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Title: Connexin 37 and Connexin 43 genotypes in correlation to cytokines in induced sputum and blood in cystic fibrosis (CF)

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Body: Background: We have provided evidence in previous studies that cytokines (IL-8, TNF alpha, LBP) measured in whole blood correlate negatively with lung function in delta 508 homozygous patients. GAP junction proteins (connexins) might be of importance for the influx of blood cells into the lung. Our aim was to assess the relationship between connexin genotypes, cytokines (IL-8, TNF-alpha and LBP) in induced sputum and blood and lung disease. Methods: 24 patients homozygous for delta F 508 (median age 20.5 y, m/f 14/10, BMI 20,35 kg/m², Shwachman score 75, FEV₁(%) 83) were examined. Sequence analysis was performed for GAP junction protein alpha 1 (GJA1/Connexin 43) and gap junction protein alpha 4 (GJA4/connexin 37). Cytokines were assessed in blood and induced sputum (IS) by chemiluminescence (DPC Biermann, Bad Homburg, Germany). Results: Here we present the first preliminary data: For 18 patients cytokine and sequence data were available. Whereas GJA1 showed only one rare heterozygous SNP (rs138386744) in one patient, four common SNPs were detected in GJA4. Two were synonymous changes, but the third variant (rs41266431) causes an amino acid substitution (GTA valine, ATA isoleucine) as well as the fourth SNP (rs1764391: CCC proline, TCCserine). For rs41266431 patients with homozygosity for the G variant (n=11) had higher IL-8 levels (median: 12.3/6.7 pg/ml, p<0.11) in whole blood than those showing heterozygosity for the G/A mutation (n=7). Conclusion: More patients have to be analyzed to substantiate these findings. For GJA4 the SNP at rs 41266431 seems a promising candidate gene.