Reviewer's report

Title: Early over expression of messenger RNA for multiple genes, including insulin, in the Pancreatic Lymph Nodes of NOD mice is associated with Islet Autoimmunity

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Reviewer: Ciriaco Piccirillo

Reviewer's report:

1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Yes.
3. Are the data sound? Generally, yes.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data? In many instances, the analysis goes well beyond the data presented.
6. Are limitations of the work clearly stated? This is occasionally done.
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Not to my knowledge.
8. Do the title and abstract accurately convey what has been found? Yes.

Major Compulsory Revisions/ Minor Essential Revisions

There are a number of concerns (minor/major, no specific order), which the authors are advised to consider:

I have read attentively the manuscript submitted by Regnault et al. and found it to address important questions regarding the gene expression basis of autoimmunity and its impact on the immunoregulation of type 1 diabetes (T1D) in NOD mice.

This study explores, with modest success, the relative changes in gene expression occurring at 5 weeks of age, a timepoint where anti-insulin autoAb are detectable and known to discriminate potential sub-phenotypes in disease progression. The authors make some interesting observations indicating that a unique gene expression signature is associated with pre-diabetic NOD mice that positive or not for anti-insulin autoAbs.

The overarching aim of this study was to characterize the differential gene expression underlying this unique sub-phenotype in NOD. The identification of changes in gene activity underlying the onset and passage of one immunoregulatory checkpoint to another more destructive checkpoint is very
important is currently under-evaluated in the current literature.

Although innovative in its experimental model and studies well-performed, the manuscript provides no coherent mechanism for the clinical outcome observed. The major weakness of this study is the lack of mechanistic definition for the described gene signature, and its relationship to autoantibody formation, T cell responses or disease progression. Is there a causative role for this gene signature and the onset of autoAb production? Is there a causative role for this gene signature and the break in T cell tolerance which is believed to occur prior to autoAb production?

How do the authors exclude the possibility that the described gene signature is merely the consequence of the ongoing autoimmunity/inflammation? How does this differ between sites of no, low and high inflammation within the same mouse? Is this gene signature simply reflecting the clinical state that is being selected for the disease stratification?

Generally, the study by Regnault et al. article requires several revisions in order to clarify the various issues addressed.