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A 3d Intestine-On-Chip Model Allows Colonization with Commensal Bacteria to Study Host-Microbiota Interaction

Authors : Michelle Maurer, Antonia Last, Mark S. Gresnigt, Bernhard Hube, Alexander S. Mosig

Abstract : The intestinal epithelium forms an essential barrier to prevent translocation of microorganisms, toxins or other potentially harmful molecules into the bloodstream. In particular, dendritic cells of the intestinal epithelium orchestrate an adapted response of immune tolerance to commensals and immune defense against invading pathogens. Systemic inflammation is typically associated with a dysregulation of this adapted immune response and is accompanied by a disruption of the epithelial and endothelial gut barrier which enables dissemination of pathogens within the human body. To understand the pathophysiological mechanisms underlying the inflammation-associated gut barrier breakdown, it is crucial to elucidate the complex interplay of the host and the intestinal microbiome. A microfluidically perfused three-dimensional intestine-on-chip model was established to emulate these processes in the presence of immune cells, commensal bacteria, and facultative pathogens. Multi-organ tissue flow (MOTiF) biochips made from polystyrene were used for microfluidic perfusion of the intestinal tissue model. The biochips are composed of two chambers separated by a microporous membrane. Each chamber is connected to inlet and outlet channels allowing independent perfusion of the individual channels and application of microfluidic shear stress. Human umbilical vein endothelial cells (HUVECs), monocyte-derived macrophages and intestinal epithelial cells (Caco-2) were assembled on the biochip membrane. Following 7 – 14 days of growth in the presence of physiological flow conditions, the epithelium was colonized with the commensal bacterium Lactobacillus rhamnosus, while the endothelium was perfused with peripheral blood mononuclear cells (PBMCs). Additionally, L. rhamnosus was co-cultivated with the opportunistic fungal pathogen Candida albicans. Within one week of perfusion, the epithelial cells formed self-organized and well-polarized villus- and crypt-like structures that resemble essential morphological characteristics of the human intestine. Dendritic cells were differentiated in the epithelial tissue that specifically responds to bacterial lipopolysaccharide (LPS) challenge. LPS is well-tolerated at the luminal epithelial side of the intestinal model without signs of tissue damage or induction of an inflammatory response, even in the presence of circulating PBMC at the endothelial lining. In contrast, LPS stimulation at the endothelial side of the intestinal model triggered the release of pro-inflammatory cytokines such as TNF, IL-1β, IL-6, and IL-8 via activation of macrophages residing in the endothelium. Perfusion of the endothelium with PBMCs led to an enhanced cytokine release. L. rhamnosus colonization of the model was tolerated in the immune competent tissue model and was demonstrated to reduce damage induced by C. albicans infection. A microfluidic intestine-on-chip model was developed to mimic a systemic infection with a dysregulated immune response under physiological conditions. The model facilitates the colonization of commensal bacteria and co-cultivation with facultative pathogenic microorganisms. Both, commensal bacteria alone and facultative pathogens controlled by commensals, are tolerated by the host and contribute to cell signaling. The human intestine-on-chip model represents a promising tool to mimic microphysiological conditions of the human intestine and paves the way for more detailed in vitro studies of host-microbiota interactions under physiologically relevant conditions.

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