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Review
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Functional Cell Models of the Gut and Their Applications in Food Microbiology — A Review

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Abstract

Animal experimentation has a long tradition for risk assessment of new drugs before they reach the clinic. To reduce expensive animal experimentation, attempts have been made to build inexpensive and convenient intestinal functional cell models to study toxicity and bioavailability of new substances along with providing relevant models to study interactions between the host, pathogens and intestinal microflora. We review the available cell lines and models of the intestine and their potential uses. Tumor derived cell lines such as Caco-2, T84 and HT-29 are widely used despite many drawbacks, which are discussed with respect to complexity of the gut, where various cell types interact with commensal microbiota and gut-associated lymphoid tissue. To address this complexity, 3D models of human and animal gut represent a promising *in vitro* system to mimic *in vivo* situation without the use of transformed cell lines.

Keywords: Cell model; Gut; Probiotics; Intestine; Pathogens; Risk assessment

Introduction

The need for appropriate intestinal cell lines has been recognised in the past decade to find a good *in vitro* model of the intestine for studying gut interactions, nutrition, toxicology and food microbiology[1]. There are few intestinal models available, although their quality and reliability are questionable because of the inappropriate experimental layout and mainly tumorigenic cell lines, which are usually used to build the models.

Intestinal models are of great interest to food and pharmaceutical industry, principally are toxicological and bioavailability tests of newly developed food ingredients and drugs inevitable for bringing products to the market. In food industry, risk assessment regarding the safety and efficacy of probiotics and new functional foods is an open issue, since food safety is of utmost concern in the western world[2].

Models of intestine are essential for research into enteric pathogens. The mechanisms of interactions between foodborne pathogens, mammalian host and intestinal microflora including mechanisms of microbial attachment and cross-talk with host epithelium and preventive and curative effects of probiotic bacteria remain largely unknown. The present review summarises available models of intestine. First we describe general functions and histology of the intestine. This information is necessary to understand drawbacks and advantages of the models, which are discussed with respect to the complexity of the gut and the cell lines used *in vitro*. Special focus is on our own studies on functional cell models of the human and animal gut[3].

The intestine

The intestine is an important internal environment where a number of processes occur in order to nourish the body and protect it against the enteropathogens or harmful substances entering the gut. The small intestine is the longest section of the digestive tube and consists of three segments forming a passage from the pylorus to the large intestine[4]: Duodenum, Jejunum (considered to be roughly 40% of the small gut in human, but closer to 90% in animals) and Ileum. The total length of the small intestine is roughly 6 m in humans. Although precise boundaries between these three segments of bowel are not observed grossly or microscopically, there are histological differences among them.

Histology of the intestine

The luminal face of the gastrointestinal tract comprises several layers which interact with the luminal contents. The mucosal epithelium, lamina propria, glycocalyx and secreted mucus each make a contribution to a "barrier function".

The gastrointestinal mucosa forms an interface [5] between the body and the lumenal environment which not only contains nutrients, but potentially damaging microorganisms and toxins. The challenge is to allow efficient transport of nutrients across the epithelium while rigorously excluding passage of harmful molecules and pathogens. This is a complex and dynamic process including both transcellular and paracellular pathways. The structure of the mucosa is defined by sheets of epithelial cells), connected laterally by tight junctions, which regulate the paracellular spaces and thereby establish the tight epithelia. Integrity of epithelia is critical since toxins and microorganisms that are able to breach the single layer of epithelial cells have unimpeded access to the systemic circulation[6].

Cell models of the gut

As described above, *in vitro* cell models of the gut should functionally resemble the *in vivo* situation. Since the gut is a complex system with many interacting cell types and the microbiota, models should take into consideration as many of these factors as possible.

Expression of tight junction proteins is necessary for the formation of epithelial barrier, integrity and polarity. Primary epithelial cells *in vivo* develop a tightly packed selectively permeable membrane with measurable transepithelial resistance (R_T, also abbreviated as TER)

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and V_T (transepithelial potential difference); *in vitro* epithelial cells that polarise should develop these features when grown on microporous membrane. Epithelial cells in combination with other cell lines (if applied in the model) should respond to environmental factors like cytokines and inflammatory molecules. Moreover, the origin of the cell lines is important since cancerogenic cells have different glycosylation , their proliferation and behaviour under environmental stimuli can be significantly altered. Characterization of cell markers, receptors and expression of functionally important proteins is also important for the elucidation of cell line functionality and determination of the differentiation or activation status [7]. Based upon this information, models can be built to study particular situations. Secretion of mucins from epithelial cells helps to distinguish mucin producing cells from normal enterocytes. Cytokeratins are characteristic epithelial cytoskeletel proteins and are involved in infections by pathogens. Alkaline phosphatase is involved in epithelial cell differentiation and maintanance of gut barrier [8].

When immune cells are used in the models, activation status is determined by the level of endocytosis, expression of MHC II, coactivator (CD80/86) and other molecules. Immature non-activated cells are useful in determination of the effects microbes could have when applied to the system; activated cells should be used to study inflammatory disorders in the intestine.

In most of the *in vitro* studies of the gut, human colon tumorigenic cell lines Caco-2, T84 and HT-29 have been widely used for attachment assays and mechanistic studies. The brief description of available cell lines of the intestinal epithelial cells it can help food microbiologists to choose the ones that are of most relevance to their studies [9].

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