A Review on *In vitro* Cell Culture Model for Bacterial Adhesion and Invasion: From Simple Monoculture to Co-Culture Human Intestinal Epithelium Model

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Authors’ contributions

This work was carried out in collaboration among all authors. Author NIH wrote the original draft. Author SASM managed supervision and review and editing. Authors RI and NH administered the project. Authors NA and LKO managed the resources. Authors NAJ and MNAM play role in funding acquisition. All authors read and approved the final manuscript.

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ABSTRACT

**Aim:** This paper reviews the different *in vitro* models of human intestinal epithelium that have been utilized for studying the adhesion and invasion properties.

**Problem Statement:** The cell adhesion and invasion are the key mechanisms of bacterial pathogenicity that determines their possible routes of transmission. Numerous investigations
related to the adhesion and invasion ability of bacterial isolates have been reported on monoculture human intestinal cells. However, the use of monoculture cells has several major disadvantages, such as the inability to reproduce the complex structure that defines the intestine and the inability to accurately predict the mechanism of bacterial adhesion and invasion.

**Approach:** Co-culture models of human intestine have been developed as an alternative to improve the monoculture epithelial cell for adhesion and invasion studies, which provide more flexibility and overcome some of the limitations

**Conclusion:** With the use of diverse *in vitro* approach, it could provide thorough information on different ability of bacterial adhesion and invasion and it could help to clarify the intricacy of host-pathogen interactions that underpin bacterial pathogenesis.

Keywords: Human intestinal cell lines; bacterial adhesion; bacterial invasion; monoculture; co-culture Caco-2/HT29-MTX.

1. INTRODUCTION

The intestinal adhesion and invasion of the epithelium are important stages in initiating the bacterial pathogenesis, as the virulent effects of intestinal pathogens rely on their ability to colonize and invade the intestinal mucosa [1-3]. Hence, the entry of bacteria into epithelial cells is essential for its pathogenicity, intracellular replication, spread to other tissues, and cause intestinal disease [4-8]. The ingested bacteria undergo the infection process in both intestinal phagocytic and non-phagocytic cells, which include bacterial adherence, colonisation, invasion, and propagation [9-10].

Due to the scarcity of accurate and specific experimental models, the molecular complexity of host-pathogen interactions in many infectious diseases, especially in humans, remains poorly understood [11]. As a result, a systematic cell culture method for examining the adhesion and invasion capabilities of bacteria is critical for understanding this host-pathogen interaction *in vitro*. Various intestinal epithelium models have been used to investigate the potential for bacterial pathogenicity via adhesion and invasion. The mucosa surface of the intestinal epithelium is a complex environment consisting of several cell types which are enterocytes, goblet cells, Paneth cells and endocrine cells. However, absorptive and goblet cells are the two main constituents of the intestine [12-13]. The Caco-2 cell lines are derived from intestinal absorptive, whereas HT29 and HT29-MTX are known as goblet cells. Caco-2 cells are originated from colon carcinoma that can be differentiated into enterocytes-like cells [14-16]. This monoculture is often used as *in vitro* model for studying cell adhesion and invasion [5,9,17]. However, the use of Caco-2 and other monocultures of epithelial cells has their own disadvantage. As no mammalian system consists of a single cell-type, these monocultures may not accurately depict intestinal physiology *in vivo*, and they do not closely simulate the composition of the normal epithelial layer which contains a variety of cell types [18-20].

Hence, in order to attain better physiological conditions, co-cultivation of two cell lines will therefore provide a model consisting of two different cell types that predominately represented in normal human intestinal epithelium, namely enterocytes and goblet mucus-secreting cells. Thus, this review aims to discuss the establishment of an *in vitro* co-culture cell model completely resembles the small intestinal epithelial layer, based on intestinal enterocytes (Caco-2) and mucus-secreting goblet cells (HT29 and HT29-MTX), to evaluate the adhesion and invasion capabilities of pathogenic and non-pathogenic bacteria.

2. MONOCULTURE OF HUMAN INTESTINAL CELLS FOR ADHERENCE AND INVASION STUDIES

The gut mucosa, which is lined with epithelial cells, is thought to be the most outer defence barrier, preventing microbes and endotoxins from reaching systemic organs and tissues [21]. Thus, studies for adherence and invasion properties of microorganisms have been carried out using single cells, also known as monocultures of human epithelial cell lines such as Caco-2 (non-mucus secreting), HT29 (low mucus secreting) and HT29-MTX (high mucus secreting) (Table 1).

Caco-2 cells are derived from human colon carcinoma and are employed as a model for mature human enterocytes since they can...
express protein features of both colonocytes and small intestinal enterocytes immediately after confluence [27,33,43]. This cell line, however, is classified as non-mucus producing cell. Caco-2 cell lines have been extensively utilized as a model to examine in vitro adhesion and invasion ability of bacteria such as Salmonella enterica, Listeria monocytogenes (L. monocytogenes), Escherichia coli (E. coli), Campylobacter jejuni (C. jejuni) and probiotics.

Table 1. Studies of bacterial adhesion and invasion using the three most common monoculture of human intestinal cells

<table>
<thead>
<tr>
<th>Monoculture</th>
<th>Bacterial Strains</th>
<th>Adhesion Study</th>
<th>Invasion Study</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caco-2</td>
<td>Salmonella enterica</td>
<td>+</td>
<td>+</td>
<td>4,22-27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>17,29-31</td>
</tr>
<tr>
<td></td>
<td>Listeria monocytogenes</td>
<td>+</td>
<td>+</td>
<td>23,28,32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>+</td>
<td>+</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>33-34</td>
</tr>
<tr>
<td></td>
<td>Campylobacter jejuni</td>
<td>-</td>
<td>+</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Probiotics</td>
<td>+</td>
<td>-</td>
<td>2,33,35-36</td>
</tr>
<tr>
<td>HT29</td>
<td>Salmonella enterica</td>
<td>+</td>
<td>+</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Listeria monocytogenes</td>
<td>+</td>
<td>+</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>+</td>
<td>-</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Campylobacter jejuni</td>
<td>+</td>
<td>+</td>
<td>38-39</td>
</tr>
<tr>
<td></td>
<td>Probiotics</td>
<td>+</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>HT29-MTX</td>
<td>Salmonella enterica</td>
<td>+</td>
<td>+</td>
<td>27,42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>+</td>
<td>+</td>
<td>42</td>
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<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Campylobacter jejuni</td>
<td>+</td>
<td>+</td>
<td>38-39</td>
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<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Probiotics</td>
<td>+</td>
<td>-</td>
<td>36,41</td>
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</table>
HT29 cells are likewise derived from colon carcinoma, but they are less differentiated than Caco-2 and have a small proportion of mucus secreting cells [27,37,43]. Several studies have been published comparing the adhesion and invasion abilities of HT29 and Caco-2 cell lines. Duary et al. [35] evaluated the adhesion properties of selected indigenous probiotic Lactobacillus strains on Caco-2 and HT29 cells. Both cell line showed a similar trend in adhesion property of the test cultures. This finding agrees with Moroni et al. [32] on the adhesion of L. monocytogenes. Their findings revealed no significant differences in adhesion between Caco-2 cells and HT29 cells, but it is of interest to note that the level of invasion was higher with HT29 cells as compared to Caco-2 cells. In contrast to the adhesion findings from Duary et al. [35] and Moroni et al. [32], Sharma and Kanwar [2] discovered that the percent of adhesion for lactic acid bacteria isolated from fermented to Caco-2 cells was lower than that of HT29 cells.

Due to the small proportion of mucus secreted by HT29 cells, the treatment of HT29 with methotrexate results in a persistent sub-population of mucus secreting cells (HT29-MTX) that have a differentiated goblet cell-like phenotype and release mucin similar to small and large intestine [27,33]. For this reason, HT29-MTX cells have been chosen in various investigations to study bacterial adherence and invasion. Burkholder et al. [42], for example, demonstrated that Salmonella Javiana adhered to HT29-MTX cells at similar levels to E. coli but had considerably more invasion than E. coli.

In particular, the majority of researchers conclude that the presence of mucus plays an important role as protective component of the normal intestinal epithelium and contributes to the pathogen adherent and invasion. Several studies have been conducted to compare the adhesion and invasion capability between HT29 and HT29-MTX cell lines. Rodrigues et al. [38] developed an experiment in 2018 to test the adhesion and invasion of C. jejuni strain towards both HT29 and HT29-MTX. They discovered that the presence of mucus affected the capacity of C. jejuni strains to adhere. In 2016, Pilchová et al. [41] demonstrated the potential probiotic effect of Carnobacterium strains to attenuate the pathogenesis L. monocytogenes. The number of probiotic strains that adhered to HT29-MTX was substantially larger than the number of strains that adhered to HT29. Their report was attentively followed the adherent trend of C. jejuni, which showed higher numbers adherent to HT29-MTX cells than the HT29 cells [40]. These results are consistent with those of Alemk et al. [39], who found 10-fold greater levels of C. jejuni infection in HT29-MTX than in HT29 cells. On the other hand, intestinal mucus, had no effect on E. coli colonization in HT29 and HT29-MTX, according to Kerneis et al. [37]. The level of bacterial adherence to the mucus secreting intestinal cells HT29-MTX also appeared to be higher than attachment to enterocyte-like Caco-2 cells [36].

From literature, there are few studies that comparing the pattern of bacterial adhesion and invasion using all three types of intestinal monoculture that have been discussed in this review. Gagnon et al. [27] studied the suitability of the mucus-secreting HT29-MTX cell model to test adhesion and invasion of Salmonella strains and compared with data obtained with the more commonly used Caco-2 and HT29 models. They found that Salmonella adhesion and invasion were more effective in HT29-MTX than in non- and low-mucus producing Caco-2 or HT29 cells, respectively. They also suggested that Salmonella might potentially permeate the protective mucus layer and subvert the mucus to facilitate invasion. Similarly, in 2019, Li et al. [30] investigated the function of MUC1 (highly expressed mucins in stomach and intestinal tract) during the invasion of Salmonella to Caco-2, HT29 and HT29-MTX cell lines. According to the results, Caco-2 and HT29 had lower level of invasion than HT29-MTX cells. They also discovered that, as compared to HT29-MTX, Caco-2 and HT29 cells express comparatively low levels of MUC1. Therefore, these findings prove that mucus aids Salmonella adherence and invasion of. The presence of mucus by HT29-MTX cells, in particular, is thought to play crucial function as protective component of the normal intestinal epithelium, enhancing pathogen adherence and invasion.

Since adhesion and invasion are the most important stages in bacterial pathogenesis, an anti-adhesion and anti-invasion therapies are needed as therapeutic strategies or antibiotic therapies to prevent bacterial adhesion/invasion to the host or detachment from the tissues at the early stages of infection [44-46]. For example, designing a synthetic peptide that mimic the structure of pilus protein will inhibit pilus
assembly (pilicides) [47]. This approach is a key strategy for preventing adhesion of *E. coli* and *Salmonella* that used the pili for initiating their virulence factor [48]. Furthermore, the adhesion of pathogenic bacteria could also be disrupted some dietary supplements that acts as receptors analogs [44, 46]. Human milk which rich in oligosaccharides and Bovien Muc1 derived from cow milk are proven to inhibit adherent of *E. coli* and *Salmonella* to the Caco-2 cell lines [49-51]. Aside from that, several compounds with anti-invasion properties were discovered to be able to inhibit adhesion and invasion in monoculture Caco-2 cells. Citrus extracts effectively reduced *Salmonella* and *L. monocytogenes* adhesion and invasion to Caco-2, according to Barbosa et al. [23]. Barzelighi et al. [24] investigated whether the presence of azurin reduced *Salmonella* and *E. coli* adhesion and invasion toward Caco-2 cells. Mechesso et al. [4] demonstrated that the presence of ginsenoside Rg3 reduced *S. Typhimurium* adhesion and invasion by two-fold when compared to those lacking Rg3. Similarly, the adherence of *S. Typhimurium* was reduced by 50-70%, and the invasion was inhibited in the presence of methyl gallate [22] and Coenzyme Q0 [25].

In addition, probiotic bacterial strains can be considered as one of the anti-adhesion therapies as they compete with the pathogens for vital growth nutrients [52]. In 2019, Śliżewska and colleagues [28] investigated the competition between probiotics and pathogenic bacteria. They discovered that probiotics reduced the adherence of pathogenic *Salmonella Typhimurium* (*S. Typhimurium*), *Salmonella Enteritidis* (*S. Enteritidis*), and *L. monocytogenes* to Caco-2 cells by up to 60%. The findings are similar to those of Tuo et al. [34], who discovered that probiotic *Lactobacillus* strains prevent *E. coli* from binding to Caco-2 cells. The anti-invasive ability of probiotics strains was also examined on *Salmonella enterica*, *L. monocytogenes*, *E. coli* and *C. jejuni*. The strains were found to have reduced invasive capacity of *S. Typhimurium* [29], *S. Enteritidis*, *L. monocytogenes*, *E. coli* and *C. jejuni* [31] with varying degrees depending on the bacterial species. The ability of probiotics as both anti-adhesion and anti-invasion were also proved to be effective against *S. Typhimurium* and *S. Enteritidis* towards Caco-2 cells [26].

3. CO-CULTURE HUMAN INTESTINAL MODEL FOR ADHERENCE AND INVASION STUDIES

It is undoubted that one single cell line or monoculture does not adequately represent the human intestine. Consistent with the hypothesis that good adherence and invasion especially in the presence of mucus, the goblet cell has been successfully used to co-cultured with Caco-2 cells as an alternate technique to imitate *in vivo* human intestinal physiology. This consideration has led to a method for bridging the gap between simple *in vitro* models and *in vivo* biological process [12,53].

The co-cultures previously proposed in literature for evaluating the mechanism of bacterial adhesion and invasion were obtained by using mucus secreting HT29 subclones which is HT29-MTX to generate a mixed population of enterocytes and mucus secreting cells (Caco-2/HT29-MTX) resembling as closely as possible the intestinal epithelium (Table 2).

Table 2. Caco-2/HT29-MTX co-culture model for bacterial adhesion and invasion

<table>
<thead>
<tr>
<th>Description of study</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Identification of potentially effective synbiotics for probiotics adherence towards intestinal mucosa</td>
<td>1</td>
</tr>
<tr>
<td>Evaluation of the effect of mucus layer by the presence of <em>Lactobacillus rhamnosus</em> and <em>E. coli</em></td>
<td>54</td>
</tr>
<tr>
<td>Effect of selected milk and milk protein fractions on the adhesion ability of selected <em>Lactobacilli</em></td>
<td>12</td>
</tr>
<tr>
<td>Effect of acid-hydrolyzed milk on the adhesion ability of probiotic strains</td>
<td>55</td>
</tr>
<tr>
<td>Effects of prebiotic fructooligosaccharides (FOS) on the adherent ability of <em>E. coli</em> (Nissle 1917)</td>
<td>56</td>
</tr>
<tr>
<td>Effects of iron concentration on <em>Salmonella</em> adhesion, invasion and cellular immune responses</td>
<td>53</td>
</tr>
<tr>
<td>Adhesion ability of probiotic, commensal and pathogenic bacterial strains</td>
<td>33</td>
</tr>
</tbody>
</table>
Bacterial adhesion is influenced by surface characteristics, which are influenced by the structure and composition of the cell wall [1,12]. Krausova et al. [1] aimed to identify potentially effective symbiotics by analyzing the adherence of bacterial strains to a Caco-2/HT29-MTX co-culture cell line model that mimicking the intestinal epithelium. They reported high adherence for all strains tested after integrating HT29-MTX cells for mucin synthesis in this model. Several intestinal bacteria have been found to be able to permeate the mucus glycan and use it as a carbon source and attachment site [57-58].

However, their results were in conflict with those obtained by Laparra and Sanz [33], who used similar model and found very low adherence by lactobacilli and bifidobacteria. They differentiated the adhesion pattern of probiotic, commensal and potentially pathogenic bacteria (E. coli and L. monocytogenes) on both Caco-2 monoculture and co-culture of Caco-2/HT29-MTX. Their findings demonstrated that bacterial adhesion values on Caco-2 monoculture were higher than those in Caco-2/HT29-MTX co-culture, implying that a mucin layer formed by HT29-MTX cells could cover putative recognition components in Caco-2 plasma membrane, rendering them inaccessible to bacteria. Above findings are supported by the fact that the presence of mucus in the model system is significant for estimating intestinal permeability as the mucus acts as a barrier against the absorption of certain compounds [54,59]. The lack of mucus in Caco-2, on the other hand, permits easy access to the cells, leading to an overestimation of their permeability [13]. Consequently, the presence of intestinal mucus may significantly affect adherence, as observed in studies with cell lines that secrete or do not secrete mucus [1].

With the goal of providing an epithelial monolayer covered with mucus that better mimicked the situation in vivo, Dostal et al. employed the Caco-2/HT29-MTX co-culture model to explore the interactions of the enteropathogen S. Typhimurium through adhesion and invasion towards intestinal cell under different iron concentrations. Under high iron conditions, Salmonella adhesion was increased by 8-fold compared to normal iron conditions while invasion was not significantly lowered. On the other hand, in low iron conditions, the invasion of Salmonella was significantly increased as compared to normal iron condition. Meanwhile, in 2020, Lim et al. [54] used Caco-2/HT29-MTX co-culture as in vitro model of gastrointestinal tract to determine how the mucus layer was affected by the presence of Gram-positive, commensal Lactobacillus rhamnosus (L. rhamnosus) and Gram-negative, opportunistic E. coli. They discovered that, when these bacteria were present and adhered to cells, the secretion of neutral and acidic mucins was altered, and the thickness of the mucus layer was enhanced. In contrast to Caco-2/HT29-MTX, monoculture of Caco-2 cells do not produce mucin and only displayed background levels of staining. However, co-culture of Caco-2/HT29-MT showed more intense staining following adhesion of L. rhamnosus and E. coli compared to that of unexposed cells.

Similarly, believing that co-cultures of Caco-2/HT29-MTX are better representation of the complex mucosa, Volštatóvá et al. reported their research in 2016 [55] and 2016 [60] regarding the adherence of probiotic Lactobacillus strain. All strains tested in their study (Lactobacillus plantarum, Lactobacillus gasseri and Lactobacillus casei) were all shown to adhere effectively to the co-culture cell lines. Kim et al. [56] also studied the adhering ability of probiotics to the identical Caco-2/HT29-MTX model used herein since the ability of bacterial strains to adhere to intestinal epithelium cells was regarded as an important selection criterion for probiotics. They discovered that prebiotic fructooligosaccharides reduced the ability of probiotic E. coli (Nissle 1917) to adhere to co-cultures Caco-2/HT29-MTX.

It is of interest to note that until now, no research on the use of co-culture Caco-2 and HT29 cells (low mucus production) to study bacterial adhesion and invasion has been published. Mostly, the co-culture model of Caco-2/HT29 were used to study intestinal permeability of the nanogels and several peptide drugs [61-62]. Therefore, the co-culture of Caco2/HT29-MTX covered with mucus could be considered as the most suitable in vitro model of human intestinal epithelium for understanding the bacterial adhesion and invasion, thus the results obtained by using this co-culture model will simulate the human intestine as close as possible.

4. CONCLUSION

Caco-2 cell line has been undoubtedly the most used and accepted in vitro intestinal cell model to
study the bacterial adhesion and invasion. However, the mechanism of adhesion and invasion are largely depending on the presence of mucus, an important protective component of the normal intestinal epithelium. Therefore, the HT29-MTX cell model may be more suitable for studying bacterial adhesion and invasion in vitro compared to Caco-2 and HT-29 cell models that secrete no or little mucus respectively. The co-culture of Caco-2 cells with the mucus-producing HT29-MTX cell line has been referred as a more predictable experimental cell model than monoculture alone due to the production of mucus that is the most important feature similar to the human intestinal mucosa. Data from this review suggest that the development of co-culture Caco-2/HT29-MTX cell model, with a better physiologically relevant characteristics of mucus layer formation, herein create an excellent in vitro system for characterizing cells–pathogens interactions via adhesion and invasion study.

DISCLAIMER
The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

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