

Editorial: RSV: a new box of delights for an old enemy

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The winter season brings joys and terrors alike to the young child and the older adult. In winter, when the wolves of RSV are running, we need a new box of delights² to counter this potentially deadly virus.

Others have summarized the misery of RSV [1]. This winter epidemic virus hospitalizes large numbers of children, causing life-threatening disease in the youngest and those with underlying respiratory or cardiac disease. Recovery may be associated with increased lifetime risks of asthma [2]. Lifetime immunity appears hard to achieve, with no effective vaccine and reinfection common. In the adult, the virus can cause mayhem in the elderly, the immunocompromised, and those with asthma and COPD.

Bringing down the wolves of respiratory viruses is challenging, and RSV has proven itself to be a particularly tough pack leader to bring down. Vaccination can lead to detrimental inflammatory responses upon encounter with the virus. mAb to RSV have prophylactic efficacy and are of use in vulnerable infants. However, antiviral drugs (ribavirin) and therapeutic antibodies to RSV have very limited value in acute disease, with their acute use mainly confined to those who are significantly immunocompromised.

This makes the trio of interventions, united around a single approach, for

acute RSV, exploited by Shirey et al. [3] in this issue of *JLB*, of great interest. This study follows a line of enquiry around the concept that driving macrophages to an alternatively activated phenotype during acute infection might promote a less destructive and more effective resolution of viral-induced lung inflammation [3]. The authors use IL-4 as a proof of concept to drive AAM development, with a corresponding reduction in RSV-related lung damage. IL-4 itself is not a very appealing therapy in humans. As RSV infection can predispose to development of asthma [2], using this pleiotropic cytokine, with its proallergic functions in children with RSV disease, would be fraught with complications. Happily, Shirey et al. [3] provide some more palatable and clinically testable options to tame the RSV wolf, using thiazolidinediones or macrolides, summarized in **Fig. 1**. Both of these options involve repurposing of existing drugs, selected because of their potential ability to push macrophages to an AAM phenotype. Both drugs have a range of actions not always well understood, exhibiting multiple actions on inflammatory pathways.

Thiazolidinediones, such as rosiglitazone, have many anti-inflammatory actions relevant to RSV infection of the lung, including down-regulation of epithelial cell NF- κ B activation [5] and reduced airway inflammation in response to endotoxin [6]. These drugs also have beneficial actions in mouse models of asthma, reducing IL-17 production [7] and up-regulating phosphatase and ten-

sin homolog to oppose PI3K signaling [8]. It is therefore an interesting conjecture that thiazolidinediones could also reduce not just RSV-induced inflammation but also the subsequent propensity to develop allergic asthma. This family of drugs is no longer used in its initial primary indication (treatment of diabetes), because of cardiac side-effects, but short course therapy may still be feasible.

Azithromycin is a macrolide antibiotic already licensed for use in children. The macrolide family of molecules is gaining rapid acceptance as an immunomodulator, as well as an antimicrobial. In clinical use, azithromycin reduces exacerbations in COPD and cystic fibrosis; is used to treat some chronic bronchiolitic conditions, such as bronchiolitis obliterans syndrome after lung transplant; and might have efficacy in noneosinophilic asthma. It has a wide possible range of actions in the control of neutrophilic inflammation [9], which is relevant, given the potentially neutrophilic nature of RSV bronchiolitis, and can also facilitate antiviral responses in airways epithelial cells [10]. There are concerns that macrolides might be asso-

Abbreviations: AAM=alternatively activated macrophage, COPD=chronic obstructive pulmonary disease, RSV=respiratory syncytial virus

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2. With thanks (and probably apologies) to John Masefield. For those who do not know, *The Box of Delights* is a children's story, published in 1935 by the Poet Laureate John Masefield, with a magic box, children, and villains causing chaos at Christmas, perfect for winter holiday reading.

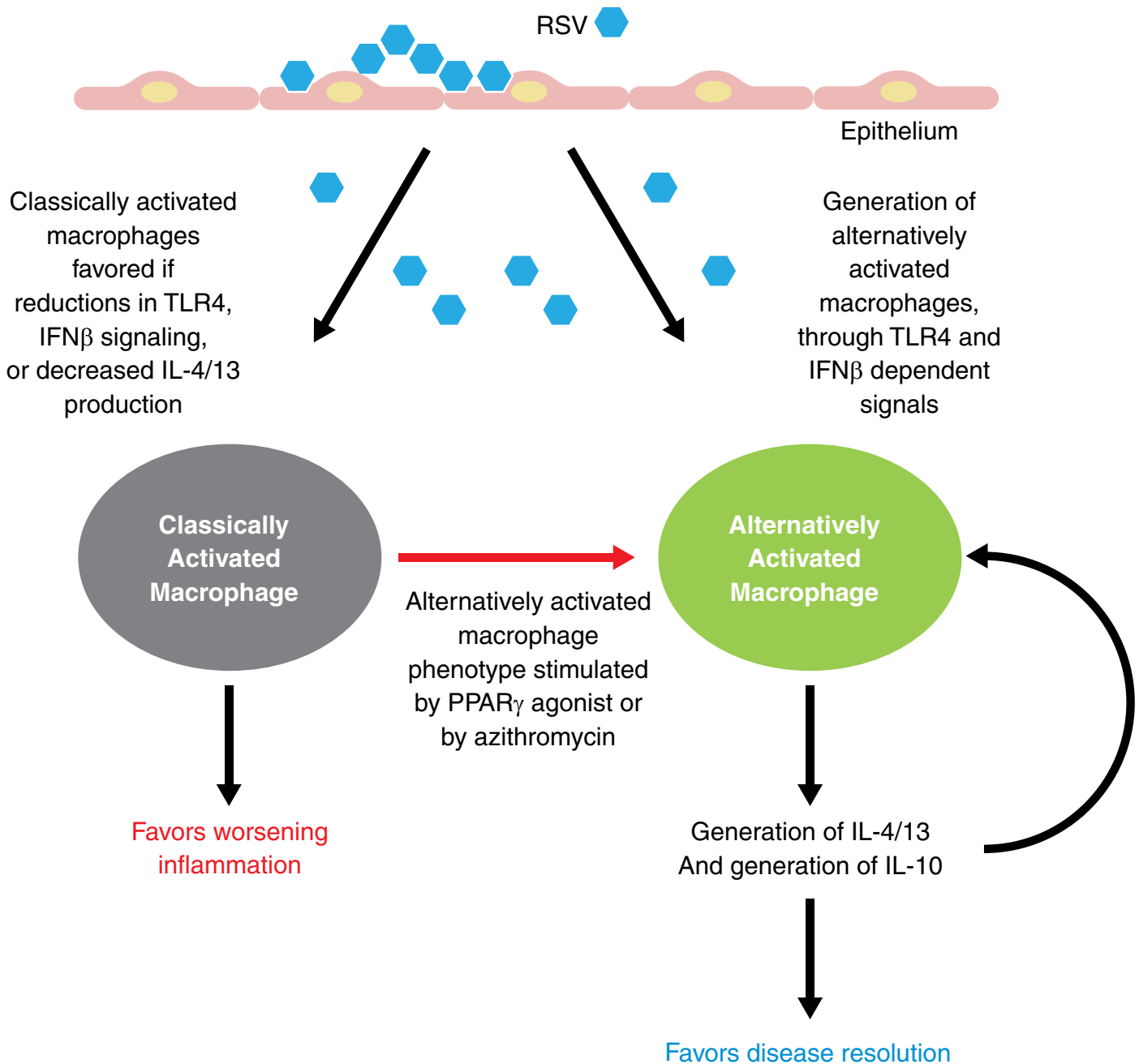


Figure 1. In the model of Shirey et al. [4], generation of AAMs during RSV infection is favored by IFN- β and TLR4 signaling and dependent on IL-4 and IL-13 production by macrophages. These AAMs are important in successful, early resolution of tissue inflammation. Particularly where IFN or TLR4 signaling is deficient, generation of classically activated macrophages is associated with worse tissue damage. Driving of an AAM phenotype by macrolide treatment or peroxisome proliferator-activated receptor γ (PPAR γ) agonists is associated with less tissue damage and suggests new ways of ameliorating RSV-induced inflammation.

ciated with small increases in risks of cardiovascular death in at-risk adult populations, and their use may be associated with the emergence of resistant micro-organisms. There is also the additional problem of extrapolating from a mouse model to human disease. Three

trials of azithromycin in acute bronchiolitis have failed to show clinical benefit [11–13], but one trial of another macrolide, clarithromycin, showed evidence that the drug may have reduced length of stay and been associated with fewer episodes of postviral wheezing [14]. The

studies of macrolide roles in RSV infection are all of small numbers and therefore, beset by the problems of making large conclusions from small clinical studies.

The fact that rosiglitazone and azithromycin exhibit pleiotropic mecha-

nisms of action that are incompletely understood suggests that the mechanisms by which they might modulate responses to RSV infection may go beyond modulation of AAM polarization, and work is required to narrow down the target pathways. The readouts of the inflammatory response in the treated mice are limited. The nature, rather than the magnitude, of the inflammatory response may be more important in determining clinical outcome, and it would have been interesting for this to have been assessed. Modulation of macrophage function in the human may influence chronic sequelae of RSV, as well as the acute illness. Infection of the lungs with influenza or RSV can induce desensitization of lung macrophage inflammatory responses that may last many months [15]. As the authors themselves are aware, any treatment that would polarize the response to RSV toward type 2 immunity will meet with a very cautious reception. In general, neonates are much more predisposed to develop Th2 immunity, so this may be a particular risk in this age group. Furthermore, neonatal alveolar macrophages exhibit significant phenotypic differences in early life [16] and may not respond to polarization signals in the same way as the adult macrophages did in this paper. Differences may be exaggerated in the macrophages from premature infants. Our lungs undergo a significant amount of development after birth, such as septation of the alveoli. Macrophages are likely to play a significant part in regulating and orchestrating these processes, and the consequences of any alteration in their function on lung development would need to be evaluated.

Thus, further work is needed to explore, in more detail, how the ap-

proaches of Shirey et al. [3] affect the acute nature of the inflammatory response to infection, the long-lasting effect on macrophage function, and the polarization of immunological responses to re-encounter with the virus and inhaled allergens. Nonetheless, as alveolar macrophages are gate-keepers of inflammatory responses in the lungs, therapies manipulating their function are of great interest, and this study suggests further ways to keep the wolves from the door. Let's hope it's not just a dream.²

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