An Intestinal Trojan Horse as Regenerative Therapy for Inflammatory Bowel Disease

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Background: Drug delivery system targeting to intestinal epithelium has a unique advantage in the treatment of Inflammatory Bowel Disease (IBD). The therapeutic efficacy is dependent on the on-site concentration of the drug at the intestinal mucosa. Nanoparticles (NPs), which can protect and release conjugated drugs on-site, have shown their ability to accumulate in the inflamed intestinal tissues. However, difficulties in optimizing the adhesion and systemic absorption of NPs have significantly limited their use in treatment of IBD. The strategy to use Trojan horse system for drug delivery can achieve improved biodistribution, increased local drug concentration, extended retention time, prolonged dosing intervals, and enhanced therapeutic efficacy. As the cell of origin, intestinal stem cells (ISCs) can build crypt-villus structure of intestinal epithelium in vitro. The isolated ISCs autonomously generate multicellular architecture in a highly stereotypical fashion which is reminiscent of normal intestine. They are good candidates as cell hosts to compose intestinal Trojan horse to treat IBD.

Methods: Primary ISCs were isolated from mice and expanded ex vivo. The harvested ISCs dramatically grew into cauliflower-like organoid structures that contained large numbers of separate crypts. These intestinal organoids developed the correct overall multicellular mucosal architecture with both Paneth cells and stem cells contained within the structures. As showed in Figure 1, a rationally designed “Trojan horse” delivery system using a combination of ISCs and NPs offers a novel and potentially advantageous approach to treat of IBD.

Results: When the ISCs were incubated with DNA-functionalized gold NPs, the particles were then absorbed by ISCs and accumulated in the lumen of organoids to form a Trojan horse. The harvested intestinal Trojan horse dramatically grew into cauliflower-like organoid structures that contained large numbers of separate crypts. These intestinal Trojan horse developed the correct overall multicellular mucosal architecture with stem cells contained within the structures (Figure 2). The NPs showed negligible adverse effect on ISCs growth and demonstrated good retention within organoids for a period of 7 days (data not shown). These data suggest that fabrication of a
“Trojan horse” delivery system combining ISCs and nanoparticle therapy is a potentially novel treatment for intestinal mucosal disruption seen with IBD patients.

Conclusions: As a new conception in drug delivery, the Trojan horse system with the synergy of nanotechnology and host cells can achieve better therapeutic efficacy to IBD. Here, we demonstrated the feasibility to encapsulate DNA-functionalized gold NPs into primary isolated ISCs to form a Trojan horse for regenerative therapy of IBD. We believe this proof-of-concept intestinal Trojan horse will have a wide variety of applications in diagnosis and therapy for IBD and other enteric disorders and diseases.