Author's response to reviews

Title: TL1-A Can Engage Death Receptor-3 and Activate NF-kappa B in Endothelial Cells

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To
Editor
BMC nephrology

Thank you for your response on our submitted manuscript entitled “TL1-A Can Engage Death Receptor-3 and Activate NF-kappa B in Endothelial Cells” for publication in BMC nephrology. We appreciate the comments of the reviewers and would like to address some of the points raised as follows:

Reviewers 1:

1. The reviewer suggests that we carry out comparative studies to assess TL1A and DR3 expression and signalling using other endothelial cells such as microvascular versus venous versus arterial. We have done the expression of DR3 on human microvascular endothelial cells and pulmonary artery endothelial cells which showed similar expression pattern. In the current report we have analyzed IκBα degradation as an indicator for NF-κB activation. The level of receptor expression is directly related to the degree of IκBα degradation. Nuclear NF-κB localization is more difficult to quantify, making it less reliable as a quantitative marker of NF-kB activation, but we would be willing to undertake studies to determine its localization.

Reviewers 2:

1. The reviewer has indicated that TL1A is also known as VEGI. TL1A and VEGI are different molecules, which have different cellular effects. TL1A is a longer variant of TL1 (also called VEGI). TL1 (VEGI) was previously identified as an endothelium-derived factor that inhibited endothelial cell growth in vitro and tumor progression in vivo (Tan et al., 1997, Zhai et al. 1999a, Zhai et al. 1999b and Yue et al. 1999). We have added this point to the introduction section. The papers quoted by the reviewer (Grimaldo et al; Zhai et al., Chew et al and Yue et al) have all used either mouse or bovine aortic endothelial cells or mouse-bone marrow derived endothelial progenitor cells (EPC) and mainly described the role of VEGI as an inducer of apoptosis. These papers had shown DR3 with a shorter molecular weight than the full length molecule. DR3 has many isoforms thus may signal differently or bind to different ligands. We have also used human EPC, but did not find similar results. All the mentioned reports are different to our study as we have focused on the pro-inflammatory effect(s) of TL1A and DR3 in normal human endothelial cells, demonstrated using both in vivo studies using DR3 knock-out mice and in vitro studies using wild type and transfected endothelial cells.

2. We have added statistics to figure legends suggested by the reviewer.

We therefore feel that we are able to fully address all of the concerns raised by the reviewers.

Yours Sincerely

Dr Jun Wang