Author's response to reviews

Title: Annexin A1 in plasma from patients with bronchial asthma: its association with lung function

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Author's response to reviews:

Dear Editor:

Manuscript ID ‘PULM-D-17-00094R3’ entitled "Annexin A1 in plasma from patients with bronchial asthma: its association with lung function”.

We wish to express our appreciation the opportunity to revise and re-submit our manuscript. We enclose a point by point response to the reviewers’ comments. We believe the revised manuscript now fulfills the high standards of BMC Pulmonary Medicine.

With my best regards

Editor Comments:
C1. Background: Decreased Levels of Lipoxin A4 and Annexin A1 in Wheezy Infants, Eke Gungor et al., 2014

Discussion: Regulation of lung fibroblast activation by annexin A1, Jia et al., 2012

Decreased Levels of Lipoxin A4 and Annexin A1 in Wheezy Infants, Eke Gungor et al., 2014

R1. Thank you for your comments

The authors agree with you point. We did our best to change the text as you suggest as following.

Background section, line 86, page 4

ANXA1 and its derivatives exert anti-inflammatory effects by inhibiting eicosanoid synthesis and leukocyte migration and stimulating inflammatory cell apoptosis as observed with glucocorticoids [12,13]. Reduced or defective annexin production has been reported in smokers and patients with inflammatory conditions such as rheumatoid arthritis, cystic fibrosis, and asthma [14-16].

-Changed-ANXA1 has anti-inflammatory effects by stimulating inflammatory cell programmed cell death and prohibiting eicosanoid synthesis [12, 13]. ANXA1 levels were decreased in smokers or patients with asthma, cystic fibrosis, and rheumatoid arthritis [14-17]. The reduced levels of lipoxin A4 (LXA4) and ANXA1 were reported in wheezy infants [17] and patients with severe asthma [18-20].

Discussion section, line 304, page 13

ANXA1 was originally reported to be induced by glucocorticoids and to inhibit phospholipase activity [24, 25]. ANXA1 is an abundant intracellular protein expressed in many cell types [27-29]. Fiore et al. show that recombinant ANXA1 or ANXA1-derived N-terminal peptides mimic the anti-inflammatory action of glucocorticoids (GCs), including inhibition of leukocyte recruitment at inflammatory sites, inhibition of proinflammatory mediators such as phospholipase A2, cyclooxygenase-2, and nitric oxide, induction of apoptosis in inflammatory cells, and induction of the anti-inflammatory cytokine interleukin-10 [30].

-Changed-ANXA1, an abundant intracellular protein expressed in many cell types, has known to be induced by glucocorticoids (GCs) and to inhibit phospholipase activity [24-29]. Recombinant ANXA1 or ANXA1-derived N-terminal peptides has similar actions like the anti-inflammatory action of glucocorticoids such as inhibition of inflammatory cells, and suppressing inflammatory mediators [26, 30].

Discussion section, line 313, page 13

The ANXA1 receptor FPR2 has been identified as a specific G-protein-coupled receptor [30]. FPR2 also binds to LXA4 (an anti-inflammatory lipid) [31] and serum amyloid protein, which
mediate ligand-specific effects. FPR2 expression has been observed in human lung fibroblasts [32, 33] and GC induces the expression of FPR2 in human myeloid cells [33].

-Changed-The ANXA1 receptor FPR2 as a specific G-protein-coupled receptor binds to LXA4 (an anti-inflammatory lipid) and serum amyloid protein, which mediate ligand-specific effects [30, 31]. FPR2 has expressed in human lung fibroblasts, and induced by GCs in human myeloid cells [32, 33].

Discussion section, line 317, page 13

ANXA1 is abundantly released into airway secretions [12] in smokers [14] and patients with inflammatory conditions of the lungs such as cystic fibrosis [15]. In these cases, a form of ANXA1 with a molecular weight of 33 kDa is released rather than the 37 kDa ANXA1, suggesting that inflammatory conditions increase the release of defective ANXA1 [16].

-Changed-ANXA1 levels in bronchoalveolar lavage fluids were higher in smokers [14] and in patients with cystic fibrosis [15]. A form of ANXA1 with a molecular weight of 33 kDa is released rather than the 37 kDa ANXA1, suggesting that ANXA1 be degraded in smokers and in patients with cystic fibrosis [16, 17].

Thank you