Reviewer's report

Title: Zinc Transporter Gene Expression is Regulated by Pro-Inflammatory Cytokines- A Potential Role for Zinc Transporters in Beta-Cell Apoptosis?

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Reviewer: shinya nagamatsu

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In this study, authors tried to elucidate the mechanisms underlying pro-inflammatory cytokines induced apoptosis in pancreatic beta cells. Because of accumulating evidence indicating the linkage between abnormal zinc homeostasis and development of diabetes, the authors examined the effect of the cytokines on gene expression involved in zinc homeostasis mainly by quantitative RT-PCR. The authors found that some of the tested cytokines down-regulated zinc transporters, and INS-1 cells over-expressing zinc transporter were more vulnerable to cytokine-induced apoptosis. From these results, the authors concluded that zinc transporter(s) would be responsible for the pro-inflammatory cytokine induced apoptosis in pancreatic beta-cells. Although this study might be the first study showing the relationship between cytokine-induced beta-cell apoptosis and regulation of gene expression involved in zinc homeostasis, this paper unfortunately does not contain enough data to support the authors’ conclusion.

Major points:

1) In order to check if pro-inflammatory cytokines could induce apoptosis in beta-cells through abnormality of zinc homeostasis, the authors should check whether the cytokine treatment would reduce the amount of zinc transporter proteins, because some of the tested mRNA levels reduced only slightly and I am not sure if the slight reductions of mRNA could really affect protein levels and zinc homeostasis in living beta cells.

2) The authors should provide the evidence that pro-inflammatory cytokines affect gene expressions specifically through cytokine receptors. Inhibitors of the signaling pathway or antibodies blocking cytokine effects should be used to confirm the authors’ conclusion.

3) The relationship between the amount of ZnT8 and pro-inflammatory cytokine induced apoptosis is obscure. If the authors think that ZnT8 is important for the cytokine-induced apoptosis, the authors should provide the evidence indicating molecular mechanism underlying its pathway.

Minor point:

1) Sample numbers should be described for all tables and figures. Values should be represented as average +/- S.D. or S.E.M.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

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.