Infectious diseases and fibrotic disorders: Potential novel targets
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CCAAT/Enhancer-Binding Protein δ: Multifaceted Regulator in Respiratory Disease

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With great interest we read the paper of Dr. Yan et al. recently published in *The American Journal of Pathology*. The authors elegantly show that CCAAT/Enhancer-Binding Protein δ (C/EBPδ) 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 intra-alveolar hemorrhage and overall these data suggest that C/EBPδ 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 as it has been suggested that the use of LPS mimics host inflammatory responses during gram-negative bacterial infections. Interestingly, however, we recently showed that C/EBPδ limits mortality in a clinical relevant gram-negative infectious disease model. Indeed, C/EBPδ−/− mice died on intranasal inoculation of *Klebsiella pneumoniae* with a medium survival time of 60 hours whereas 40% of wildtype 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 wildtype and C/EBPδ−/− 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in bronchial lavage fluid (BALF) of C/EBPδ−/− mice as compared to wildtype mice 24 hours after LPS instillation (unpublished observations). Strikingly, however, at six hours after LPS instillation, cytokine levels were significantly increased in the BALF of C/EBPδ−/− mice compared to wildtype controls. At a first glance, these conflicting data point to a very complex role of C/EBPδ in infectious disease. This notion is underscored by our recent findings that C/EBPδ potentiates mortality during gram-positive pulmonary bacterial infections.

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. This traditional view was recently challenged however by showing that the host response to *Klebsiella* does not solely depend on TLR-4 signaling. Indeed, TLR-2−/− mice are more vulnerable to *Klebsiella* infection as compared to wildtype 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 (i.e. C/EBPδ) in different inflammatory pathways, conclusions drawn in the perspective of bacterial infections should be made with care. In conclusion, it is evident that C/EBPδ 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 fully appreciate the role of C/EBPδ in infectious disease. We should therefore refrain from suggesting extrapolation to human disease and clinical implementation until further studies are performed.

REFERENCES