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Title: Epithelial NF-κB regulates bacterial translocation in the respiratory tract

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Body: Background: Streptococcus pneumoniae (Sp) is a pathogen that colonizes the mucosal surfaces of the respiratory tract and causes severe pneumonia and invasive disease. The transcription factor NF-κB is central in the regulation of the innate immune system. It was the aim of this study to examine the function of epithelial NF-κB in regulating the translocation of Sp colonizing the upper respiratory tract into the lung and the blood stream. Methods: To generate a constitutive knockout RelA/p65 in epithelial cells relaF/F mice were crossed with CCSPCre animals to generate a relaF/F CCSP mouse line (RelA/p65). To generate mice with constitutive activated NF-κB in epithelial cells IκBαF/F mice were crossed with CCSPCre animals to generate a IκBαF/F CCSP mouse line (IκBα).The upper-respiratory tract of mice was colonized with a type 6A isolate of Sp. Survival, bacterial translocation into the lung, colonization densities and levels of cytokines were determined. Results: There was no difference in the colonization levels of Sp in the upper-respiratory tract between WT-, RelA/p65-, and IκBα-mice. IκBα-mice showed reduced bacterial translocation into the lung as compared to WT- and RelA/p65-mice. Epithelial depletion of RelA/p65 resulted in decreased survival whereas constitutively activated NF-κB resulted in enhanced survival of mice colonized with Sp. Epithelial RelA/p65 mice had increased levels of inflammatory cytokines in the lung whereas constitutive activation of NF-κB resulted in reduced cytokine levels upon bacterial colonization. Conclusion: These results show that epithelial NF-κB controls bacterial translocation from the upper-respiratory tract into the lung and invasive bacterial disease.