Infectious diseases and fibrotic disorders: Potential novel targets
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CCAAT/enhancer-binding protein delta (C/EBPδ) plays a minor role in renal host defense against uropathogenic *Escherichia coli*.

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Urinary tract infection (UTI) is a common complication following renal transplantation, with a reported incidence of 6-86%. More than 70% of UTIs are caused by gram-negative bacteria, among which *Escherichia coli* is the main causative pathogen. CCAAT/enhancer-binding protein delta (C/EBPδ), a member of the C/EBP family of transcription factors, is strongly induced by inflammatory cytokines and recently emerged as an essential player during gram-negative bacterial infections. Indeed, C/EBPδ−/− mice were highly susceptible to *E. coli*-induced peritonitis and *Klebsiella pneumoniae*-induced pneumonia. Here, we determined whether C/EBPδ would also limit UTI. To this end, we assessed C/EBPδ expression during murine UTI using kidney sections of wildtype mice inoculated with uropathogenic *E. coli* into the bladder. A characteristic hallmark of this model is the vast recruitment of inflammatory cells to the site of infection. Interestingly, C/EBPδ expression was high in these (infiltrating) inflammatory cells (Fig. 1A and B). Next, we compared UTI in wildtype and C/EBPδ−/− mice (provided by Dr. Sterneck), and bacteria rapidly spread into the kidney irrespective of the genotype (Fig. 1C and D). The subsequent clearance of bacteria both locally in the bladder as well as in the kidney was also not (significantly) affected by C/EBPδ. Rather unexpectedly, C/EBPδ deficiency even seemed to slightly potentiate bacterial clearance, as evident from a trend toward lower bacterial loads in the kidney of C/EBPδ−/− mice 48 h after inoculation. Because C/EBPδ has been suggested to play an important role in the regulation of the inflammatory response, we next determined inflammatory cytokine/chemokine production. However, levels of the inflammatory mediators measured were independent of C/EBPδ expression (Fig. 1E and F), and seemed a mere reflection of the bacterial load. In line with this, neutrophil influx in the kidney was increased in both wildtype and C/EBPδ−/− mice at 24 and 48 h, but to a similar extent in both genotypes. Overall, we show that C/EBPδ does not potentiate bacterial clearance during UTI, but may slightly inhibit bacterial clearance. This seems in line with the fact that C/EBPδ−/− mice are relatively resistant to pneumococcal pneumonia. However, C/EBPδ potentiates this latter infection in a manner specific for phosphorylcholine-containing bacteria; therefore, C/EBPδ cannot affect UTI caused by phosphorylcholine-negative *E. coli* via this mechanism. Our data are in contrast with studies in which C/EBPδ deficiency leads to impaired bacterial clearance and increased mortality during bacterial infection. Interestingly, C/EBPδ only influenced bacterial outgrowth in a high-dose bacterial infection model. In our UTI model, a high dose of *E. coli* was inoculated, and the bacterial dose can consequently not explain the seeming discrepancy between the different studies. Obviously other differences, such as the infection site and disease-causing pathogen, may lead to the observed differential role of C/EBPδ. We hypothesize, however,
Figure 1. C/EBPδ expression in kidney and contribution of C/EBPδ to bacterial clearance and inflammatory response during urinary tract infection (UTI). C/EBPδ immunohistochemical staining in kidney before (A) and 24 h after UTI (B). C/EBPδ is expressed in epithelial cells before and after infection (arrowhead) and in infiltrating monocytes/macrophages and lymphocytes (arrow), but seems low in granulocytes (*). Bacterial outgrowth (colony-forming units [CFU], C and D) and cytokine production (E and F) in bladder (C and E) and kidney (D and F) homogenates from wildtype (□) and C/EBPδ−/− mice (▲), 24 and 48 h after inoculation with 1 x 10⁹ CFU Escherichia coli strain 1677/mouse. Single experimental data are depicted as individual symbols, lines represent mean. KC, keratinocyte chemoattractant; MIP, macrophage inflammatory protein; IL, interleukin.
that C/EBPδ limits gram-negative infections during later stages of disease (as suggested in reference 8 and 9), and consequently C/EBPδ will only be relevant in models in which the infection is not rapidly cleared (as is the case in the UTI model). Irrespective of the actual explanation, our data show that C/EBPδ is not an important factor in host defense against UTI.

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C/EBPδ IN URINARY TRACT INFECTION

REFERENCES