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Review article

Modeling infectious diseases and host-microbe interactions in gastrointestinal organoids

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ABSTRACT

Advances in stem cell research have allowed the development of 3-dimensional (3D) primary cell cultures termed organoid cultures, as they closely mimic the *in vivo* organization of different cell lineages. Bridging the gap between 2-dimensional (2D) monotypic cancer cell lines and whole organisms, organoids are now widely applied to model development and disease. Organoids hold immense promise for addressing novel questions in host-microbe interactions, infectious diseases and the resulting inflammatory conditions. Researchers have started to use organoids for modeling infection with pathogens, such as *Helicobacter pylori* or *Salmonella enteritica*, gut-microbiota interactions and inflammatory bowel disease. Future studies will broaden the spectrum of microbes used and continue to establish organoids as a standard model for human host-microbial interactions. Moreover, they will increasingly exploit the unique advantages of organoids, for example to address patient-specific responses to microbes.

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1. Introduction

The human gastrointestinal tract is the prime interface for interactions with microorganisms. The healthy gastrointestinal tract is a finely tuned ecosystem of trillions of organisms, predominantly bacteria but also including bacteriophages, viruses and eukaryotes, collectively termed the microbiota. Food intake constantly introduces new microorganisms that can threaten this equilibrium. Perturbations in host-microbe interactions can lead to severe pathologies, such as inflammatory bowel disease (IBD), gastric ulcers and gastric cancer (reviewed in Abraham and Medzhitov (2011) and Suerbaum and Michetti (2002)), and therefore homeostatic mechanisms aim to minimize invasions of pathogens whilst maintaining beneficial interactions with the microbiota. These pathologies affect large numbers of people, with

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globally more than 700,000 deaths per year caused by gastric cancer alone, rendering the study of these diseases of prime importance (Ferlay et al., 2015). Recent advances in stem cell research have allowed the development of new model systems, termed "organoids" for their striking resemblance to organs. Organoids can be grown which represent many different organs, including the brain, liver, pancreas, lung, esophagus, stomach, small intestine and colon (reviewed in Clevers (2016)). Recent reviews have highlighted the general features of organoids (Clevers, 2016; Fatehullah et al., 2016; Huch and Koo, 2015; Lancaster and Knoblich, 2014) and also focused specifically on gastrointestinal stem cells and organoids (Dedhia et al., 2016; Werner et al., 2016). In this review, gastrointestinal organoids will be discussed with respect to their use in studying infectious diseases, host-microbe interactions and inflammation.

2. Gastrointestinal organoids and their advantages for studying host-microbe interactions

Organoids can be derived from two sources: (i) pluripotent stem cells (PSCs) or (ii) adult stem cells (ASCs) (Fig. 1). PSCs can be obtained from embryos (embryonic stem cells, ESCs) or by reprogramming somatic cells (induced pluripotent stem cells, iPSCs). ASCs reside in self-renewing tissues, such as the gastrointestinal tract, and either constantly renew the epithelium or can be activated to repair tissue upon damage. Both PSCs and ASCs have tremendous regenerative capacity, and in the past decade researchers have utilized increased understanding of the niche factors that favor stem cell maintenance to grow both types *in vitro* into organoids (reviewed in Clevers (2016) and Lancaster and Knoblich (2014)). In 2009, Sato and colleagues isolated intestinal crypts and the stem cells residing therein, placed them in a mouse sarcoma-derived extracellular matrix and supplemented the culture with three factors: the Wnt agonist R-spondin (RSPO), epidermal growth factor (EGF) and noggin (NOG), an inhibitor of bone morphogenetic protein (BMP). Under these conditions, intestinal stem cells proliferate and initially form small cysts which grow further into budding structures that can be expanded apparently without limits by splitting and re-seeding (Fig. 1). The cultures contain highly polarized, differentiated cells of the intestinal lineages and exhibit an astonishing capacity to self-organize into domains that harbor the different cell types of both the crypt and villus domains (Sato et al., 2009). Mouse gastric organoids similarly reproduce the gastric epithelium *in vitro* (Barker et al., 2010). Following this, gastrointestinal organoids derived from human ASCs or PSCs were described soon after (Sato et al., 2011; McCracken et al., 2011, 2014; Bartfeld et al., 2015), so opening new avenues for infection research.

Classically, infection research uses 2D cultures of cancer cell lines or animal models (Fig. 2), although both of these systems have their drawbacks. Standard transformed cancer cell lines often

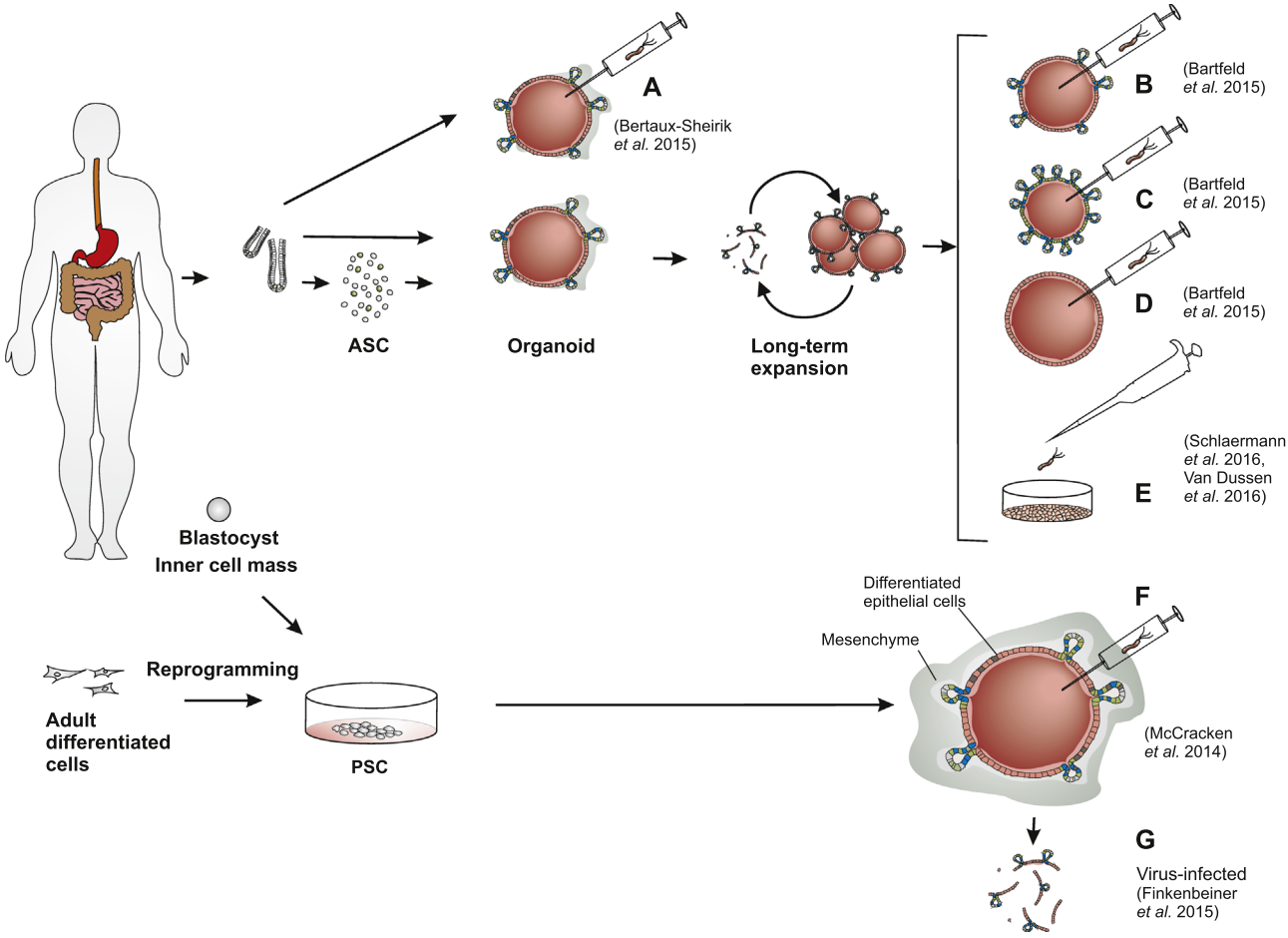

Fig. 1. Gastrointestinal organoids can be grown from adult stem cells (ASCs) or pluripotent stem cells (PSCs). After initial seeding, some ASC-derived cultures contain a mesenchymal compartment (A). Long-term culture of ASC-derived, purely epithelial organoids provides infection researchers with unlimited access to primary cells (B-E). Long-term human cultures contain many different lineages of the original tissue (B) and can be directed into specific lineages (C/D) (Bartfeld et al., 2015; Sato et al., 2011). PSC-derived organoids contain a mesenchymal compartment and differentiated epithelial cells (F). Bacteria are commonly microinjected into organoids (A, B, C, D, F), but can also be added into the supernatant of organoid-derived 2D cultures (E). Viral infection has been established using mechanical disruption (G). Examples of studies using human organoids for infection are given in the figure; please see main text for details and examples for mouse organoids.