Secreted Brain-Derived Neurotrophic Factor and Asthma Severity

To the Editor:

We note with interest the recent report in the *Journal* by Watanabe and colleagues (1) involving brain-derived neurotrophic factor (BDNF) expression and asthma severity. This report is a significant step in highlighting the emerging importance of noncanonical roles of neurotrophins in the lung.

Although extensively recognized in the nervous system, BDNF and its receptors have been localized to the lung (2, 3). Altered BDNF levels have been reported in asthma, allergy, and even lung cancer (3, 4). A possible mechanistic role for BDNF has been suggested in airway inflammation, remodeling, and hyperreactivity (3, 5, 6). All these reports obviously raise questions regarding cell sources versus targets of BDNF. Watanabe and colleagues demonstrate a potential relationship between altered BDNF isoforms in airway epithelial cells with asthma severity (1). Here, the contribution of the Th2 cytokine IL-13 in regulating BDNF exon VIIb splice variant expression in sputum and in epithelial cells points to bronchial epithelium as at least one source. Interestingly, Western blot data showed mature and pro-BDNF in sputum of all subjects, but substantial BDNF expression was not observed in epithelial cells except in some patients. This leads to questions regarding the source of BDNF, particularly in severe asthma. Certainly, immune cells could be one alternate source. We previously showed that human airway smooth muscle (ASM) releases substantial BDNF, which is increased by insults such as cigarette smoke (5) or pro-inflammatory cytokines such as TNF- α (6). Accordingly, ASM-derived BDNF could explain the dichotomy between total BDNF in sputum versus lack of BDNF production by epithelial cells. In terms of release, we demonstrated that BDNF secretion is Ca^{2+} -dependent and involves TRPC3 channels (6), which are upregulated in asthma (6). Accordingly, enhanced ASM-derived BDNF secretion may be relevant in asthma.

Regardless of source, an important unanswered question is the functional role BDNF plays in asthmatic airways. Here, the finding by Watanabe and colleagues showing both pro- and mature BDNF in sputum is interesting and should be explored further. Mature BDNF activates full-length TrkB receptors and can enhance ASM $[\text{Ca}^{2+}]_i$ (4) or genomically increase expression of pro-contractile proteins in ASM. In contrast, pro-BDNF activates p75NTR receptor with more complex effects, yet p75NTR may not be as relevant to ASM contractility. Accordingly, future studies should explore the functional importance of pro-BDNF in the airway, in addition to any mature BDNF effects on other lung cells that express TrkB. Overall, the novelty of the data presented in the Watanabe study highlights the potential for developing BDNF as a physiologically relevant biomarker or, ultimately, a therapeutic target in asthma. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply

From the Authors:

We thank Dr. Wang and colleagues for their thoughtful letter and excellent points regarding the potential importance of brain-derived neurotrophic factor (BDNF) in asthma, as well as its cellular source. We are in clear agreement that this (and earlier studies) suggest further study of neurotrophins in asthma is needed.

Regarding the cellular source, Wang and colleagues previously showed Ca^{2+} -dependent regulation of BDNF secretion in human airway smooth muscle (ASM) (1). In contrast, we focused on epithelial cells and did not address ASM expression. However, we did find robust mRNA and protein expression in pure cultures of human airway epithelial cells, supporting at least some contribution from these cells. Further, although ASM could certainly contribute, we believe that the close proximity of epithelial cells to the airway lumen (and the sputum collection) make human airway epithelial cells the more likely source. The correlation of BDNF levels with airway hyperresponsiveness observed in our study (2) supports an effect of BDNF on airway hyperresponsiveness but, unfortunately, does not help determine a source.

However, in prior murine studies, BDNF was more strongly expressed in bronchial epithelial cells, while moderately expressed in ASM, being further enhanced in the epithelium after allergen challenge (3–5). According to these reports, we immunostained for BDNF (Santa Cruz Biotechnology, Santa Cruz, CA) on human tissue from one healthy subject and one patient with severe asthma. BDNF staining was observed in the bronchial epithelial

layer and a few inflammatory cells (likely eosinophils or mast cells). The intensity of BDNF staining in the epithelium of the patient with severe asthma was greater than in the healthy control subject (6), whereas minimal staining was observed in either subject's ASM, suggesting epithelial cells may be a more prominent source. However, much more study is clearly needed.

Thus, we agree that the main cellular source for BDNF in human asthmatic airways remains to be determined and that further studies of this fascinating pathway in human disease are urgently needed. ■

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