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MECHANISMS



Serum IFN γ -induced protein 10 (IP10/CXCL10): association with asthma exacerbations and severity in children

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ABSTRACT

Objective: Asthma is a chronic disorder of the airways, in which chemokines coordinate airway inflammation and determine its severity. We aimed to study the chemokine interferon γ -inducible protein 10 kDa (IP10/CXCL10), a member of the CXC receptor 3 (CXCR3) ligand family, at the protein level in the serum of children, to evaluate the association between CXCL10 and exacerbations of childhood asthma.

Methods: Patients experiencing an asthma exacerbation (42 patients) and stable patients (43 patients) were investigated for serum CXCL10 levels.

Results: Patients with an asthma exacerbation expressed significantly higher CXCL10 levels in the serum than stable patients ($p < 0.001$). Additionally, CXCL10 values were elevated in severe asthma compared with moderate and mild disease ($p < 0.001$). In patients experiencing asthma exacerbations, higher values of CXCL10 were observed in atopic patients compared with non-atopic patients ($p = 0.027$) and in uncontrolled and partly controlled patients compared with controlled patients ($p = 0.046$).

Conclusions: CXCL10 is proposed as an inflammatory serum marker for asthma exacerbations and worsening asthma symptoms. The levels of CXCL10 are representative of the clinical severity of asthma.

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Asthma; atopy; CXCL10; IP-10; severity

Introduction

Children with asthma can experience progressive worsening of symptoms and lung function requiring urgent medical intervention (1). These asthma exacerbations decrease quality of life and may be life threatening due to respiratory failure. Exacerbations are precipitated by allergens, viral respiratory infections, environmental pollutants, or tobacco smoke. Important risk factors for exacerbations include asthma severity and the degree of asthma control (2). Exaggerated multicellular airway inflammation, bronchial hyper-responsiveness, and airflow obstruction characterize asthma exacerbations (3).

Chemokines and cytokines play a central role in asthma airway inflammation by recruiting and activating multiple inflammatory cells (4). Airway inflammation is associated with the secretion of the interferon γ -inducible protein 10 kDa (IP10, CXCL10) from various cells. Important cellular sources of CXCL10 expression in asthma include endothelial

cells, smooth muscle cells, bronchial epithelial cells, neutrophils, eosinophils, T cells and monocytes (5). The receptor for CXCL10, CXCR3 mediates CXCL10 functions such as promoting the chemotactic activity of CXCR3 expressing cells, inducing apoptosis, regulating cell growth and proliferation, and regulating angiostasis. CXCR3 is predominantly expressed by activated T lymphocytes, innate lymphoid cells, natural killer cells and dendritic cells, in addition to mast cells and eosinophils (6). CXCR3 ligands, namely CXCL9, CXCL10, and CXCL11 have been considered to be part of the T helper (Th) 1 immune response because they are produced by cells in response to stimulation by interferon (IFN) γ , although CXCL10 is also induced by IFNs α/β and weakly by tumor necrosis factor (TNF) α (7,8). CXCL10 can also stimulate antigen-dependent IFN γ production from peripheral blood mononuclear cells up to 120-fold (9).

Elevated concentrations of CXCL10 have been described in asthma. The level of CXCL10 was reported to be higher in asthmatic sputum than in

healthy individuals and CXCL10 expression was detected within infiltrating cells in the bronchial epithelium and submucosa of asthmatics (10,11). Higher quantities of CXCL10 were associated with severe airflow obstruction and decreased lung function in asthmatics (12). Expansion of a distinct subset of T helper cells expressing high amounts of CXCL10 transcripts has been described in asthmatics without allergy compared with asthmatics with allergy (13). Meanwhile, high CXCL10 levels in the serum were predictive of viral-induced acute asthma. Since chemokines have been a significant target in recently developed asthma therapies (14), it has been suggested that targeting high levels of CXCL10 may potentially prevent and treat childhood asthma exacerbations. In this study, we aimed to evaluate the serum levels of CXCL10 in children with bronchial asthma. We sought to study the association between CXCL10 and exacerbations of childhood asthma, questioning whether CXCL10 level may be linked to the degree of severity and control in asthma.

Patients and methods

This cross sectional study included 85 children presenting to the Specialized Children Hospital of Cairo University. Participants were aged between 2 and 12 years old and had previously been diagnosed with bronchial asthma in accordance with the Global Initiative for Asthma (GINA) criteria (1). Diagnosis was made using detailed history taking, clinical examination and pulmonary function tests for children older than 5 years. Of the 85 participants enrolled, 42 were treated for an asthma exacerbation at the Emergency Department (ED) and 43 had stable asthma followed up at the outpatient Allergy Clinic. Management of asthma exacerbations in the ED included supplemental oxygen, short acting β_2 agonist and systemic corticosteroids after blood sampling. Children with stable asthma had not experienced an exacerbation or received systemic corticosteroids in the preceding 4 weeks. All children with any febrile episode were excluded. Asthma severity was evaluated retrospectively, based on the level of stepwise treatment required to control symptoms and prevent exacerbations. Children were assessed for the degree of asthma control based on symptom control and risk for poor asthma outcome such as exacerbations. They were described as controlled, partly controlled and uncontrolled asthma (1). Approval of the study protocol was obtained from the departmental ethical committee at the Faculty of Medicine, Cairo University.

Measurement of interferon gamma-induced protein 10 (IP10, CXCL10)

Venous blood samples were collected from all children and the serum was stored at -20°C until the time of assay. CXCL10 was measured in serum samples using a sandwich Enzyme-Linked-Immuno-Sorbent Assay (ELISA) kit (Thermo Fisher Scientific) according to the manufacturer's instructions. The concentration of CXCL10 present in the samples was calculated from the generated standard curve based on the intensity of the colored product.

Statistical analysis

Comparisons between quantitative variables were performed using the non-parametric Kruskal-Wallis and Mann-Whitney tests. Correlations between quantitative variables were done using Spearman correlation coefficient. Receiver operator characteristic (ROC) curve analysis was performed to determine the optimal cut-off of CXCL10 for detecting an asthma exacerbation. *P* values less than 0.05 were considered as statistically significant. Data were analyzed using the statistical package SPSS (Statistical Package for the Social Sciences) version 20.

Results

Patients

Eighty-five children with asthma were included in this study (Table 1). The median age of the 85 children was 6 years and 65% of them were males. There were 43 children who were stable and 42 with an asthma exacerbation. Seventy-nine percent of patients with exacerbations resided in urban areas, which was significantly higher than stable patients (58%) ($p=0.043$). Patients who had an exacerbation also had asthma diagnosed for longer than stable asthma patients ($p=0.023$). Since asthma is a heterogeneous disease, it has been divided into subgroups according to atopy, severity and asthma control. Atopy was present in most children (82%), which was comparable between stable patients and patients experiencing an exacerbation ($p=0.366$). Other atopic manifestations, in the form of atopic dermatitis, allergic rhinitis, and allergic conjunctivitis were present in 26%, 69% and 32% of all patients, respectively. In terms of absolute eosinophil count; patients with an exacerbation had significantly higher blood eosinophil counts than those with stable asthma ($p=0.004$). When patients were classified according to severity, severe asthma patients

Table 1. Characteristics of patients with asthma.

Variable	Patients with asthma (n=85)	Patients with stable asthma (n=43)	Patients with asthma exacerbation (n=42)	p value
Age (years)	6 (2–12)	6 (2–12)	6 (2.5–12)	0.399
Age, n (%)				
2–5 years	39 (46)	21 (49)	18 (43)	0.580
6–12 years	46 (54)	22 (51)	24 (57)	
Males, n (%)	55 (65)	25 (58)	30 (71)	0.200
Duration of asthma (years)	3 (0.5–6)	2 (0.5–5)	3 (0.5–6)	0.023
Urban residence, n (%)	58 (68)	25 (58)	33 (79)	0.043
Passive tobacco exposure, n (%)	75 (88)	36 (84)	39 (93)	0.191
Atopic disease, n (%)	70 (82)	37 (86)	33 (79)	0.366
Family history of atopy, n (%)	57 (67)	26 (60)	31 (74)	0.191
Blood eosinophils (per μ l)	328 (63–1853)	258 (74–1296)	432 (63–1835)	0.004
Asthma severity, n (%)				
Mild	50 (59)	32 (75)	18 (43)	0.006
Moderate	27 (32)	10 (23)	17 (40)	
Severe	8 (9)	1 (2)	7 (17)	
Asthma control, n (%)				
Controlled	21 (25)	11 (26)	10 (24)	0.850
Partly controlled/ Uncontrolled	64 (75)	32 (74)	32 (76)	

p values for stable asthma versus exacerbations <0.05 were considered statistically significant.
Values are presented as median and range or number (%).

had comparable blood eosinophil counts to milder counterparts ($p=0.988$). Patients with an asthma exacerbation had more severe disease than those with stable asthma ($p=0.006$). Of all patients, 75% showed partly controlled or uncontrolled asthma. Due to the small number of uncontrolled patients, comparison was performed with uncontrolled and partly controlled combined, versus controlled patients.

Interferon gamma-induced protein 10 (IP10, CXCL10) in asthma patients

CXCL10 serum protein levels were analyzed in all asthma patients. Children with an asthma exacerbation

($n=42$) had higher median CXCL10 levels compared to those with stable disease ($n=43$) (median 140 and 38 pg/ml respectively, $p<0.001$; **Figure 1a**). When all asthma patients ($n=85$) were classified into groups that reflected clinical asthma severity, serum CXCL10 values were significantly elevated in severe asthma compared to moderate and mild disease (median 375, 180 and 41 pg/ml respectively; $p<0.001$; **Figure 1b**).

The relationship between the levels of CXCL10 and the duration of asthma in all patients was assessed. Serum CXCL10 levels did not demonstrate a significant correlation with increasing duration of the disease ($r=0.117$, $p=0.285$). In addition, higher values of serum CXCL10 levels were not associated with

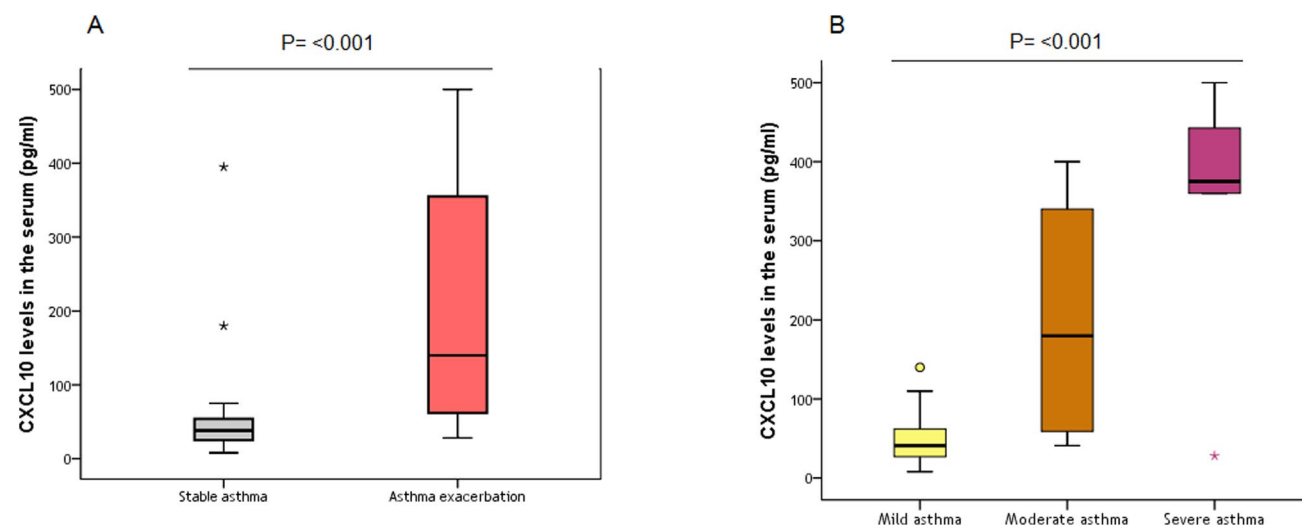


Figure 1. CXCL10 levels in serum were increased in patients with exacerbations compared to patients with stable asthma (A) and in patients with severe asthma compared to milder forms (B).

younger age ($r = -0.150$, $p = 0.172$). Nonetheless, higher values of serum CXCL10 levels were associated with a trend toward increasing eosinophil counts in all patients ($r = 0.201$, $p = 0.066$).

CXCL10 levels in patients with asthma exacerbations

The 42 children with an asthma exacerbation were further examined. The values of CXCL10 were not significantly related to age group ($p = 0.242$) or sex ($p = 0.123$) (Table 2). Children with exacerbations were more commonly living in urban areas, however, the effect of residence did not impact CXCL10 level in the serum ($p = 0.519$). When patients with an exacerbation were classified according to atopy, significantly higher values of serum CXCL10 were observed in atopic patients compared with non-atopic patients ($p = 0.027$). Of the 42 patients with an exacerbation, 10 (24%) patients were found to be well controlled. CXCL10 levels significantly distinguished controlled asthma from partly controlled and uncontrolled asthma in patients with exacerbations ($p = 0.046$) and also in stable patients ($p = 0.042$).

Given that serum CXCL10 levels were different in children with exacerbations of asthma compared to those with stable asthma, we investigated whether it could be used to diagnose asthma exacerbations. ROC analysis was used to determine the optimal cutoff for this inflammatory marker in diagnosing an asthma exacerbation (Figure 2). The optimal cutoff for CXCL10 was at 59 pg/ml (area under the curve =

0.880; 95% confidence interval = 0.807–0.953); values at or greater than this threshold indicated an exacerbation with a sensitivity of 81%, and specificity of 84%.

Discussion

In the present study, the chemokine CXCL10 served as a serum marker of asthma exacerbations as patients with exacerbations expressed significantly higher CXCL10 levels in the serum than stable patients. One important predictor of exacerbations is asthma severity. Nine % of all patients had severe asthma. Severe asthma was more frequent in patients experiencing asthma exacerbations than patients with stable asthma. Our results suggest that the differences in CXCL10 were representative of the clinical severities of asthma as CXCL10 levels were markedly elevated in severe asthmatics compared with those with milder asthma.

Multiple stimuli can induce CXCL10 production. However, the levels are high in the setting of type 1 inflammation, an inflammatory pattern that is significantly associated with severe asthma in children and adults (15). CXCL10 is implicated in establishing type 1 inflammation because it is induced in response to IFN γ and recruits IFN γ producing cells to the site of inflammation. Relatively high CXCL10 gene expression, correlating strongly with IFN γ levels in the bronchoalveolar lavage (BAL) cells and with measures of poor disease control, has been observed in 50% of severe asthma patients (8). The high CXCL10 expression observed in severe asthma was associated with mast cell infiltration of the airways, potentially

Table 2. CXCL10 levels in children with asthma according to age, sex, atopy, residence and asthma control.

CXCL10 (pg/ml)	Patients with stable asthma (n = 43)	Patients with asthma exacerbation (n = 42)
Age		
2–5 years	38.0 (9.0–395.0)	212.0 (40.0–500.0)
6–12 years	35.0 (8.0–75.0)	110 (28.0–400.0)
<i>p</i> value	0.269	0.242
Sex		
Male	37 (15–180)	110 (28–490)
Female	39.5 (8–395)	287 (60–500)
<i>p</i> value	0.721	0.123
Urban residence		
Urban	38 (8–73)	140 (30–500)
Rural	38 (9–395)	110 (28–380)
<i>p</i> value	0.863	0.519
Atopy		
Non-atopic	35 (20–75)	61 (28–380)
Atopic	38 (8–395)	210 (30–500)
<i>p</i> value	0.700	0.027
Asthma Control		
Controlled	42.0 (24–395)	65.5 (40–360)
Partly controlled/ Uncontrolled	32.5 (8–75)	200 (28–500)
<i>p</i> value	0.042	0.046

p values < 0.05 were considered statistically significant.
Values are presented as median and range.

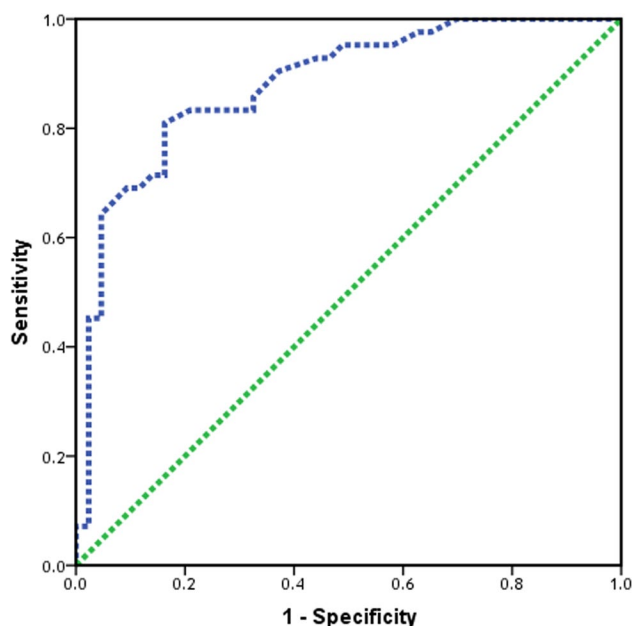


Figure 2. ROC analysis for CXCL10 levels in identifying asthma exacerbations. Values at or greater than the optimal cutoff indicated an exacerbation, with a sensitivity of 81% and specificity of 84%.

enabling the coordination of type 1 and type 2 inflammation. Severe asthma has been recognized to be due to an airway inflammation with a neutrophil predominant or mixed neutrophil and eosinophil phenotype in the sputum (16). Importantly, CXC chemokines induced by $\text{IFN}\gamma$, CXCL9 and 10 were considered as strong promoters in mixed neutrophilic and eosinophilic airway inflammation (10). Using an animal model of severe asthma, it was shown that elevated $\text{IFN}\gamma$ leads to increased inflammatory infiltrates in the lung, high airway resistance, and poor response to corticosteroid treatment (17). It is acknowledged that asthma is a collection of multiple phenotypes, resulting in unique response to therapy. Consistent with evidence that corticosteroid responsiveness is confined to type 2 asthma; the $\text{IFN}\gamma$ /CXCL10 pathway was not responsive to corticosteroids in severe asthma (8,18). This would limit the clinical usefulness of additional corticosteroid treatment in breaking the underlying inflammatory pattern. Given the role of CXCL10 in promoting a type 1 inflammation, interventions to disrupt the $\text{IFN}\gamma$ /CXCL10 pathway or the CXCR3 receptor may improve disease symptoms in some severe asthmatics.

Irrespective of asthma severity and adequate disease treatment, patients may experience acute exacerbations of symptoms and loss of disease control. Not only patients with severe asthma and uncontrolled asthma are at risk for acute exacerbations, but exacerbations

may occur in patients with mild and controlled asthma (19). CXCL10 was a significant marker of exacerbations in our study, as we observed increased values in patients with exacerbations compared to stable patients. In patients experiencing exacerbations, CXCL10 values were higher in atopic asthmatic children compared with non-atopic children. In exacerbations of asthma in the clinical setting, there may be different signatures of inflammation according to the underlying phenotype of the patient. The most common form of asthma in children is atopic asthma (20). Indeed, atopy was present in most of our patients (82%) and was comparable between stable asthma patients and patients experiencing exacerbations. Allergen sensitization and exposure to allergens triggering exacerbations frequently cause type 2 inflammation. Type 2 high asthma is driven by allergen-specific Th2 cells and is identified by the presence of allergen-specific IgE in serum and high blood eosinophil counts (4). After allergen challenge, CXCL10 in BAL fluid was found to be elevated to substantial levels, that were quite similar to those of Th2 chemokines (21). New insights into the paradigms of type 2 asthma have been revealed and the importance of type 1 cells and mediators as an integral component of asthma pathogenesis in patients with allergy has been identified (22). IgE sensitization significantly enhanced the gene expression for CXCL10, in airway smooth muscle cells, at the promoter level (23). Furthermore, good response to omalizumab therapy, a monoclonal antibody against IgE, was predicted by high baseline levels of serum CXCL10 and IL-12 as well as high blood eosinophil counts (24).

Rather than type 2 inflammation, up regulated type 1 mediators including $\text{IFN}\gamma$ -induced CXCL9, 10, and 11 were reported in asthma exacerbations in children (25). CXCL10 can directly activate eosinophils which are important effector cells of asthma exacerbations (26). Both increased CXCL10 levels and elevated eosinophil numbers were associated with asthma exacerbations in our study. Trends in CXCL10 levels were positively correlated to the numbers of blood eosinophils in all patients. CXCL10 can enhance eosinophil adhesion to vascular endothelial cells, which is a crucial step in eosinophil recruitment to the asthmatic airways. The increase in sputum eosinophils was found to be significantly associated with loss of asthma control in longitudinal studies (27). CXCL10 can also stimulate eosinophil functions such as superoxide anion generation, degranulation and the production of type 1 and type 2 cytokines (28), potentially enabling the collaboration of type 1 and type 2

inflammation. Regulation of the CXCL10/CXCR3 pathway could be significant for regulating eosinophilic airway inflammation. This is supported by the finding that the leukotriene receptor antagonist, montelukast inhibits eosinophil adhesion induced by CXCL10 (29).

While allergenic exposure has been linked to asthma exacerbations, the evidence linking combustion-derived particulate matter to exacerbations is also considerable. Combined exposure to allergen and diesel extract may create an immunological setting that is capable of precipitating exacerbations (30). We observed that children experiencing exacerbations were more commonly living in urban areas compared to stable asthmatics. However, the effect of residence did not impact CXCL10 level. Although diesel extract was previously found to have an additive effect on several markers of allergic and non-allergic inflammation in the airway of atopic patients, single exposure to allergen independently showed a more pronounced effect on CXCL10 than diesel extract (30).

There is evidence of a quantitative synergistic interaction between allergen sensitization and viral infection in exacerbations (2). Rhinovirus-induced asthma exacerbations in children become more severe as allergen-specific IgE levels increase (31). A high Th1 and IFN γ signature is clinically induced in viral infection, although IFN γ is produced by a variety of immune cells, verifying why it is a challenge to treat exacerbations (3). Virus-specific Th1 cells were found to coordinate with allergen-specific Th2 cells to promote airway inflammation in allergic asthmatic individuals even after the infection resolved and the virus cleared. Both Th1 and Th2 chemoattractants, CXCL10 and CCL22, were strongly induced in infection. Meanwhile, in uninfected asthmatic individuals, higher numbers of virus-specific Th1 cells, but not allergen-specific Th2 cells, were associated with worse lung function (22). It was shown that CXCL10 produced by rhinovirus-infected epithelial cells can direct airway smooth muscle cell chemotaxis and fibroblast migration (32,33), thus it seems plausible that CXCL10 could contribute to the airway remodeling in patients with asthma. It is likely that some of the exacerbation events in our study were triggered by viral infections, although we did not systematically study the cause of the exacerbation. Even though we could not specify the cause of exacerbation, and so could not determine the most important factor in CXCL10 production such as allergic or viral factors, our observations collectively confirm that CXCL10 is an inflammatory biomarker of exacerbations.

A dynamic approach to asthma management based on asthma control, rather than severity has been

recommended (1). Asthma control is the result of the interplay between the underlying phenotype, the environment and the response to treatment (34). In patients with an asthma exacerbation, we observed that elevations of CXCL10 levels were intensified in partly controlled and uncontrolled patients compared with controlled patients. The effect of CXCL10 and type 1 inflammatory cytokines could be to modify the disease, to worsen asthma control and to promote susceptibility to exacerbations. However, it is important to note that an extensive molecular network contributes to the loss of control and the development of asthma exacerbations (3). This network is composed of cytokines, chemokines, signaling transducers and functional proteins. In contrast, we found that stable asthma patients showed higher CXCL10 levels in controlled patients compared to less controlled patients. The expression of CXCL10 can be induced by diverse stimuli, which can lead to differential levels of CXCL10 production and differential degrees of asthma control in stable patients compared to patients with asthma exacerbations. In addition, there is significant heterogeneity between individual asthmatic patients. Increased understanding of the inflammatory pathways and responses that lead to the loss of asthma control and asthma exacerbations, including different grades of severity of exacerbations, is needed. Longitudinal studies of patients in stable disease and in exacerbations are important to identify personalized treatment approaches tailored to improving disease control and reducing the risk of exacerbations.

Conclusion

CXCL10 is a relevant inflammatory marker of asthma exacerbations in children. Increased levels of CXCL10 are representative of the clinical severity of asthma.

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Declaration of interest

The authors report no conflicts of interest.

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