

Dear Professor Stephen Cristol:

Find enclosed the electronic submission of the manuscript entitled "**SOMATOSTATIN PROTECTS PHOTORECEPTOR CELLS AGAINST HIGH GLUCOSE-INDUCED APOPTOSIS**" to be considered for publication in Molecular Vision.

A large number of cellular and molecular studies in experimental animals and patients with diabetic retinopathy (DR) have shown that retinal neurodegeneration is an early event in the pathogenesis of the disease. Somatostatin (SST) is one of the most important neuroprotective factors synthesized by the retina. It has been reported that SST levels decreased in parallel to retinal neurodegeneration at early stages of DR. In this study we found that the treatment with SST increased the cellular viability and prevented the induction of apoptosis (programmed cell death) in 661W photoreceptor-like cell line cultured under high glucose (HG)-supplemented medium; this effect being likely mediated through a decrease in the activation of caspase-8. Moreover, we detected an activation of calpain-2 associated to hyperglycemia-induced cell death, as well as an increase in PTP1B protein expression, both with a pattern of cleavage that was absent in the presence of SST. Also, our data have revealed that SST not only plays a role as an antiapoptotic factor, but also is involved in the activation of the IGF-IR and AKT survival pathway in both 661W cells and retinal explants. In conclusion, this study provides new mechanistic insights by which SST mediates the antiapoptotic and prosurvival effects during DR.

Looking forward to the Editorial decision of the manuscript and with our thanks for reviewing this work.



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INSTITUTO DE INVESTIGACIONES BIOMÉDICAS "ALBERTO SOLS", IIBM

Sincerely,

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