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Different Isoforms of Glutathione Peroxidase Cause Opposing Effects During the Development of Allergic Asthma in Mice

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Dear Editor:

Recent studies identified increased levels of oxidative stress and alterations of antioxidant enzymes in the lungs of asthmatic individuals and in experimental animal models, suggesting that the increase in oxidative stress may significantly contribute to the characteristic features of allergic respiratory diseases (1). Won *et al*. (9) as well as our own work (4) focused on the role of glutathione peroxidases (GPx) in the development of experimental allergic asthma in mice. After allergen sensitization and subsequent airway challenges with ovalbumin of GPx1 knock-out mice, Won *et al.* observed an attenuation of allergen-induced eosinophilic infiltration and airway hyperresponsiveness compared with wild-type mice. In our asthma mouse model, we showed that GPx2 knock-out mice behaved in the exact opposite way: ovalbumin airway challenges after sensitization induced increased allergen eosinophil inflammation and airway hyperreactivity compared with the corresponding wild-type mice. Taken together, these results indicate that different GPx activities cause opposing effects during the development of allergic asthma.

All four GPx family members (GPx1–4) have been reported to be expressed in human lungs (3), with ~95% of the GPx enzyme activity attributable to GPx1 (6). GPx2 expression in healthy lungs from mice is marginal, whereas high constitutive expression is found in the gastrointestinal tract (5). In lungs from allergen-challenged mice, GPx1 as well as GPx2 gene expression is upregulated (4, 7). According to Won *et al.*, GPx1 plays a role as an early trigger to determine the induction and direction of the inflammatory processes. The data from the study by Won *et al*. suggest that the lack of GPx1 causes intracellular reactive oxygen species (ROS) accumulation in naive T cells, acting as a key mediator for the induction of proliferation and differentiation into Th1 cells. In the absence of GPx1, higher ROS levels are induced, impeding Th2 and Th17 development and thus significantly diminishing the development of allergic airway inflammation. In contrast, GPx2 is an effector in the process of inflammation, regulated by ROS (2) as well as inflammatory mediators (4). Increased levels of GPx2 were found after hyperoxia-induced lung injuries (2), suggesting that GPx2 is a critical component of the pulmonary antioxidant defense system, in which GPx1 is playing a lesser role (6). The mechanisms underlying the protective role of GPx2 against allergic airway inflammation are not well understood yet. But the opposing effects of GPx1 and GPx2 support the hypothesis that GPx2 might exert enzymatic effects beyond mere antioxidant activities. Indeed, GPx have been reported to inhibit prostaglandin synthesis (8), thus reducing the expression of proinflammatory mediators known to play an important role in the pathogenesis of allergic asthma. Additionally, our results (4) suggest that GPx2 is mainly expressed by airway epithelia, whereas Won *et al.* more specifically addressed the role of GPx1 in T cells.

A possible scenario to explain the opposing effects of GPx1 and GPx2 is as follows: GPx1 is constitutively expressed in healthy lung with the ability to enhance inflammatory responses against, for example, allergens by inducing differentiation and proliferation of Th2 and Th17 cells. GPx2, on the other side, shows negligible constitutive expression in the lungs; its upregulation is induced by proinflammatory signals as a defense mechanism and might be significantly reduced in GPx1-null mice because of the lack of inflammation. In GPx2-null mice, the expression of GPx1 triggers the induction of inflammatory processes, which are even enhanced in the absence of GPx2 as a member of the antioxidant defense system. Further studies are needed to fully understand the complex role of antioxidant enzymes in the development of allergic airway inflammation. The opposing effects of only two of these enzymes, however, visualize a multifaceted system of pro- and anti-inflammatory enzymes that maintain the balance between necessary immune responses to danger signals and unwanted inflammatory responses to harmless environmental proteins. To find the right tune for this balance might open new and promising treatment strategies for a variety of inflammatory airway diseases.

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Abbreviations Used

GPx = glutathione peroxidases
ROS = reactive oxygen species
Th = T helper cell

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Response to Meyer *et al.*

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To the Editor:

Meyer *et al.* attempted to interpret the seemingly opposite effects of glutathione peroxidase (GPx) 1 and 2 in airway inflammation as reported in our (5) and their (2) works. Lung epithelial cells are important for the expression of a variety of chemokines in airway inflammation. In particular, eotaxin expression by lung epithelial cells increases eosinophil infiltration, which is a prominent characteristic of chronic inflammation. Although the specific expression of GPx2 in lung epithelial cells and its protective roles in ovalbumin-induced airway inflammation have been clearly validated (2), the molecular mechanisms have not yet been distinctly characterized. For instance, the effects of GPx2 (or reactive oxygen species [ROS]) on the expression of chemokines such as IP-10, MIG, CXCL10, and eotaxin in lung epithelial cells would be good to explain the protective roles of GPx2 in allergic airway inflammation. In addition, GPx2 suppresses COX2 expression in tumor migration and invasion (1), indicating that GPx2-mediated inhibition of COX-2 may prevent the synthesis of inflammation mediators leukotrienes, thromboxanes, and prostaglandins in lung epithelial cells. It is important to note that a recent report suggests that GPx1 specifically controls Th-cell differentiation by modulating ROS and subsequently inflammatory immune response (5). GPx1 deficiency increased ROS in T cells, thus resulting in decreased Th2- and Th17-cell development and attenuated airway inflammation. GPx1 is thus suggested to play a key role in fine-tuning ROS level during Th-cell differentiation. However, the precise functions of GPx1 in lung epithelial cells remain to be clarified. In addition, GPx isoforms such as GPx2, GPx1, and GPx4 could be increased in the lung by antigenic challenge (3, 4). GPx2 expression is specifically increased by NRF2 activation, whereas GPx1 and GPx4 were prominently induced by selenium in a dose-dependent manner, implying the presence of distinct signaling pathway to induce GPx isoforms in a cell-specific and signal-dependent manner. It is therefore reasonable to conclude that both GPx1 and GPx2 eliminate ROS, but the expression and regulatory mechanisms of GPx1 and GPx2 may be distinct across cell types.

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