CORRESPONDENCE

CCAAT/Enhancer-Binding Protein δ

Multifaceted Regulator in Respiratory Disease

To the Editor-in-Chief

With great interest we read the paper by Yan et al¹ recently published in *The American Journal of Pathology*. The authors elegantly show that CCAAT/enhancer-binding protein δ (C/EBP δ) drives cytokine production, neutrophil accumulation, and lung vascular leakage in a murine model of lipopolysaccharide (LPS)-induced acute lung injury. These phenotypes were accompanied by enhanced intraalveolar hemorrhage, and overall these data suggest that C/EBP δ plays an important role in LPS-induced lung inflammatory responses and injury. These data are particularly interesting as LPS is a potent activator of innate immune responses via Toll-like receptor (TLR)-4, and it has been suggested that the use of LPS mimics host inflammatory responses during Gram-negative bacterial infections.² Interestingly, however, we recently showed that C/EBP δ limits mortality in a clinically relevant Gram-negative infectious disease model.³ Indeed, C/EBP $\delta^{-/-}$ mice died on intranasal inoculation of *Klebsiella pneumoniae* with a median survival time of 60 hours, whereas 40% of wild-type mice were still alive at the end of the observation period. Surprisingly, we did not observe any differences in cytokine production and/or neutrophil accumulation between wild-type and C/EBP $\delta^{-/-}$ mice. As we were intrigued by these data, we performed experiments similar to those of Yan et al (intranasal LPS instillation), and we also observed reduced cytokine expression in bronchoalveolar lavage fluid (BALF) of C/EBP $\delta^{-/-}$ mice as compared to wild-type mice 24 hours after LPS instillation (unpublished data). Strikingly, however, at six hours after LPS instillation, cytokine levels were significantly increased in the BALF of C/EBP $\delta^{-/-}$ mice compared to wild-type controls (unpublished data). At a first glance, these conflicting data point to a very complex role of C/EBP δ in infectious disease. This notion is underscored by our recent findings that C/EBP δ potentiates mortality during Gram-positive pulmonary bacterial infections.⁴

As already indicated, LPS exerts its role in innate immunity via TLR-4. Interestingly, TLR-4 is implicated as the TLR for the recognition of *Klebsiella* by virtue of its capacity to sense LPS present in the outer membrane of this pathogen.⁵ This traditional view was recently challenged, however, by showing

that the host response to *Klebsiella* does not solely depend on TLR-4 signaling.⁶ Indeed, TLR-2^{-/-} mice are more vulnerable to *Klebsiella* infection as compared to wild-type mice, and TLR2 seems to play a dual role in the host response to *Klebsiella* pneumonia, irrespective of the presence of TLR4. The complex interaction between host and pathogen is therefore not properly mimicked by instillation of agents targeting single TLR pathways. Hence, although such experiments do provide useful information on the role of individual factors (ie, C/EBP δ) in different inflammatory pathways, conclusions drawn in the perspective of bacterial infections should be made with care.

In conclusion, it is evident that C/EBP δ is an important player in infectious disease, but its role seems complex and is far from understood. Only by integrating results from different experimental models will we be able to appreciate fully the role of C/EBP δ in infectious disease. We should therefore refrain from suggesting extrapolation to human disease and clinical implementation until further studies are performed.

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Authors' Reply

We are pleased that Duitman et al are enthusiastic about our recent findings¹ and have found our results valuable and interesting. Although it is difficult to compare our data to their new *in vivo* studies because their data are not published and no experimental details are available—such as background strain, sex, etc, of the mice—their finding that C/EBP δ deficiency impairs long-term cytokine production in the LPS lung injury model supports our conclusions. It is critical to note that the effects we observed on inflammatory mediator production in the C/EBP δ knockout mice are consistent with the reduction in lung injury, which is the important biological endpoint of our

study. Based on our study and published work by Duitman et al³ that C/EBP δ seems to play opposite roles in *Klebsiella pneumoniae*-induced pulmonary infection and pneumococcal pneumonia,⁴ we agree that C/EBP δ may play a complex role in inflammation and infectious diseases. Additional studies are very welcome in this regard.

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