Bioengineered human pyloric sphincters with functional muscle and nerves

The gastrointestinal (GI) tract is a hollow tube that primarily functions to mediate the digestion of the food that we eat into forms of energy and nutrients that the cells and our body can use. The appropriate movement of food materials, a process known as peristalsis, is essential to digestion. The two cell types that are responsible for peristalsis are smooth muscle cells (SMCs) and neurons. The neurons provide a signal that tells the SMCs when to contract and relax at the appropriate time so that food materials are properly digested and passed in the right direction. There are a number of GI diseases that target the SMCs and neurons leading to inappropriate movement of food which results in severe negative health impacts. Due to the complexity associated with the interactions between GI muscle and nerve cells that must occur for proper peristalsis it is difficult to develop therapies that can recapitulate these activities. Therefore, bioengineering functional replacement organs may be one of the only options to successfully treat these types of GI disorders. The aim of this study

This study aims to bioengineer for the first time innervated human pylorus constructs utilizing autologous human pyloric sphincter SMCs and human neural progenitor cells (NPCs). Autologous SMCs and NPCs were co-cultured in dual layered hydrogels and formed concentrically aligned pylorus constructs. Innervated autologous human pylorus constructs were characterized through biochemical and physiologic assays to assess the phenotype and functionality of SMCs and neurons. SMCs within bioengineered human pylorus constructs displayed a tonic contractile phenotype and maintained circumferential alignment. Neural differentiation within bioengineered constructs was verified by positive expression of ?III-tubulin, neuronal nitric oxide synthase (nNOS) and choline acetyltransferase (ChAT). Autologous bioengineered innervated human pylorus constructs generated a robust spontaneous basal tone and contracted in response to potassium chloride (KCl). Contraction in response to exogenous neurotransmitter acetylcholine (ACh) and relaxation in response to vasoactive intestinal peptide (VIP) and electrical field stimulation (EFS) was also observed. Neural network integrity was demonstrated by inhibition of EFS-induced relaxation in the presence of a neurotoxin or nNOS inhibitors. Partial inhibition of ACh-induced contraction and VIP-induced relaxation following neurotoxin treatment was observed. These studies provide a proof of concept for bioengineering functional innervated autologous human pyloric sphincter constructs that generate a robust basal tone and contain circumferentially aligned SMCs which display a tonic contractile phenotype and functional differentiated neurons. These autologous constructs have the potential to be used as (1) functional replacement organs and (2) physiologically relevant models to investigate human pyloric sphincter disorders.

Publication

Bioengineered human pyloric sphincters using autologous smooth muscle and neural progenitor cells.

Rego SL, Zakhem E, Orlando G, Khalil B.

Tissue Eng Part A. 2015 Nov 12