Reviewer's report

Title: Systemic inflammation links to atherosclerosis via C3aR1; results of a human in vivo LPS infusion study.

Version: 1 Date: 20 April 2011

Reviewer: Caspar Grond-Ginsbach

Reviewer's report:

The experimental part of this study is well done and yielded interesting results: Monocytes were carefully isolated from peripheral blood samples from healthy, young volunteers treated with bacterial LPS infusion or from control, treated with saline infusion. By cDNA microarray analysis up-regulation and down regulation of several genes was identified. By these valuable in vivo experiments the authors showed that LSP infusion induced a rapid transcriptional response in monocytes and they identified several genes with strong alterations in the concentration of detectable transcript. The data were validated by independent PCR.

Unfortunately, the authors do neither describe, nor discuss these results in detail. Instead they mention earlier unpublished in vitro experiments, in which LPS stimulation induced a total of 1127 genes. Six of the genes observed in the current study were also among the 1127 differentially expressed genes of that unpublished study. Among these six genes, C3aR1 was considered most interesting.

The current manuscript therefore is an unlucky combination of 1) very valuable experimental work (which should be published) and 2) an interesting discussion of unpublished own data, of published genetic data and of the current experimental data. The discussion - needless to say - is based on the assumption, that the LPS induced inflammatory response in monocytes is a proper model for atherosclerosis.

In my opinion, this manuscript needs major revisions.

1) The authors should present the cDNA microarray data from in vivo LPS treated human volunteers. These experiments suggested, that several genes are differentially regulated. C3aR1 is one of them (with modest p-values, compared to other genes like CSPG2). In their discussion, authors should comment on the experimental work. It is likely, that the monocyte isolation (about 1 hour and different steps) had effect on transcription and RNA stability; the high fold change and low p-values of C3aR1 suggests that the variance of the transcripts levels was particularly high, the differential expression of CD14 is to be discussed, etc.

2) The editor might suggest that the authors include the in vitro data (yet unpublished) in the current article and discuss the in vitro and in vivo monocyte
expression profiling findings together.