

Answering reviewer,

As the reviewer said, the main cause of Slow-transit constipation is the change of ICC, but the causes and final results of the change are still to be studied. Studies have shown decreased numbers of ICC and alterations in the number of myenteric plexus neurons expressing the excitatory neurotransmitter substance P in the gut wall of patients with this disorder. The recent London classification of gastrointestinal neuromuscular diseases also lists hypoganglionosis, inflammatory neuropathy and degenerative leiomyopathy as other causes of STC. That is to say, the pathogenesis of STC is very complex, and the study which has linked constipation to this signaling pathway and TNX protein is important.

At this stage, it was found that the expression level of the TNX protein was positively correlated with the TGF- $\beta$ /Smad signaling pathway in the colon tissues of STC patients. The direction of transdifferentiation can be inferred according to the morphological changes in ICC observed under electron microscopy and the patterns of specific expression factors after differentiation, such as  $\alpha$ -SMA in the smooth muscle phenotype. Furthermore, ICC transdifferentiation rather than apoptosis or death was verified. Then, based on the cytological animal experiments, the changes in the TGF- $\beta$ /Smad signaling pathway and the occurrence of STC under the two conditions were explored through gene knockout and overexpression of the TNX protein. Based on the result of Molecular Biology, we may find new and potential signal molecules to explain the reasons of colonic fibrosis and decreased motility.