a growing need to address the age-specific challenges