Reviewer's report

Title: Decreased Semaphorin3A expression correlates with disease activity and histological features of rheumatoid arthritis

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Reviewer: maria Lopez-Armada

Reviewer's report:

Rheumatoid arthritis is a chronic autoimmune inflammatory disease that has an impact on many people. In the present manuscript “Decreased Semaphorin3A expression correlates with disease activity and histological features of rheumatoid arthritis” by Shu Takagawa et al., the authors investigated whether Semaphorin3A, that plays a regulatory role in immune responses, is expressed in synovial tissues and is associated with disease activity and the histological features of synovial tissues from RA patients. The authors show that a reduction of Sema3A mRNA expression in RA synovial tissues may contribute to pathogenesis of the RA. This is a potentially interesting study, but I have a few questions I would like to ask.

Major:

1. The experiments done are sound, clear and well presented. The main problem of the data is that they lack novelty. To this reviewer, Sema3A immunohistochemical studies are one of the most novel revelations in this study, however they are weakly demonstrated. Probably these results would be clearly explained with a semiquantitative score for each immunohistochemical staining in order to test the statistical significance of these data. The representative photomicrograph of all determinations should be maintained.

In relation, it has been reported before that synovial tissue specimens derived from OA and RA patients exhibited very low levels of Sema3A mRNA expression without no significative differences between OA/RA synovial tissue versus healthy controls and even lower difference between OA/AR (Alfonso Catalano, J Immunol 2010). An explanation about this discrepancy should be included.

In the same way, the quantification of serum level of sema3A in RA and OA patients would be interesting to strengthen the results showing that reduction of Sema3A expression in RA synovial tissues may contribute to pathogenesis of the disease.

2. How do you explain that VEGF expression levels did not exhibit a significant correlation with DAS28-CRP? And that the VEGF signal is so weak in RA synovial tissue? The authors should think of explaining in a satisfactory way the lack of correlation.

Minor:

1. Check which is the most common abbreviation of neuropilin, NRP (your
2. Include in the abstract that Sema3A was decreased in RA patient samples vs OA.

3. The medication of each OA patient should be included. Since medication may affect the expression levels of several molecules this information should be inserted.

4. Since the first evidence as to the key role for Sema3A in autoimmune arthritis was published by Alfonso Catalano (Alfonso Catalano, J Immunol 2010) and Vadasz et al (Vadasz et al, Arthritis Res Ther, 2012), these references should also be included the first time the implication of Sema 3A is mentioned in the exacerbation of autoimmune diseases (line 24).

5. Since in the first section of results (page 10) an evaluation of infiltration of immune cells has been performed, it would be better to also include in this section the results obtained with CD20.

6. Since recently, it has been reported that sema3A promotes regulatory T cells by enhancing IL-10 production and as the authors discussed how the reduction of Sema3A may abrogate the functions of regulatory T cells, thus allowing for the infiltration and focal aggregation of autoreactive lymphocytes in the sublining layer, it could be interesting to know the levels of IL-10 expression by immunohistochemistry in OA and RA synovial tissue as well as if a correlation between IL-10 levels and sema3A is present.

**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