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Opposing effects of nasal epithelial NQO1 and HO-1 expression on upper and lower airway symptoms in adolescents with asthma

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Summary

NQO1 and HO-1 expression in nasal epithelium are inversely correlated indicating that non-NRF2 mechanisms may play an important role in regulation of these genes. Further, NQO1 and HO-1 expression have opposing relationships with upper and lower airways symptoms, suggesting that induction of phase II enzymes could result in pleiotropic clinical effects.

Keywords

NQO1; HO-1; NRF2; Oxidative Stress; Asthma; Nasal Epithelium

Oxidative stress plays an important role in asthma.[1] Nuclear factor (erythroid-derived 2)-like 2 (NRF2), a b-zip transcription factor, appears to be critical in this context as it regulates the expression of important antioxidant genes.[2] As such, small molecule activators, such as sulforaphane, are being pursued as therapeutic agents in asthma.[3] NRF2 target genes, including NAD(P)H dehydrogenase quinine 1 (NQO1) and heme oxygenase 1 (HO-1), are routinely assessed as markers of NRF2 activity both in laboratory and clinical settings with an underlying assumption that greater expression of these NRF2 target genes is a marker of a more robust anti-oxidant response which should protect against airway inflammation and asthma symptoms.

To test the hypothesis that greater HO-1 and NQO1 gene expression is associated with less airway inflammation, better lung function, and fewer asthma symptoms, we examined relationships between expression of these NRF2 target genes and clinical features of asthma in non-smoking Baltimore City adolescents (14–17 years, n=22) with moderate to severe asthma (detailed methods available in the online repository). Study participants were

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predominantly African American (85%) and male (55%). Eighty-two percent had public health insurance. Ninety percent of participants had at least one positive skin test. NQO1 and HO-1 mRNA levels in nasal epithelium were inversely correlated (r_s=−0.43, p=0.04; Figure 1a). Higher NQO1 expression was associated with more days of exercise-related symptoms (r_s=0.44, p=0.04) and slowed activity due to asthma (r_s=0.57, p=0.006) (Figures 1d and 1e). NQO1 expression was not associated with days of asthma symptoms (r_s=−0.24, p=0.27). In contrast, higher HO-1 expression was associated with fewer days of slowed activity due to asthma (r_s=−0.45, p=0.03; Figure 1c) and asthma symptoms (r_s=−0.43, p=0.05). Higher HO-1 expression was also associated with fewer days of exercise-induced symptoms (r_s=−0.27, p=0.21; Figure 1b), but this finding was not statistically significant. NQO1 expression was positively correlated with days of cough without a cold (r_s=0.48, p=0.03) whereas HO-1 expression was negatively correlated with this symptom variable (r_s = −0.56, p=0.01). NQO1 expression was also higher among subjects with rhinoconjunctivitis (Figure E1 in online repository) resulting in greater odds of rhinoconjunctivitis symptoms (OR [95% CI]: 1.32 [1.02–1.70]), while higher HO-1 expression was associated with a lower non-significant odds of rhinoconjunctivitis symptoms (OR [95% CI]: 0.36 [0.12–1.08]). Overall, higher NQO1 expression was positively associated with upper and lower respiratory symptoms while higher HO-1 expression was inversely associated upper and lower respiratory symptoms.

Relationships between NQO1 and HO-1 expression and rescue medication use and percent change in FEV_1 with bronchodilator were consistent with the relationships observed with upper and lower respiratory symptoms. For example, although not statistically significant, there were trends towards a negative correlation between HO-1 expression and response to bronchodilator and a positive correlation between NQO1 expression and response to bronchodilator (Table E1 in online repository). No relationships were observed with either F_ENO or FEV_1/FVC.

These results demonstrate a consistent inverse relationship between HO-1 expression and a variety of upper and lower airway clinical outcomes. Our findings support the observation that greater HO-1 expression may mitigate against asthma symptoms. This is supported by previous investigations that found higher HO-1 expression in airway epithelial cells to be protective against asthma via regulatory T cells, IL10, and membrane bound TGF-1 production. [4,5,6] In contrast, higher NQO1 expression was positively associated with upper and lower airways symptoms, suggesting that induction of NQO1 expression may not be accompanied by an improvement in upper or lower airway symptoms and that simultaneous induction of both HO-1 and NQO1 expression may result in limited clinical effects. These findings may have important implications for the use of NQO1 and HO-1 gene expression as biomarkers in the development of oxidative stress-targeted therapy. Specifically, induction of NQO1 expression as a marker of potential clinical efficacy should be viewed with some skepticism as our findings highlight the challenge of predicting clinical effects from *in vitro* and biomarker studies of putative therapeutic agents. Furthermore, the inverse correlation between HO-1 and NQO1 expression indicates that there are likely NRF2-independent regulatory mechanisms which significantly influence the expression of both or at least one of these genes. [7] In fact, recent data demonstrate post-transcriptional regulation of HO-1 mRNA by miRNA and stabilization in a MAPK-dependent manner. [8, 9]The activity of these regulatory mechanisms may influence the ability of NRF2 inducers to upregulate anti-oxidant defense genes and could provide an explanation for the inverse correlation between HO-1 and NQO1 expression in our study population. Ultimately, though, human trials are needed in order to understand the clinical effects of non-specific augmentation of the oxidative stress response.

There are limitations of our study that should be considered. It is possible that nasal corticosteroid use could have biased our results. However, of the 22 participants, only 2 reported using nasal corticosteroids making this an unlikely source of bias. The study population was small, urban, and predominantly African American, so whether our findings are applicable to other populations is unknown. In addition, the study was cross-sectional, so associations between gene expression and clinical outcomes could be examined, but how HO-1 and NQO1 expression change over time within an individual is not clear. Nevertheless, the inverse correlation between expression of these two anti-oxidant genes in airway epithelial cells and their opposing relationships to upper and lower respiratory symptoms is striking and serves to highlight potential pitfalls in our understanding of the clinical impact of pathways that control oxidative stress in asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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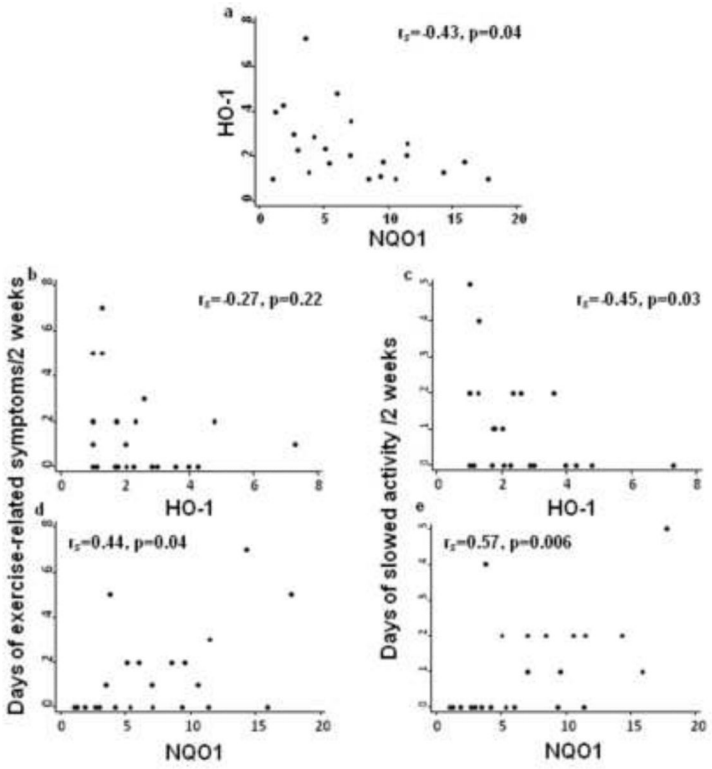

Figure 1.

Scatterplots of gene expression and asthma symptoms. (a) NQO1 and HO-1 mRNA levels were inversely and significantly correlated in this population. HO-1 mRNA levels were inversely correlated with days of (b) exercise-related symptoms and (c) slowed activity .NQO1 mRNA levels were positively correlated with days of (d) exercise-related symptoms and (e) slowed activity.