Editorial

Diesel exhaust particle exposure during pregnancy promotes development of asthma and atopy

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Key words: *Diesel exhaust particle, asthma, atopy, oxidative stress, NK cells, pregnancy*

Environmental effects strongly influence the development of atopic diseases, including asthma. The importance of these effects does not appear to be evenly distributed throughout life; instead, effects that occur during the first year of life and especially during the neonatal period appear to be particularly important.[1] Relatively recently, evidence has accumulated that even the intrauterine environment can strongly influence the later development of atopy and asthma. In addition to evidence that the development of atopy in the child correlates more strongly with the presence of maternal than paternal atopy,[2] epidemiologic studies have suggested that maternal cigarette smoking[3,4] and exposure to diesel exhaust and traffic-related particles, heavy metals, antibiotics, alcohol,[5] and house dust mites[6] can increase the child's risk of atopy, asthma, or both, whereas maternal pet exposure[7] and exposure to farm animals[8] and the buildings that house them[9] can have the opposite effect.

Studies in rodents have generally provided results that are consistent with human epidemiologic studies. Purposeful exposure of pregnant rodents to urban particulate matter, diesel exhaust particles (DEPs), or titanium dioxide particles increased the allergic response of their offspring to allergen immunization,[10,11] whereas maternal inoculation with LPS[12] or bacterial species that are associated with farm animals[13] had the opposite effect. Both human cord blood studies and these rodent studies provide some evidence about how maternal environmental exposure affects the predisposition of the developing fetus to allergic disorders by demonstrating the effects on T_H1,[6,12] T_H2,[6,12] and regulatory[3,14] cells, as well as cytokine levels, Toll-like receptor expression,[8,15] IgE levels,[7] DNA methylation,[16] histone acetylation,[13] and microRNA expression.

The effects of prenatal and perinatal DEP exposure on the development of atopy and asthma have been studied more thoroughly than most other environmental influences. DEPs do not induce a T_H2 response themselves but act as an adjuvant that promotes the development of a T_H2/T_H17 response to protein antigens.[17,18] Several mechanisms appear to be involved, including induction of thymic stromal lymphopoietin,[19] GM-CSF[20] and IL-17[18] production, suppression of IFN-γ production,[21] and activation of mast cells,[22] basophils,[23] and dendritic cells.[24] DEP T_H2 adjuvanticity has also been shown to depend on reactive oxygen intermediates[17] and the attraction of monocytes and dendritic cells to the lungs through the chemokine receptor CCR2.[25] The article by Manners et al[26] in this issue of the *Journal* carries these observations further by (1) confirming that treatment of pregnant mice with DEPs increased the ability of ovalbumin inoculation to induce allergic airway disease in their offspring; (2) demonstrating, for the first time, a critical role for T_H2/T_H17 cytokine–secreting natural killer (NK) cells in the increased susceptibility of the offspring to allergic airway disease; and (3) associating this increased susceptibility with activation and increased transcription of the aryl hydrocarbon receptor (which promotes an IL-17 response,[27] as well as oxidative stress[28]) and additional genes that are associated with an oxidative stress response.

Promotion of IL-13 production by NK cells, as shown in the pregnancy model of Manners et al[26] has not been described in models that studied DEP effects in nonpregnant mice. Although it might be argued that NKT cells, rather than NK cells, are responsible for IL-13 production in the pregnancy model, because NKT cells have been reported to be essential for the development of other models of allergic airway disease[29] and the treatment used by Manners et al[26] to deplete NK cells also depletes NKT cells, Manners et al found that NKT cells were the most common IL-5/IL-13/IL-17–secreting spleen cells in their model. However, a more selective approach, such as the use of NKT cell–deficient CD1d-deficient mice, is required to obtain a definitive result.

The apparent requirement for NK cells in the pregnancy model raises the question of whether DEPs promote a T_H2 response in the offspring of treated pregnant mice in the same way that they promote a T_H2 response in nonpregnant mice. They might not; although titanium dioxide particles, like DEPs, that have been depleted of their associated organic molecules[30] do not promote a T_H2 response in nonpregnant mice, the treatment of pregnant mice with titanium dioxide particles has strong T_H2 adjuvanticity in both the pregnant mice and their offspring.[11] As with the effect of titanium dioxide particles, it is not known whether DEPs administered to pregnant mice act directly on the developing fetus to promote T_H2 responsiveness, as postulated by Manners et al,[26] or act indirectly through an effect on the maternal immune system.

In summary, Manners et al[26] have made an important contribution to our understanding of DEP predisposition to asthma by confirming that effects that occur during pregnancy promote disease in offspring, by delineating how DEPs promote oxidative stress and IL-17 production, and by providing evidence for a critical role for NK cells in the process. Despite my caveats, their work

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Disclosure of potential conflict of interest: F. D. Finkelman declares that he has no relevant conflicts of interest.

Received for publication March 27, 2014; accepted for publication April 3, 2014.

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J Allergy Clin Immunol 2014;■■■:■■■-■■■.
0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2014.04.002

paves the way for further mechanistic studies and provides further evidence for the importance of limiting DEP exposure.

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