

Correspondence

Eosinophil apoptosis-inducing drugs risk worsening rather than resolving asthma

To the Editor:

I read with interest the comprehensive mouse study by Kiwamoto et al,¹ demonstrating the possibility that airway glycans can bind sialic acid-binding, immunoglobulin-like lectin (Siglec)-F to induce eosinophil apoptosis. This work is presented as an addition of drugable opportunities² targeting Siglec-8 (human variant of mouse Siglec-f). The general hypothesis is that novel therapeutics, which induce eosinophil apoptosis, shall “limit lung eosinophilia in asthmatic patients.”¹ However, there appears to be a narrow line between inducement of apoptosis, which is currently considered a desirable effect, and inducement of primary necrosis, which is likely a pathogenic mechanism in asthmatic patients.³ Kiwamoto et al¹ do not mention this caveat. Hence it seems important to highlight the risk that proapoptotic drugs might induce eosinophil necrosis.

A recent review has summarized the occurrence of regulated primary necrosis of eosinophils in asthmatic patients.³ In bronchial tissues conspicuous free eosinophil granules unravel prior and ongoing eosinophil necrosis. The free granules are laden with and release cationic proteins. In experimental guinea pig asthma and in human severe asthma (clinically uncontrolled asthma and lethal asthma), occurrence of eosinophil necrosis has been demonstrated to associate significantly with epithelial derangement. It appears that already in the circulation eosinophils in patients with severe asthma are abnormally prone to undergoing primary necrosis.³

A wide range of asthma-relevant challenges has caused eosinophils to promptly succumb to necrosis. The necrosis involves chromatolysis and cell membrane rupture.³ Hence nuclear and cytosolic danger-associated molecular patterns are also released.

In allergic mice with already established lung eosinophilia, Uller et al⁴ demonstrated that treatment with anti-Fas mAb, an archetypal proapoptotic agent, caused significant primary necrosis of eosinophils in lung tissues. Although this effect was associated with reduced bronchoalveolar lavage fluid eosinophilia, lung tissue inflammation was much aggravated. It is possible that reduced transepithelial elimination of tissue eosinophils (that could not migrate if they were dying) contributed to reduced lumen eosinophilia.

In an elegant study involving human primed eosinophils, Kano et al⁵ demonstrated that Siglec-8 induced primary necrosis with spilling of free eosinophil granules. Interestingly, the switch from apoptosis to primary necrosis was accomplished merely

through exposure of eosinophils to IL-5.⁵ Kiwamoto et al¹ do not discuss the work by Kano et al.⁵

Along with IL-5, numerous candidate molecules can be involved in priming of eosinophils for necrosis. Supporting the importance of widespread priming effects, necrotic eosinophils abound in bronchial walls of asthmatic patients. By contrast, there is still lack of compelling proof of occurrence of apoptotic eosinophils *in vivo* in human lung tissues (reviewed by Persson and Uller³).

Death mode markers might not always distinguish well between apoptotic and necrotic eosinophils. Hence it is possible that apoptosis might have been overreported. For example, previous reports on Siglec-8-mediated eosinophil “apoptosis” in both IL-5- and IL-33-treated eosinophils might have involved primary necrosis.⁶ Indeed, the possibility of unwanted inducement of primary necrosis in primed eosinophils might have to be generalized to include proapoptotic agents in general. Thus Kano et al⁵ have devised approaches in a novel field of critical therapeutic research on switching between apoptosis and necrosis of eosinophils. This would be a clinically relevant segment adding to the currently exploding interest in regulated cell necrosis.⁷

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