Reviewer's report

Title: Whole genome assessment of the retinal response to diabetes reveals a progressive neurovascular inflammatory response.

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Reviewer: Elia Duh

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This study provides a comprehensive analysis of gene expression changes in an experimental model of diabetic retinopathy (DR) after 1 and 3 months of diabetes.

A better understanding of gene expression changes in DR is highly important, since diabetic retinopathy is a leading cause of blindness in the US and industrialized nations and is the most common microvascular complication of diabetes. A comprehensive profiling of gene expression changes could shed important insights into this condition and aid in the identification of gene targets for therapy.

The current study is performed by researchers who are recognized experts in diabetic retinopathy. Overall, this is an impressive study, well-designed, carefully conducted, and comprehensive in scope. An important aspect of the study is the careful characterization of the diabetic rats, especially with regard to retinal vascular permeability and apoptosis at the time-points studied. This allows one to relate changes in retinal gene expression over time (1 and 3 months) to corresponding functional changes in the retina, i.e., vascular permeability and apoptosis. Significant functional alterations were found at 3 months, but not 1 month, thereby allowing the analysis of gene expression changes both prior to and at the time of these important phenotypic changes.

Using the Codelink rat whole genome microarray system, a large number of DNA elements are examined, yielding 22,578 probes with a detectable signal. Therefore, a wealth of data has been generated that will likely prove to be a valuable resource to the diabetic retinopathy research community. The study yields very interesting results, from global trends in gene expression changes to multiple specific genes of potential importance to DR. The overall finding is that gene expression changes increase markedly with duration of diabetes, both in number of genes and degree of change. Furthermore, ontological analysis demonstrates concomitant regulation of functional groups of genes. Particularly interesting is the significant induction of gene ontologies for the processes of cytokine production, immune response, and inflammatory processes. This is an important finding, since there is an increasing appreciation for the role of pro-inflammatory processes in the progression of DR. An additional interesting finding is the downregulation of a group of genes related to neuronal function, which sheds insight to the neuronal dysfunction that occurs in early DR. Finally,
quantitative PCR is performed for a subset of genes and confirms gene expression changes in 26 of the 32 genes tested. A few of these genes were previously found to be similarly regulated in DR, while many others represent novel findings and represent attractive targets for future studies. The authors include a very good discussion of many of these genes in the context of the published literature and DR.

As the authors discuss in the introduction, a few previous studies have been performed characterizing genomic or proteomic changes in DR. However, this study takes advantage of the latest microarray technology to give the most comprehensive analysis yet, with multiple novel insights, both at the level of functional gene classes and specific genes. Needless to say, the functional validation of these candidate genes will await future analysis, but the study succeeds in its goal to relate global gene expression changes to the progression of diabetic retinopathy.

**What next?:** Accept without revision

**Level of interest:** An article of importance in its field

**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