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REVIEW

Development of Microfluidic Platforms: Human Uterine Cervix-on-a-Chip

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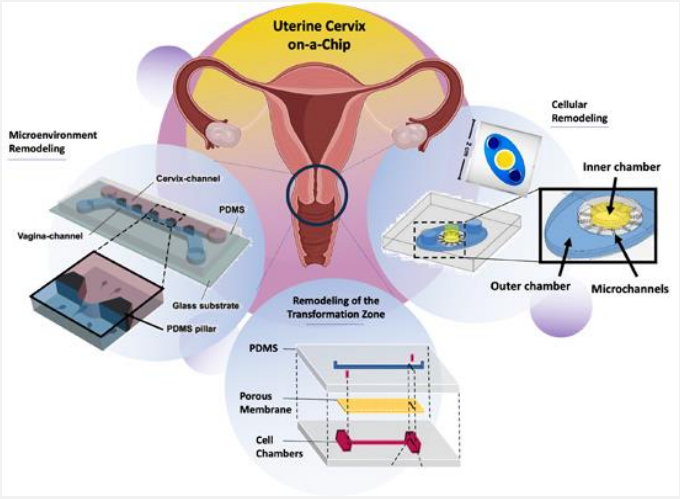
ABSTRACT



Infections, endometriosis, and carcinomas are just a few of the conditions that can affect the uterine cervix in humans. Since the architecture and physiology of the human uterine cervix in humans and other primates differ greatly from that of the majority of frequently used animal models, *in vitro* models of the human uterine cervix play an increasingly essential role in both fundamental and translational research. The function of existing *in vitro* models of the human uterine cervix commonly relies on the use of established cervical epithelial cell lines, such as columnar and squamosal epithelial cells, which line the endocervical canal and ectocervical zone of the cervix, respectively. Consequently, there is a great need for a better model to study human uterine and its related diseases. Recently, microfluidics systems called "Organs-on-Chip" provided an opportunity to fulfill that requirement. These platforms incorporate artificial or real tiny tissues grown inside microfluidic chips. The chips are made to regulate cell microenvironments and preserve tissue-specific functionalities in order to resemble human physiology more closely. Organs-on-Chip platforms have attracted interest as a next-generation experimental platform to study human uterine cervix physiology and diseases. Moreover, the impact of medicines in finding a solution for cervical cancer by combining advancements in tissue engineering and microfabrication. In this study, we reviewed the latest studies in designing the human uterine cervix-on-a-chip.

Keywords: Drug delivery, human papillomavirus, microfluidics, organ-on-chip

1. Introduction

Cancer is a rapidly growing public health concern and is one of the leading causes of death globally [1–4]. Despite being preventable and treatable, cervical cancer continues to be a major worldwide health burden [5,6]. It was the fourth most common cancer to be diagnosed in 2020 with 570,000 new cases annually, and the fourth most common reason for cancer-related deaths among women [6]. Although the frequency of advanced and metastatic cervical cancer has been reduced through early diagnosis using PAP-smear screening and improved treatment of locoregionally advanced disease by chemo-radiation, advanced/recurrent and metastatic disease remains a major cause of cancer death in women [7]. Nearly one-third of patients who present with invasive cervical cancer will die of their disease [8,9].

There has long been an interest in establishing an *in vitro* model for the development of carcinoma of the uterine cervix. The recent association between the human papillomavirus (HPV) and cervical cancer has renewed interest in the culture of normal human cervical epithelial cells. Although human cervical keratinocytes have been employed as target cells for HPV transfection, further information is still lacking on the normal cells' growth characteristics [10]. The normal uterine cervix is comprised of two distinct regions. The ectocervix is comprised of a stratified, non-keratinizing squamous epithelium, and the endocervix is comprised of a single layer of mucus-secreting columnar

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cells and scattered ciliated cells folded into villi [8,10,11]. The ectocervix and endocervix adjoin at the squamocolumnar junction, where a process termed squamous metaplasia frequently occurs. As a result of this metaplasia, the simple columnar endocervical epithelium is replaced by a uniform, immature squamous epithelium that eventually becomes a mature, stratified squamous epithelium. This area of metaplastic epithelium, the transformation zone, is the common site for the development of squamous neoplasia [12,13]. The exact mechanism of squamous metaplasia is not known, but it is hypothesized that the metaplastic cells originate from the proliferation of endocervical cells, either undifferentiated reserve cells or columnar muco-secretory cells [14]. It has been demonstrated that mature, mucus-secreting endocervical cells maintain their ability to replicate *in vivo*. In addition, there is evidence that the metaplastic process may occur *in vitro* [15,16]. (**Figure 1**)

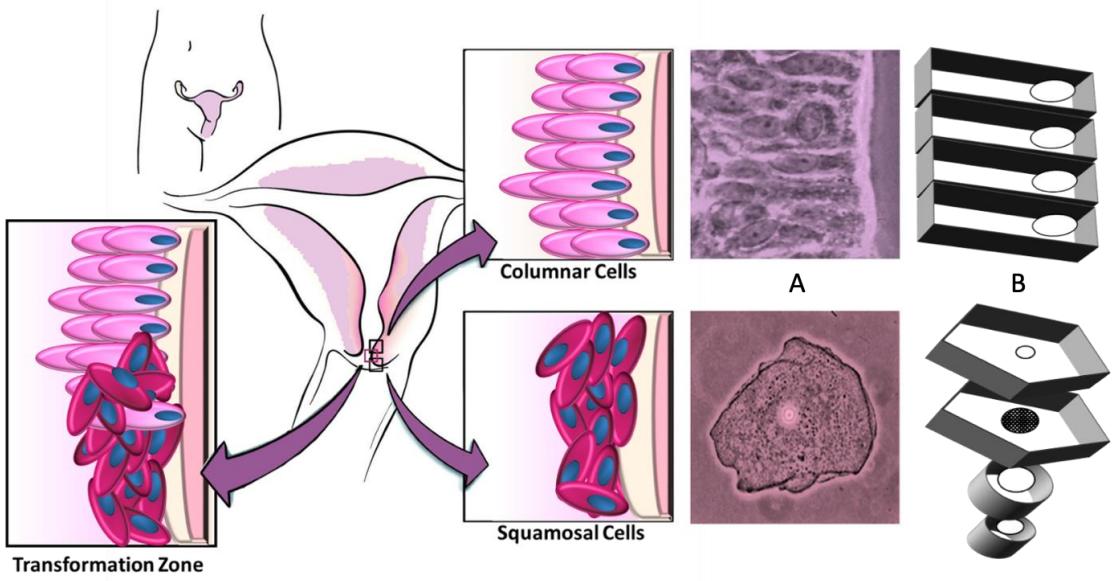

Figure 1. Distribution of epithelial cells in the transformation zone of the human uterine cervix. (**A**) Cytological pictures, and (**B**) 3-dimensional shape of the cells.

Using an organ culture model, several investigators have shown that endocervical tissue exhibits a progressive change of columnar epithelium into tissue resembling squamous metaplastic epithelium [17,18]. Whether these observed changes truly represent an alteration in gene expression remains to be determined. The ease with which human keratinocytes can be propagated *in vitro* has increased with the development of growth media capable of sustaining serial growth without the use of a feeder fibroblast layer or serum supplements [17,19]. However, published work on the characterization of serum-free growth of normal epithelial cells has been predominantly restricted to neonatal foreskin cultures, adult epidermal cultures, and bronchial epithelial cultures [20–24]. There is significant evidence, however, to suggest that all stratified squamous epithelial are not equivalent, particularly with regard to the pathogenicity of the human papillomavirus. For example, it has been observed that different sites in the body, including the mouth, larynx, and cervix, are associated with distinct subtypes of human papillomavirus [25–28]. Furthermore, Kreider *et al*. have shown that cervical and foreskin tissue, but not abdominal skin, are permissive to HPV-11 infection *in vitro* [29]. In addition, the responsiveness of genital tract epithelia to sex steroids suggests that cervical squamous epithelia may differ fundamentally from other squamous epithelia. It is, therefore, reasonable to assume that cultured keratinocytes derived from the cervix may exhibit differences in proliferation and gene expression when compared to neonatal foreskin or epidermal keratinocytes [30–32].

On other hand, *in vitro* models have always been a central feature of biomedical research, and it has been proved that their use is increasing over time [33]. To study human uterine cervix diagnosis, there is a need for a trusted *in vitro* model [34]. Although using conventional 2D cell culture techniques provides us with important information on the cervical epithelial layer's function in cervical remodeling, each cell type (ectocervical, transformation zone, and endocervical epithelial cells) is investigated separately and these systems are restricted in their ability to mimic the *in*

vivo physiological environment [35]. Therefore, 2D cell cultures are unable to give a deeper knowledge of these processes due to the intercellular interaction features and effects [36,37]. Ectocervical, transformation zone, and endocervical epithelial cells are thought to work together *in vivo* to shield the amniotic cavity against ascending infections that start in the vagina. Hence, a significant disadvantage of conventional 2D culture is the absence of cellular connections, which makes it challenging to comprehend how the various areas of the cervical epithelial layer contribute to cervical remodeling [38].

While *in vivo* animal models help us to understand how the cervical lining changes during pregnancy, these studies are costly and rarely replicated in humans. Therefore, a microfluidic-based compartmentalized co-culture system that replicates the intricate multicellular structure of human organs is an approach to overcoming these difficulties [39]. These organ-on-chip technologies can bridge the gap between 2D or mixed cell culture models, animal models, and human-based research by more accurately simulating the physiological circumstances and reactions of human organ systems [40]. In this article, we reviewed current approaches in the investigation of the uterine cervix in the format of organ-on-chip.

2. Available organ-on-chip models for cervical cancer investigations

The normal uterine cervix is comprised of two distinct regions. The ectocervix is comprised of a stratified, non-keratinizing squamous epithelium, and the endocervix is comprised of a single layer of mucus-secreting columnar cells and scattered ciliated cells folded into villi [41]. The ectocervix and endocervix adjoin at the squamocolumnar junction, where a process termed squamous metaplasia frequently occurs [42]. As a result of this metaplasia, the simple columnar endocervical epithelium is replaced by a uniform, immature squamous epithelium that eventually becomes a mature, stratified squamous epithelium [43]. This area of metaplastic epithelium, the transformation zone, is the common site for the development of squamous neoplasia [44,45] Available organ-on-chip models for cervical cancer investigations are summarized in **Figure 2**.

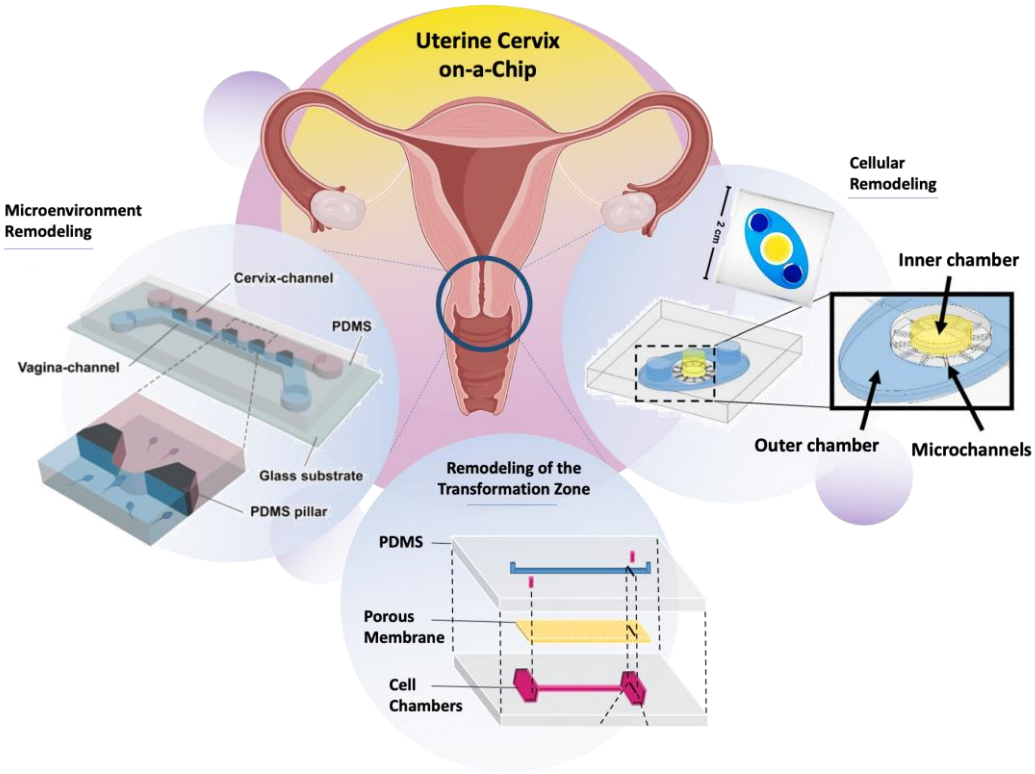

Figure 2. Available organ-on-chip models for cervical cancer investigations.

2.1. Remodeling of the transformation zone

The first attempt to design and develop a cervix on a chip was to mimic the transformation zone of the uterine cervix to examine the mechanism of action of the Human papillomavirus (HPV). This microfluidic device is prepared by demolding cured poly dimethyl siloxane (PDMS). On the chip, cell culture and co-culture of ectocervical epithelial cells (Ect1/E6E7) and endocervical epithelial cells (End1/E6E7) cell lines were carried out, and the functionality of the device to be used as an *in vitro* model for HPV infection and cervical cancer studying were evaluated [34] (**Figure 3**).

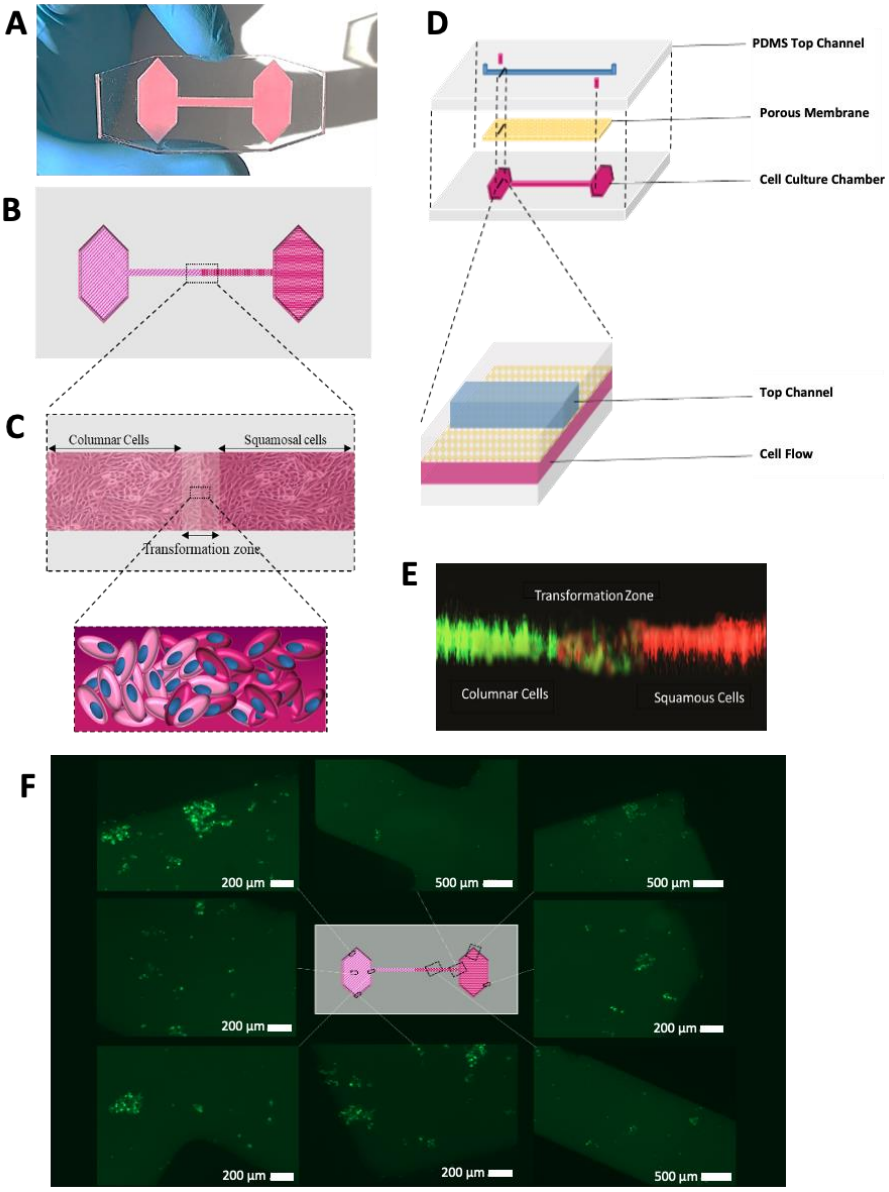

Figure 3. (**A**, **B**, **C**) Illustration showing the distribution of epithelia of the ectocervix (dark pink) and endocervix cells (pale pink) placed on the lower chamber of the chip. (**D**) Two PDMS layers are aligned and irreversibly bonded to form two sets of parallel microchannels separated by 22-µm-thick polycarbonate membranes, containing an array of through-holes with an effective diameter of 22-µm. Scale bar, 200 µm. (**E**) Long-term microfluidic co-culture produces a tissue-tissue interface consisting of a single layer of the Columnar epithelium (stained with Cell Tracker Green) closely next to a monolayer of the Squamous epithelium (stained with Cell Tracker Red), both of which express intercellular junctional structures stained with antibodies to VE-cadherin. Scale bar, 50 µm. (**F**) Growth of the cells in different parts of the chip after 7 days. Reprinted with permission from [34].

One of the most interesting findings of this study resulted from a scratch test indicating that both cell lines could grow from both sides of the chip to reach each other in order to make the transformation zone and the squamocolumnar junction. To track the 2D migration of the cells, a specific mold containing 4 cubic holes (5mm x 5mm x 5mm) has bonded on a glass slide (**Figure 4A**). Human Ect1/E6E7 ectocervix and End1/E6E7 endocervix were cultured in keratinocyte growth medium inside the mold crosswise. Cell morphologies at their adhesion, prior to migration, during migration, and post-migration have been tracked on daily basis. This test demonstrated that two types of cells grew toward each other. (**Figure 4B**) It may unveil a possible signaling connection between two different types of epithelial cells.

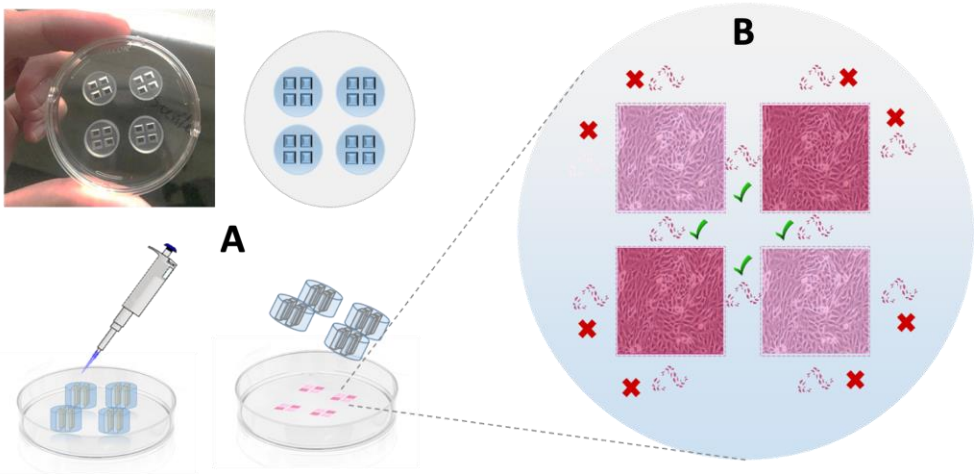

Figure 4. 2D cell migration (scratch test), (**A**) the specific mold to culture two types of epithelial cells in a crosswise order, (**B**) Navigating cells in different directions. Reprinted with permission from [34]

This established uterine cervix-on-a-chip is simple, effective, and easy to operate. It is expected to have important applications in the personalized treatment of HPV infection lesions and cervical cancer and to play a potential role in other clinical treatments and tissue engineering.

2.2. Cellular remodeling

Preterm birth is linked to damage to the cervix epithelial layer brought on by inflammation and infection [46]. An organ-on-chip of the cervical epithelial layer was created, which consists of two co-culture chambers recapitulating the ectocervical and endocervical epithelial layers, to study the intercellular connections (**Figure 5**) [47]. How cells from each unique location interacted with one another and how they contributed to preserving cervical integrity in response to lipopolysaccharide (LPS) and tumor necrosis factor-alpha (TNF) stimulations, were two main questions of that study. Both epithelial cells' cellular migration inside the microchannels was promoted by the co-culture of ectocervical and endocervical cells. Both LPS and TNF enhanced apoptosis, necrosis, and senescence as well as elevated pro-inflammatory cytokine production by cervical epithelial cells in comparison to untreated controls. In conclusion, the cervix-on-a-chip developed an *in vitro* model that can accurately represent the ectocervical and endocervical areas of the cervix.

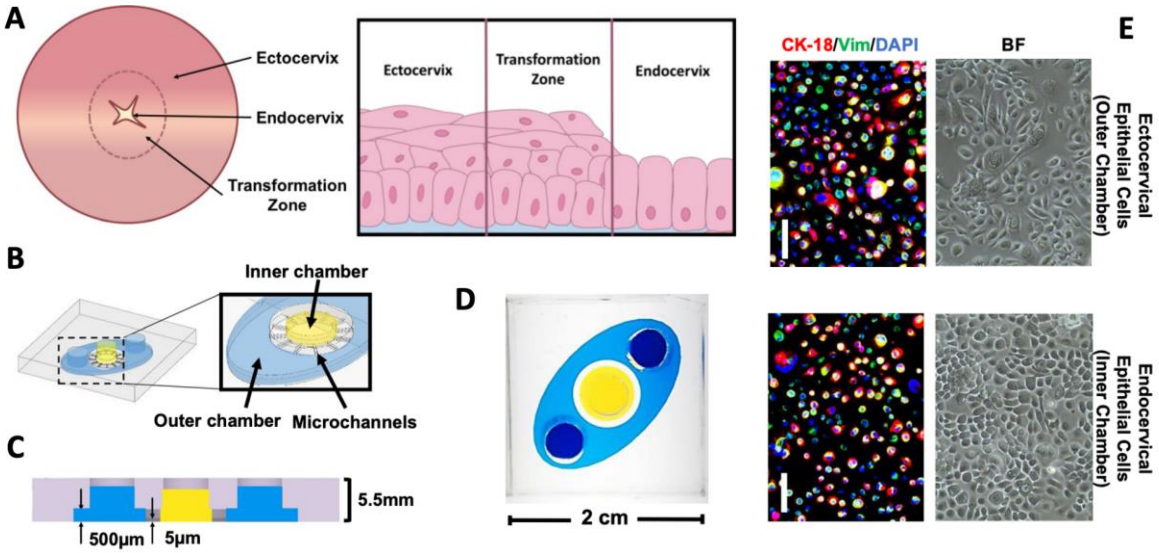

Figure 5. Organ-on-chip of the cervical epithelial layer. Ectocervical and endocervical epithelial cells are cocultured in the organ-on-chip of the cervical epithelial layer in order to mimic the cervical epithelial layer in vitro. Cells can move via type IV collagen-filled microfluidic channels to construct the cervix's transformation zone epithelium. (**A**) A schematic illustration of the cervical epithelial layer's architecture. Gross morphological view on the left; cross-sectional view on the right. (**B**) The organ-on-chip of the cervical epithelial layer design is depicted in three dimensions and has two cell culture chambers divided by 24 shallow microchannels. (**C**) A cross-sectional image illustrating the height difference between the microchannels, which are 5 m tall, and the cell culture chambers, which are 500 m tall. (**D**) A picture of the organ-on-chip of the cervical epithelial layer device with the inner endocervical epithelial cell culture chamber and the outside ectocervical epithelial cell culture chamber filled with blue and yellow dye, respectively, respectively. (**E**) Cell morphology as well as CK-18 (red) and vimentin (green) expression are shown in bright-field and fluorescence microscopy images of the ectocervical epithelial and endocervical epithelial cell cultures in the organ-on-chip of the cervical epithelial layer. Blue dye (4′,6-diamidino-2-phenylindole) is used to stain nuclei. 500 m is the scale bar. Reprinted with permission from [47].

2.3. Microenvironment remodeling

The cervix, which serves as the entrance for sperm swimming into the female reproductive canal, is stuffed with cervical mucus, which is crucial to sperm motility. Male infertility will result from sperm being unable to pass through the cervical mucus-cervix microenvironment. However, it is still unclear how the sperm navigate the cervix microenvironment. In order to simulate the cervix microenvironment and create a chip that can be used to research sperm behavior and selection, hyaluronic acid (HA) was employed as a synthetic version of cervical mucus [48]. In addition, Biggers-Whitten-Whittingham (BWW) was used as the sperm culture medium. Sperm buildup in HA demonstrated that it acted as a sperm reservoir akin to cervical mucus. The departure of sperm from HA displayed greater motility than those entering into HA, indicating that HA serves as a filter to only choose sperm with high activity. This research creates a useful platform to investigate the complex relationship between sperm and the cervix microenvironment, and elaborate swimming indications offer a promising cervix chip for sperm selection with demand-driven kinematic properties. Additionally, the cervix chip's benefit of being simple, quick, and very effective makes it practical to employ in clinical infertility diagnosis (**Figure 6**).

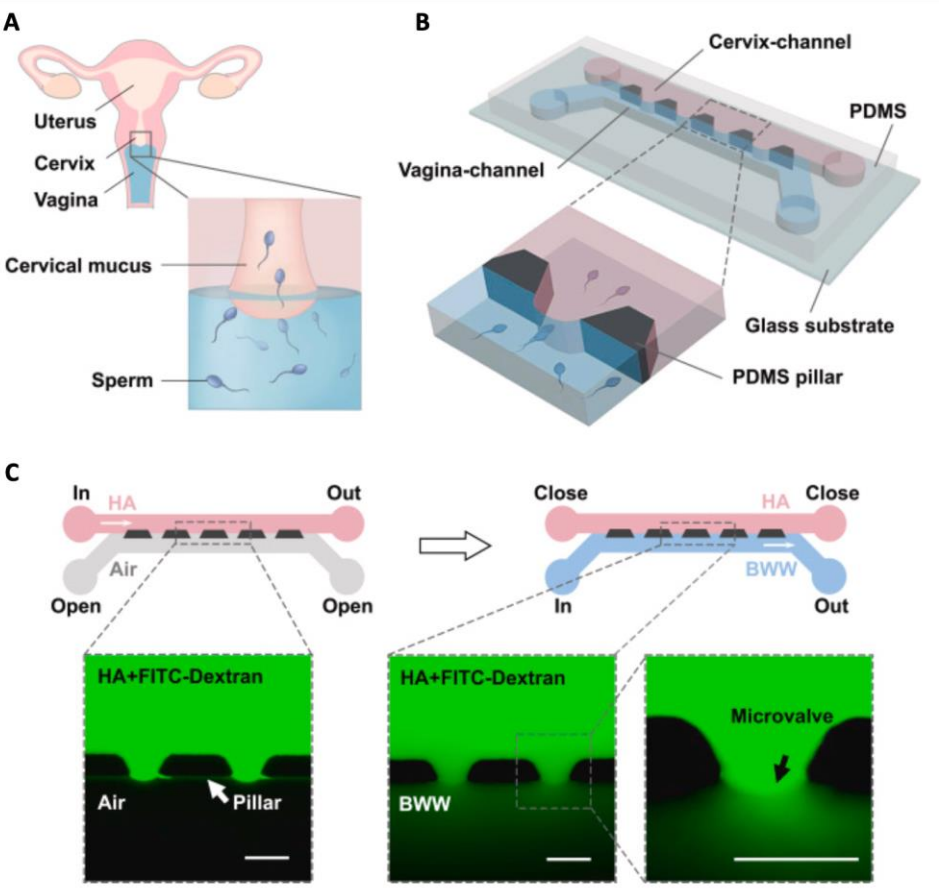

Figure 6. A chip that replicates the cervical milieu seen in the female reproductive system. (**A**) a diagram showing the female reproductive system. The cervix is magnified using the black box. Pink and gray indicate cervical tissue, pink represents cervical mucus, and blue represents the vagina. (**B**) Cervix chip schematic diagram. The pillar array is positioned evenly spaced inside the channel's half-width. In contrast to the blue vaginal channel, which was filled with BWW, the pink cervix indicates the channel that was filled with HA. The inserts below represent the HA-BWW interface and are zoomed in. The surrounding pillars form a meniscus that functions as a microvalve to regulate the sperm pathways. A cervical microenvironment is created. By delivering HA and FITC-Dextran to the cervix channel, a meniscus was created. (**C**) The cervix-intake channels and outflow were then sealed with gel film. The entrance and outflow of the vaginal canal were sealed by gel film while BWW medium was pulled in. It developed into the HA-BWW interface. 100 m is the scale bar. Reprinted with permission from [48]

3. Conclusions

In this study, available microfluidic human cervix-on-a-chip models have been described. Mutually, the cervical stromal-epithelial cell interactions were permitted in the discussed model; nevertheless, the previous transwell method has significant drawbacks, such as difficulties in applying local stimulation to a single compartment and restricted imaging of cellular migrations. Another cervix-on-chip model is used for a planar structure that enables the growth of both ectocervical and endocervical epithelial cells in two chambers linked by a single microchannel, enabling the creation of the squamocolumnar junction. These models are supplemented by the third cervix-on-chip, which offers improved intercellular connections, sensitive measurement capabilities for measuring membrane permeability and biomolecule propagation, and real-time imaging capabilities for monitoring cellular activities. In conclusion, the Human uterine cervix-on-a-chip may provide a powerful alternative *in vitro* model for studies on uterine physiology, real-time, high-resolution imaging, and analysis of biological responses in the cervix, as well as drug development. However, still more investigations are required to reach a better and more complete cervix-on-a-chip model.

Conflict of interest

The author declares any conflict of interest.

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