Homeostatic Role for Nuclear Factor-KappaB in the Lung

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Rationale: Recent mice studies demonstrate that inhibition of basal activity of the transcription factor, Nuclear Factor-KappaB (NF-kB) in skin, gut, and liver results in severe inflammation. Furthermore, NF-kB related disruption of homeostasis has been implicated in incontinentia pigmenti and colitis in humans. The purpose of this study was to determine whether constitutive NF-kB is essential to lung homeostasis.

Methods: Sheep were instrumented to permit measurement of arterial oxygenation (paO2), pulmonary vascular resistance (PVR), peripheral blood neutrophil (PMN) count, and pulmonary endothelial permeability (lung lymph protein clearance, Clp). Sheep were given intravenously the pharmacologic inhibitor of IkBa phosphorylation Bay11 (6 mg/kg) or, on a separate day 1 week apart, vehicle and measures made for 5 hours. After Bay11, animals were euthanized and lung wet:dry weight ratio (W/D) determined. Statistical analysis used repeated measure ANOVA with post hoc Tukeys.

Results: Bay11 inhibition of NF-kB caused marked pulmonary edema whereas infusion of the control vehicle caused no physiologic changes. With Bay 11, paO2 decreased significantly ($p<0.001$) after 2 hours and remained low (5 hour paO2 decreased by 34.6 ± 3.6(SD) torr, n=5). Clp increased significantly ($p<0.001$) from baseline at 3 hours and remained high (baseline=3.0 ± 0.75; 5hour=25.5 ± 7.0, (n=3). W/D ratio was 60% higher than control values (PBS =5.46 ± 0.44; Bay 11=8.78 ± 0.49). PVR increased slightly in the last two hours of the experiment. PMN count did not change. Protein rich fluid filled the airways postmortem (protein concentration control = 0.0115 mg/ml; Bay11= 0.5924 mg/ml). A cell permeable form of mutant IkBa which cannot be degraded and which inhibits NF-kB in cells and in sheep lungs (EMSA) caused a 15 torr decrease in paO2 and a 10-fold increase in Clp, confirming the Bay11 results. Results were also confirmed in swine where Bay 11 produced pulmonary edema that was dose related and severe at higher doses (10 mg/kg) without any increase in PVR or circulating IL-6, TNFa, or neutrophil count indicating a non-inflammatory endothelial permeability defect. In cultured human pulmonary endothelial cells, constitutive NF-kB activation was completely inhibited by Bay 11 and microarray analysis showed alterations in integrin receptor gene expression.

Conclusion: Inhibition of NF-kB causes increased permeability pulmonary edema without inflammation. We speculate that constitutive NF-kB activity is essential for maintaining pulmonary endothelial barrier function. The dual role of NF-kB in maintaining lung fluid homeostasis and as a mediator of the inflammatory response should dictate caution in targeting its inhibition as potential therapy for inflammatory diseases.