Reviewer's report

Title: TRAIL Death Receptor-4, Decoy Receptor-1 and Decoy Receptor-2 expression on CD8+ T cells correlate with the disease severity in patients with rheumatoid arthritis

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Reviewer: Francis Chan

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Bisgin et al. analyzed the expression of TRAIL/TRAIL receptors on CD4+ and CD8+ T cells in Rheumatoid Arthritis patients. The authors identified that there is significant difference in the expression of TRAIL receptors DR4, DcR1 & DcR2 on both peripheral blood CD4+ and CD8+ T cells between RA patients and control individuals. Also, the authors found that the high expression of TRAIL receptors on CD8+ T cells positively correlated with the patients' DAS scores in RA patients. Hence, the authors concluded that monitoring TRAIL receptor profiles is of potential use in the prognosis of RA. However, the results are too preliminary and there are several major flaws with the manuscript.

Major comments:

1. The authors concluded in Fig. 1 that the CD4/CD8 ratios of RA patients were unchanged compared with the controls. However, the %CD4+ and % CD8+ cells were shown separately. The proper way to present the results will be to show the CD4/CD8 ratio for each individual in the sample pool.

2. There are a series of problems with the method and interpretation of results presented in Figs. 2 and 3. The authors’ results appear to show that RA patients express a higher level of TRAIL and TRAIL receptor expression in CD8+ cells than in CD4+ cells. Assuming that the majority of CD4- cells in Fig. 2B are CD8+ cells, why did the authors not detect an increase in TRAIL receptor expression in the CD4- population? This raises the concern of whether the proper staining controls (e.g. isotype antibody controls should be used for every sample) have been used. The authors are reminded that it is not unusual that basal staining of any receptors differs greatly from one individual to the other.

3. Even assuming that the FACS stainings were done properly, there are still issues with the results in Figs 2-3. For example, the authors claimed that TRAIL receptors and TRAIL expression in CD4+ T-cells were increased in RA patients. However, CD4+ T-cell expression of these markers was negligible and thus this reviewer questions the biological significance of any modest increases observed by the authors. In Fig. 2C and 3C, how was the fold increase determined? Was it by mean fluorescence or by percentage? The percentages of cells in the FACS plots should be shown and the panels for RA patient and control should be labeled properly. The poor presentation of the data renders interpretation of these results difficult.
Could any increases in TRAIL or TRAIL receptor expression observed in RA patients be simply a consequence of T cell activation? The authors should examine the activation status of the T-cells (e.g. by staining with CD25, CD69 etc.). Also, how does the expression of TRAIL and TRAIL receptors compare with other more well-studied markers for RA (e.g. IL-17)? This is especially important given the small sample size (20) that the authors used in the study.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.