The review by Koizumi and Ishikawa is timely given the recent advances in the field, and well balanced. The authors may consider improving the manuscript by addressing the following minor points:

Heterogeneity of tissue Treg cells fat, gut, etc... should be discussed in greater detail, in particular given recent transcriptomic and single cell transcriptomic data addressing tissue adaptation (Miragaia Immunity 2019). The authors should also discuss how metabolism regulates Treg cell fate and function. Usually Wollenberg et al J Immunol 2011 is also cited as a founding reference regarding Tfr cells (together with ref 17 and 18 cited in the document). Some key differences between Tfr and Treg cells should be further discussed namely: Loss of CD25 upon terminal differentiation (Sakaguchi PNAS 2017), IL-2-independence (Botta Nature Immunol 2017), immature phenotype of Tfr cells in the blood vs tissue (Fonseca Sci Immunol 2017), unique repertoire characteristics (Maceiras Nature Commun 2017).

We appreciate the helpful reviewer’s comments to improve our manuscript. Considering the comments, we have made the following revisions.

1. In lines 59-64, we have mentioned functions of VAT-Treg and colonic Treg cells.
2. In lines 398-408, we have discussed roles of cellular metabolism in eTreg differentiation.
3. In lines 69 and 310, we have added the reference.
4. In lines 67-71, we have added key characteristics of Tfr cells according to the reviewer’s suggestion.