Reviewer's report

Title: Cytokine gene polymorphisms and serum cytokine levels in patients with idiopathic pulmonary fibrosis

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Reviewer: Grethe Neumann Andersen

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To the authors of "cytokine gene polymorphisms and serum cytokine levels in patients with idiopathic pulmonary fibrosis".

I have now only a one major and one minor concern and think that the manuscript will soon be ready for publication:

Concerns:

Major:
The authors are asked to state the IL-10 (-1082, -819, -592) GCC, ACC and ATA haplotype carrier rates and the haplotype frequencies in IPF patients and controls as well as the correlations between these haplotypes and the extent of the different lung changes, lung function measurements and PaO2. This is because these haplotypes have been found to be associated with another Th2 driven disease, namely Sjögrens syndrome (see Hulkkonen J et al, Arthritis and Rheumatism 2001).

Minor:
Please state more explicitly which base pair you have in mind each time you mention them. As for example in the abstract under “Results” you write: TNF-alpha GG, IL-6 GG and CG and IL-10 ACC ATA genotypes. Please change this to: TNF-alpha (-308) GG, IL-6 (-174) GG and CG and IL-10 (-1082, -819, -592) ACC ATA.

Please also state the examined base pair number in other places in your manuscript, like for example in the Abstract under “conclusion” TGFbeta1 (codon 10, codon 25) CC GG and under “Results” page 12, line 8: IL-10 (-1082, -819, -592) etc. line 11 TGFbeta1 (codon 10, codon 25) etc and in the “Discussion” page 15 line 1: IL-10 (-1082, -819, -592) ACC ATA, page 17 line 3: TGFbeta1 (codon 10, codon 25) TC GG etcetera and page 18 line 5 TNF-alpha (-308) GG genotype etc.

Also in table 4 and table 6, please write:

IL-10 ( -1082, -819, -592), TGFbeta1 (codon 10, codon 25)

It was interesting to see the correlations between the presence of cytokine polymorphisms or genotypes and the extension of the different lung parenchymal changes as well as the results of PaO2 and lung function measurements.
I especially noted that a greater extent of honeycombing was correlated to the presence of the G allele in the -308 promoter region of the TNFalpha gene. The G allele is thought to be associated with a low production of TNFalpha. A low production of TNFalpha, which is considered to be a Th1 cytokine – predominantly, would mean that the Th2 driven fibrosing process in the lung in IPF would be less counteracted and thereby may become more extensive.

IFNgamma is another Th1 cytokine. In IFNgamma, the +874 TT genotype has been associated with high cytokine production. However, in this study there were no associations between genotype, allele frequency and the extension of lung changes or the results of lung function tests or PaO2 measurements.

IL-6 is a cytokine with many properties, among them Th2 and pro-inflammatory. In this study the IL-6 -174 G allele was associated with more extensive ground glass changes and reticulation. The G allele is also thought to be associated with a higher production of IL-6. IL-6 is a pleitropic cytokine and higher levels may act to attract leukocytes to the affected lung area, resulting in ground glass changes.

In this study, patients with the IL-10 (-1082, -819, -592) ACC ATA genotype had more extensive honeycombing than other genotypes. IL-10 genotype is also coupled to cytokine production in the way that persons with the GCC haplotype are low producers while persons with ATA are high. The finding is interesting as IL-10 is considered to be both a Th2 cytokine and to have tolerance inducing properties. It is still an enigma whether IL-10 in IPF is a friend or a foe.

TGFbeta is probably the most studied and the most interesting cytokine in the pathogenesis of IPF. Polymorphisms in codon 10 and 25 resulting in genotype TT (codon 10) and GG (codon 25) may lead to high growth factor production, while persons with TC (codon 10) and GC (codon 25) may be intermediate producers and persons with CC (codon 10) and CC (codon 25) low producers. In this study the authors found that TC (codon 10) GG (codon 25) led to more extensive ground glass changes and correlated to lower PaO2.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests