CD6-ALCAM Pathway is Elevated in Patients with Severe Asthma

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Introduction

Clinical Need:

- A subset of severe asthma patients have persistent airway inflammation despite high dose inhaled and/or oral corticosteroid therapy
- Steroid insensitivity in a portion of these patients may be driven by non-classical T2 inflammatory pathways.

The CD6-ALCAM pathway:

- CD6 is a co-stimulatory receptor on T-cells and certain innate lymphoid cells that binds activated leukocyte cell adhesion molecule (ALCAM) on antigen presenting cells and endothelial and epithelial tissues
- The CD6-ALCAM pathway plays an integral role in modulating T cell activation and trafficking and is central to immune mediated inflammation.
- The pathway is implicated in T2 (T_h2), non-T2 (T_h1/T_h17) and innate lymphoid cells (group 2) driven responses responses, demonstrating effects in multiple disease models including allergic asthma.

Objective:

- Examine the CD6-ALCAM axis as a potential target for severe asthma.

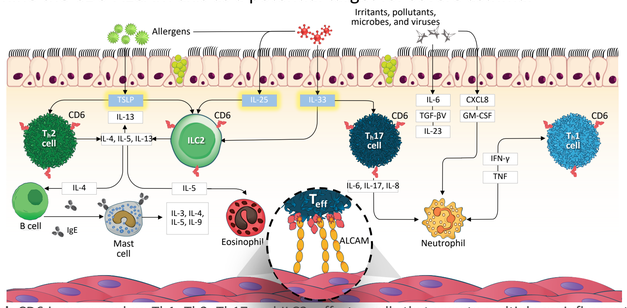


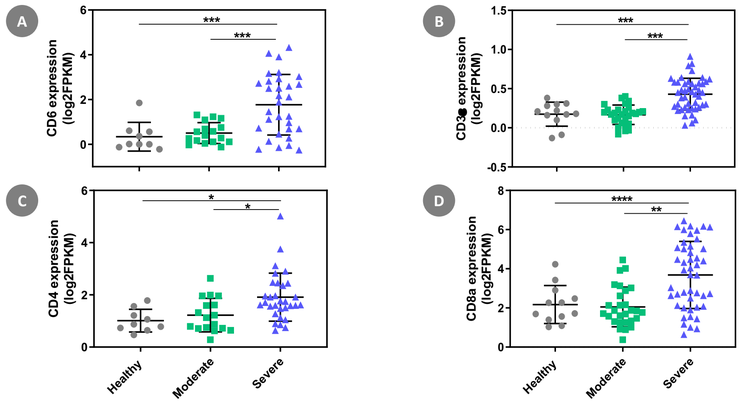
Figure Legend: CD6 is expressed on Th1, Th2, Th17 and ILC2 effector cells that secrete multiple proinflammatory cytokines implicated in asthma pathogenesis. ALCAM is expressed on antigen presentation cells that activate effector cells. ALCAM is also expressed on endothelial and smooth muscle cells where it plays a role in trafficking of CD6+ effector cells. Adapted from Israel E, *et al*., N Engl J Med. 2017;377(10):965-976.

Methods

- To examine CD6 expression and other genes associated with the pathway, we analyzed a publicly available gene expression microarray dataset from BAL cells of non-asthma, moderate asthma and severe asthma patients derived from two multi-center observational studies BOBCAT and MAST [1-3]. Global microarray normalization using the vsn package[4]. Log2 intensities are shown in figures 1 and 2. Differential expression was calculated with limma package[5].

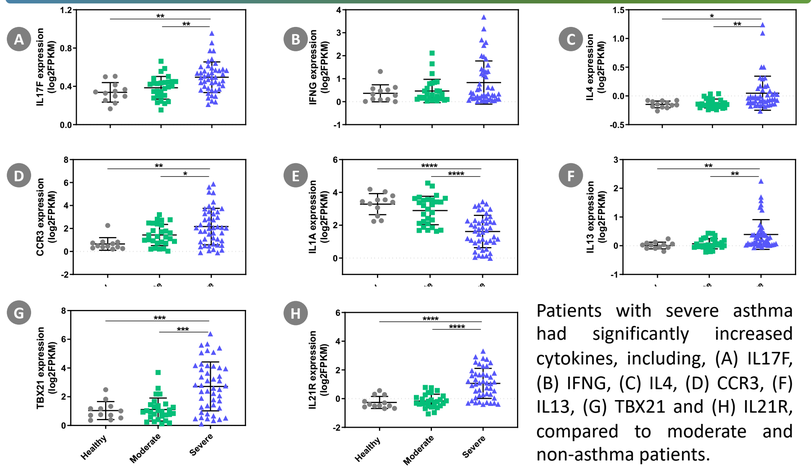
- To examine ALCAM levels, sputum was collected from 22 characterized asthmatics on inhaled corticosteroids. Patients were categorized by >3% or <3% sputum eosinophils (sp-Eos; n=11/group). The supernatant processed from plugs (dispersed in phosphate buffered saline), was further diluted 1:5 and ALCAM levels measured by ELISA (R&D Biosystems).

Figure 1



Patients with severe asthma had significantly increased expression of (A) CD6 with concomitant increases in T cell markers (B) CD3, (C) CD4, and (D) CD8 compared to moderate and non-asthma patients. (****p<0.001, *p<0.05*)

Figure 2

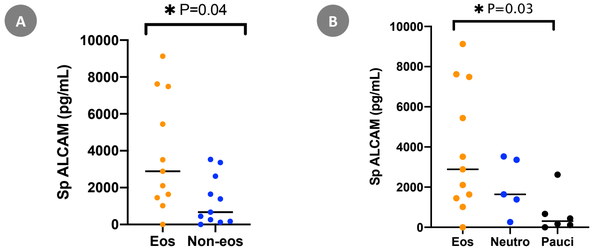


Patients with severe asthma had significantly increased cytokines, including, (A) IL17F, (B) IFNG, (C) IL4, (D) CCR3, (F) IL13, (G) TBX21 and (H) IL21R, compared to moderate and non-asthma patients.
(****p<0.001, *p<0.05*)

Figure 3

	Eos (%)	Non-eos (%)	p-value
n	11	11	----
Sex (M)	7 (63)	5 (45)	0.3
Atopic (n,%)	8 (72.7)	5 (45.4)	0.4
Age	53.55 (15.6)	56.00 (18.6)	0.74
BMI	28.10 (3.7)	27.27 (7.2)	0.74
FEV_1%	76.67 (17.5)	71.87 (23.8)	0.6
FEV_1/FVC	0.65 (0.036)	0.67 (0.04)	0.71
Blood eosinophil	0.55 (0.44)	0.28 (0.29)	0.11
Sp eosinophil %	28.92 (18.86)	0.75 (0.79)	*0*
Sp neutrophil %	28.31 (16.78)	63.10 (30.07)	*0.04*
FEG (median)	3 (0-3)	0 (0-1)	*0.0001*
ICS (median)	1000 (250-2000)	1000 (0-3200)	0.9
OCS (median)	0 (0-7.5)	0 (0-7.5)	>0.9

Table 1. Sputum was collected from 22 characterized asthmatics on inhaled/oral corticosteroids (not on any anti-T2 biologics). Patients were categorized by >3% or <3% sputum eosinophils (sp-Eos; n=11/group)



(A) Analysis of sputum ALCAM levels revealed significantly higher concentrations in eosinophilic vs non-eosinophilic patients (3.8±3 vs. 1.2±1.3ng/mL; p=0.04). (B) When non-eosinophilic patients were categorized by neutrophilic (n=5) or paucigranulocytic (n=6), ALCAM levels were significantly higher in eosinophilic vs. paucigranulocytic patients (0.6±0.9 ng/mL; p=0.03).

Conclusions

The data indicate that the CD6-ALCAM pathway is elevated in severe asthmatics and may be a viable target in the treatment of severe, uncontrolled asthma. The ability to detect ALCAM in sputum may provide a non-invasive approach to further examine this pathway. Blockade of CD6 is currently being tested in a clinical trial for the treatment of severe asthma. Clinical Trial Identifier: NCT04007198

References: [1]*Sun et al., Sci. Signal. 2015 Dec 1;8(405):ra122;* [2]*Jia et al., J Allergy Clin Immunol. 2012 Sept; 130(3): 647–654.e10;* [3]*Simpson et al., Nat Immunol. 2014 December ; 15(12): 1162–1170;* [4] Huber W et al., Bioinformatics 2002;18 Suppl 1:S96-104; [5] Ritchie et al., 2015 Nucleic Acids Res. 2015 Apr 20;43(7):e47