Serum Mmp-3, Mmp-13, And Timp-4 Predict Fev1 In World Trade Center Exposed New York City Firefighters

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RATIONALE: The collapse of the WTC on 9/11 exposed over 12,000 firefighters to an intense irritant exposure. FEV_1 declined 439ml over the following six months in 7364 never-smokers, and had an annualized reduction of 25ml. Within the total cohort, some individuals recovered while others had progressive lung function decline. Serum drawn between 10/2001 and 3/2002 is available for biomarker studies. To better understand why some individuals progressed and others recovered, we conducted a series of preliminary nested case-control biomarker studies. We have reported that biomarkers of inflammation, metabolic syndrome and cardiovascular risk expressed within 6 months of 9/11/2001 predicted risk of abnormal FEV_1 years later. Some serum biomarkers were associated with increased risk or abnormal FEV_1 while others predicted reduced risk. We have now investigated how early expression of proteases and antiproteases affect subsequent FEV_1.

METHODS: We used Luminex technology to measure serum MMP-1,2,3,7,8,9,12,13 (Affymetrix) and TIMP-1,2,3,4(R&D Systems) expressed prior to 4/2002 in 270 never-smoking patients who had FEV_1 measured subsequently at subspecialty pulmonary evaluation prior to 3/2008. We used clustering to analyze the relationship of protease/antiprotease balance and linear regression models (adjusted for age, 9/11 exposure intensity, BMI) to test MMP and TIMP ability to predict FEV_1. Data management and statistics were performed using SPSS.

RESULTS: All TIMPs clustered together while there were three groups of MMP expression: MMP-2 and 9; MMP-1,3 and 8; MMP-7,12 and 13. A multivariable linear model demonstrated that elevated MMP-13 predicted lower FEV_1 whereas elevated MMP-3 and TIMP-4 predicted increased FEV_1. The R-squared of the model increased from 0.13 to 0.19 when serum biomarkers were added. The range of MMP-13 expression in post-9/11 serum drawn before 3/2002 was 10-3,737 pg/mL; each 10-fold increase in MMP-13 was associated with a 122ml decrease in FEV_1 on spirometry performed on average 32 months post 9/11/2001. The range of MMP-3 was 168-36,789(pg/ml); each 10-fold increase was associated with a 296ml increase in FEV_1. The range of TIMP-4 was 6-3,616pg/ml; each 10-fold increase was associated with a 470ml increase in FEV_1.

CONCLUSIONS: Serum MMP-3, MMP-13, and TIMP-4 early after WTC exposure predicts FEV_1 years after the even. Increased MMP-3 and TIMP-4 are associated with improved lung function whereas increased MMP-13 is associated with reduced lung function. This suggests that injury and healing pathways are different. By developing explicit criteria of protease and antiprotease imbalance, treatment of these different pathways may be possible to limit injury and encourage repair.

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