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Editorial

Is TLR4 Critical for Neutrophil Apoptosis in Occupational Asthma?

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▸ See the article "Toll-Like Receptor 4 Deficiency Aggravates Airway Hyperresponsiveness and Inflammation by Impairing Neutrophil Apoptosis in a Toluene Diisocyanate-Induced Murine Asthma Model" in volume 12 on page 608.

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Patients with occupational asthma (OA) experience a latency period of exposure to causative agents and suffer from immunological reactions during acute re-exposure to the agents at the workplace.[1,2] To date, more than 300 agents, such as isocyanates, wheat flour, and grain dust, have been suggested to be involved in the pathogenesis of OA. Among the causative agents, toluene diisocyanate (TDI) is a highly reactive chemical which is the most prevalent cause of OA worldwide.[3] Although the pathogenic mechanism of airway inflammation in OA has not been completely determined, a significance of neutrophil infiltration and activation has been intensively highlighted. The significantly increased number of neutrophil elastase-expressing neutrophils in the airway mucosa of patients with TDI-induced OA (TDI-OA) has been revealed.[4] In addition, sputum myeloperoxidase and interleukin (IL)-8 levels were markedly elevated by TDI bronchial challenges in patients with TDI-OA,[5,6] suggesting that neutrophilic airway inflammation is a prominent characteristic of TDI-OA. Neutrophils predominantly contribute to innate immune responses mainly via Toll-like receptor 4 (TLR4) that binds to lipopolysaccharide (LPS). Although the TLR family currently includes 10 human TLRs that function as pattern recognition receptors for a wide range of bacteria, TLR4 is regarded as the major LPS receptor. When TLR4 on the surface of neutrophils is stimulated with LPS, multiple genes involved in cell growth, survival and activation are up-regulated in addition to the up-regulation of cytokine and chemokine genes.[7] To our knowledge, highly activated neutrophils mediated by TLR4 signaling may have a responsibility for the pathogenesis of airway inflammation of TDI-OA; the recent study published in the current issue of the *Allergy, Asthma & Immunology Research* has demonstrated that TLR4 deficiency enhances neutrophil infiltration, leading to deteriorated airway inflammation.[8] The authors suggested TLR4 as a negative regulator of TDI-induced neutrophilic airway inflammation. To induce TDI-OA, wild-type or TLR4$^{-/-}$ C57BL/10J mice were sensitized and challenged with TDI. As a result, TDI exposure significantly enhanced airway hyperresponsiveness and reduced expression of IL-17A in TLR4$^{-/-}$ mice compared to those in wild-type mice. Another recent study has suggested that IL-17F rather than IL-17A underlies neutrophilic airway inflammation in a steroid-resistant TDI-OA.[9] In addition to cytokine production, TDI exposure inhibited neutrophil apoptosis with markedly up-regulation of B-cell lymphoma-2 (BCL-2) in TLR4$^{-/-}$ mice. However, reactive oxygen species (ROS)-related immune responses were suppressed in TLR4 deficiency as NLRP3 expression and caspase-1 activity were significantly reduced. Oxidative stress inducing ROS production is an important feature of TDI-OA.[10] Finally,

blockage of BCL-2 decreased neutrophil recruitment, indicating that TLR4 attenuates asthmatic symptoms in TDI-OA through promoting neutrophil apoptosis independent of ROS. Apoptosis is evolutionarily well-conserved programmed cell death controlled by the BCL-2 family of proteins, which contains both pro-apoptotic and pro-survival members that balance the decision between cellular life and death.[11] Therefore, dysregulation of apoptosis is associated with multiple diseases as a delay of neutrophil apoptosis induces necrotic cell death, resulting in increased host tissue damage. For a long time, LPS has been widely known to suppress constitutive neutrophil apoptosis via TLR4, while the present study showed unexpectedly opposite data in TLR4 deficiency addressing the controversial but vital role of TLR4 in the pathogenesis of TDI-OA. Although evidence directly linking TLR4 to BCL-2 in the regulation of neutrophil apoptosis is still lacking, some study demonstrated that inhibition of TLR4 by using small RNA enhanced the expression of BCL-2, leading to reduction in neutrophil apoptosis.[12] Nevertheless, further investigations are needed to confirm the relation between TLR4 and neutrophil apoptosis in the pathogenesis of TDI-OA.

TLR4 has a particular role in the regulation of neutrophil life span, activation and apoptosis. The management of inappropriate or excessive neutrophils by inhibition of TLR4 signaling has been proposed to decrease neutrophil survival in the ways that may be amenable to pharmacological antagonisms.[13] Especially, various TLR4 modulators have been studied in sepsis caused by TLR4-abnormal activation via LPS, but specific treatment has not yet limited. In inflammatory airway diseases, such as asthma and chronic obstruction pulmonary disease, inhibition of TLR4 signaling has also been suggested to be a promising therapy through reducing of neutrophil recruitment and activation.[14] In contrast to these general strategies, Chen *et al*.[8] revealed that induction of TLR4 expression may have a potential benefit in alleviating neutrophilic airway inflammation in TDI-OA by increasing neutrophil apoptosis. However, further studies are necessary for exploring the significant effect of highly expressed TLR4 on neutrophil apoptosis.

In conclusion, TLR4 deficiency may possibly contribute to impaired neutrophil apoptosis by up-regulation of BCL-2, leading to enhanced neutrophilic airway inflammation in TDI-OA. Therefore, up-regulation of TLR4 or down-regulation of BCL-2 (both inducing neutrophil apoptosis) could be a novel therapeutic approach to protecting from TDI exposure in patients with OA.

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