

Integration of Enteric Neurons into Intestinal Model Systems*

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The enteric nervous system (ENS) is the extensive neural network that lines the intestinal tract. It contains roughly the same number of neurons as the spinal cord (100-300 million) and can function independently of the central nervous system. It is involved in many diseases affecting the gastrointestinal tract including irritable bowel syndrome and Hirschprung's disease, and diseases such as diabetes, multiple sclerosis, Parkinson's, and Alzheimer's, which can have intestinal components¹. Furthermore, it has been theorized that dysfunction in the intestine and ENS may be related to psychiatric disorders, such as in anxiety and depression². Intestinal symptoms are often present in children with autism, and it has been suggested that the intestinal microbiota may play a role in the disease^{3,4}. Animal studies have shown that mice lacking any intestinal bacteria (germ free) exhibit a higher response to stress and a lower level of social interaction than normal animals⁵. These findings indicate a possible connection between the central and enteric nervous systems in regards to behavior. Much more extensive research is required in these areas to determine the specific role and mechanisms of the ENS in disease, which facilitates the need for an intestinal model that includes enteric neurons.

Enteric neurons are located in close proximity to the layer of epithelial cells that line the intestine. These epithelial cells are continuously renewing and form a crypt-villus structure. At the bottom of the crypts are intestinal stem cells, which can differentiate into a number of phenotypes required for proper intestinal function. Neurons are found in the submucosa directly below the stem-cell containing crypts.⁶ Traditional models of the epithelial layer use immortalized cells derived from human colorectal adenocarcinoma cells (Caco-2)^{7,8}, thus cannot show changes in heterogeneous differentiation in response to changes in the extracellular environment. These models are typically only used for drug or metabolite transport studies. Recently, cultures derived from intestinal stem cells have been used, which provide a more realistic model of the healthy intestine and allow for differentiation into the multiple cell types found in the epithelial layer⁹. No current models of the intestine incorporate neurons, even though their close proximity to stem cells suggests their involvement in stem cell fate.

A tissue engineered model system combining intestinal stem cells and enteric neurons would provide a key platform for the study of the neural components of intestinal diseases. It would allow for investigations into how the intestinal environment affects neural signaling and how neurons influence differentiation of epithelial stem cells. It could also be used as an initial model for neuromodulation of the intestine for treatment of disease, where low frequency stimulation of afferent neurons has been shown to have beneficial effects in a variety of organs innervated by the autonomic nervous system¹⁰. This model could lead to developments in treatment and better understanding of autism, depression, irritable bowel syndrome, and many other diseases of the neurogastroenterological tract.

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