

The Developmental Origin of Cervical and Vaginal Epithelium and Their Clinical Consequences

A Systematic Review

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■ Abstract

Objective. Studies on the development of the embryological and fetal development of the cervix and the vagina are rare and mostly go back to the first decades of the last century. The aims of this review were to present the latest knowledge concerning the developmental origin of cervical and vaginal epithelium and to point out new results in the context of different clinical findings.

Materials and Methods. Relevant studies published between 1910 and 2013 were identified via PubMed, MEDLINE, OVID, Web of Science, and EMBASE. The reference lists of retrieved articles were reviewed to locate additional articles. Each abstract was reviewed, and the appropriate publications were obtained and reviewed as well. A total of 33 articles and 8 book chapters were selected for citation in this review.

Results. New objective findings clearly show that human prenatal epithelialization of the cervix and vagina results in 3 morphogenetically determined units: (i) the Müllerian columnar epithelium of the endocervix, (ii) the Müllerian squamous epithelium of the ectocervix and the upper vagina, and (iii) the vaginal squamous epithelium of the lower vagina.

Conclusions. These results are of high clinical relevance and may provide new insight into the histogenesis of ectopy, vaginal adenosis, and the congenital transformation zone. They should be added to the explanations in gynecological, colposcopic, and gynecopathological textbooks. ■

Key Words: uterovaginal anlagen, histogenesis, ectopy, vaginal adenosis, congenital transformation zone

Studies on the development of the human uterovaginal anlagen (UVA) mostly go back to the first decades of the last century [1–6]. Altogether they are rare and subjective. Objective diagnostic morphological methods such as immunohistochemistry were not available at that time. However, the older studies are still the basis for current embryological and clinical and pathological textbooks [7–10]. In the last decade, new studies of UVA including objective immunohistochemical analysis were published. The aims of this study were to review the major theories for the developmental origin of cervical and vaginal epithelium, to define the recent knowledge, and to point out new results in the context of different clinical findings.

STUDY SELECTION

A review of the literature was undertaken for articles published between 1965 and August 31, 2013. Relevant studies were identified via PubMed, MEDLINE, OVID, Web of Science, and EMBASE. The reference lists of retrieved articles were reviewed to locate additional articles. Each abstract was reviewed, and the appropriate publications were obtained and reviewed as well. A total of 33 articles and 8 book chapters were selected for citation in this review.

RESULTS

In the past, 4 major theories for the developmental origin of vaginal and cervical epithelium were published [11]:

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The “urogenital sinus (UGS) and Müllerian duct (MD) origin theory” hypothesized that the squamous epithelium of the upper two-thirds of the vagina (Müllerian vagina) and the ectocervix develops from the caudal portion of the MDs and that the lower portion (sinus vagina) develops from the UGS [4, 8, 12–18].

In the “Müllerian duct (MD) and Wolffian duct (WD) origin theory,” the WDs contribute to the squamous epithelium of the vagina [13, 19–22].

The “Müllerian duct (MD) origin theory” proposes that the WDs play a role in the downward growth of the Müllerian-derived vagina and/or in the formation of the hymen but do not contribute to the squamous vaginal epithelium [23, 24].

The “urogenital sinus (UGS) origin” theory suggests that the entire squamous epithelium of the cervix and vagina are originated solely from the UGS of endodermic origin [5, 7, 25–27]. In this view, the squamous epithelium derived from the UGS grows upward and replaces the original columnar epithelium of mesodermal MD origin.

In the last decade, functional morphological studies concerning UVA development models published by Kurita et al. [11, 28–31] focused on mice and mice models. They showed that during mice development, the MDs undergo a morphogenetic transformation from simple tubes into distinct organs and then differentiate to diverse epithelial cell types with a unique morphology in each anatomic region. Within this process, the transcription factor p63, induced by mesenchyme of the vagina, cervix, and uterine corpus during development, was regarded to play a key role in the determination of epithelial cell fate. The authors supposed epithelial plasticity to be restricted to small groups of so-called stem cells in cervix and uterus.

Recently, Fritsch et al. [32] reported histologic and immunohistochemical results based on nearly complete prenatal human stages of UVA. By application of antibodies raised against various cytokeratins, progenitor cells, transcription factors, and smooth muscle actins as well as antibodies indicating cell survival, angiogenesis, and mesenchymal origin, this study was able to characterize the epithelial and mesenchymal structures at defined embryological and fetal stages. Fritsch et al. [32] report that:

1. The most caudal vaginal epithelium is exclusively UGS epithelium derived; all the upper vaginal epithelium a converted or transformed vaginal Müllerian epithelium.

2. The original squamous epithelium of the cervix is of vaginal Müllerian origin. In contrast, the columnar cervical epithelium is of uterine Müllerian origin and includes columnar reserve cells with the plasticity to transform into squamous epithelium.
3. In late fetal life, cervical glands migrate from the epithelial surface of the cervical canal into the underlying stroma. They spread caudally toward the external cervical os. The original squamocolumnar junction (SCJ) is clearly detectable from week 24 onward and is situated within the cervical canal during all stages of fetal life. In the newborn, this border tends to grow caudally toward the external cervical os.

DISCUSSION

Vaginal Epithelialization

After delivery, the vaginal mucosa is a stratified squamous epithelium composed of distinct layers. The recent study by Fritsch et al. [32] obtained objective information on the development of epithelial structures of the vagina based on immunohistochemical findings at defined embryological and fetal stages. In contrast, all of the older theories concerning the developmental origin of vaginal epithelium (UGS + MD origin theory; MD+WD origin theory; MD origin theory; UGS origin theory) are based on subjective histologic observations. The results by Fritsch et al. [32] confirm the “UGS + MD origin” theory of vaginal epithelialization, in which the upper two-thirds of the vagina (Müllerian vagina) develop from the caudal portion of the MDs and the lower portion (sinus vagina) develops from the UGS. In the light of these objective results, all older theories are negated. In particular, the common concept of an upward growth of UGS squamous epithelium that replaces a Müllerian columnar epithelium of the vagina up to the original SCJ [8, 9, 33, 34] seems to be defeated.

The different origin of epithelialization of the upper and lower vagina is important for the understanding of vaginal carcinogenesis: The majority of squamous cell carcinomas of the vagina develop through vaginal intraepithelial neoplasia triggered by transforming infection with high-risk human papillomaviruses (HPVs) and other HPV persistence risk factors. Clinically, it is well known that vaginal (pre)cancer occurs predominantly in the upper one third of the vagina, while the middle and lower thirds are involved in less than 10% [35]. This is probably due to the different vulnerabilities against high-risk HPV of the vaginal Müllerian squamous epithelium

that is of mesodermal origin and the squamous epithelium derived from the UGS that is of endodermal origin. The dual mechanism of the epithelialization of the vagina is also consistent with the clinical compartment theory of the distal vagina [36].

Histogenesis of Vaginal Adenosis

The normal vaginal squamous epithelium usually does not contain any glandular elements, except for occasional remnants of Gartner's duct. Vaginal adenosis is a rare condition in which columnar epithelium exists within the vagina. Fritsch et al. [32] showed that during prenatal life, Müllerian vaginal epithelium develops from a multilayered cubic epithelium into a stratified squamous epithelium. A vaginal columnar epithelium, as often described, does not exist. In patients with vaginal adenosis, exogenous or endogenous stimuli may alter the process of differentiation of the immature Müllerian epithelium and foci of glandular epithelium can develop within the squamous epithelium. In utero exposure to diethylstilbestrol is the most well-documented exogenous substance that can modify the development of vaginal epithelialization and can cause vaginal adenosis. Diethylstilbestrol is an orally active synthetic estrogen that was used to prevent adverse pregnancy outcome and thus was routinely given to pregnant women from the 1940s to the 1960s. The assumption that vaginal adenosis develops through missing transformation of a primary columnar epithelium of the vagina into a stratified squamous epithelium is no longer tenable [5].

Cervical Epithelialization

The original epithelium of the ectocervix is a stratified nonkeratinizing squamous epithelium. The normal epithelium of the endocervix is a single-layer columnar epithelium with tall mucin-secreting cells. It lines the so-called cervical glands. Its junction with the original squamous epithelium is usually located near the external os. Metaplasia of the squamous epithelium denotes the gradual transformation of the columnar epithelium into squamous epithelium. The transformation zone (TZ) is where squamous metaplasia occurs. It extends from the original nonkeratinizing squamous epithelium of the ectocervix to the mucin-producing columnar epithelium of the endocervix.

Fritsch et al. [32] showed that the original squamous epithelium of the cervix is of vaginal Müllerian origin and the columnar cervical epithelium is of uterine Müllerian origin that includes columnar reserve cells with the

plasticity to transform into squamous epithelium. These different origins of original squamous epithelium and columnar epithelium of the cervix are important for the concept of the cervical TZ and the understanding of cervical carcinogenesis: The metaplastic squamous epithelium of the cervical TZ (uterine Müllerian origin) is an important landmark because it is located where 90% of cervical (pre)cancerous lesions arise [37]. In contrast, only 10% of cervical (pre)cancer arises from the original squamous epithelium of the cervix (vaginal Müllerian epithelium). This is probably due to the different vulnerabilities against high-risk HPV of the original squamous epithelium (outside the TZ; vaginal Müllerian epithelium) and the metaplastic squamous epithelium (inside the TZ; uterine Müllerian epithelium). The topography of abnormal colposcopic findings with regard to the TZ (inside or outside) was introduced into the 2012 International Federation of Cervical Pathology and Colposcopy terminology. It is reported as an independent predictor of high-grade squamous intraepithelial lesions [38].

Histogenesis of Ectopy

Ideally, the original SCJ lies at the external os. *Ectopy* is present when the SCJ lies outside the external os. Fritsch et al. [32] reported that, in late fetal life, endocervical columnar Müllerian epithelia migrate from the epithelial surface of the cervical canal into the underlying stroma to form glands. Later, they spread caudally toward the cervical orifice. The original SCJ is clearly detectable from week 24 onward and is situated within the cervical canal during all stages of fetal life. Ectopy occurs because of the relocation of the original SCJ onto the ectocervix.

These results are consistent with the older concept of the so-called last gland that histologically and permanently marked the distal extent of the columnar epithelium [39]. The last gland is important because its position is constant. It is a landmark separating the endocervical mucosa (columnar epithelium) proximally and the original squamous epithelia distally. The last gland is also the focal point for the distribution of the stromal connective tissue and blood vessels of the outer area of the cervix. These structures accompany any change in the location of the last gland and serve as permanent markers of its position from intrauterine life to postmenopause [37].

The assumption that ectopy occurs when conversion of the Müllerian columnar epithelium to squamous

epithelium is arrested and the Müllerian columnar epithelium remains on the ectocervix is no longer tenable [8] (see also vaginal adenosis).

Histogenesis of Congenital Transformation Zone

The congenital TZ (CTZ) is a rare colposcopic finding of a large faintly acetowhite and iodine yellow area extending into the anterior or posterior fornix. In contrast to the normal glycogenized vaginal squamous epithelium, histologically, the squamous epithelium of a CTZ is nonglycogenated. The origin of this finding is unclear.

Fritsch et al. [32] showed that the original SCJ is situated within the cervical canal during all stages of fetal life and does not extend to the vaginal fornices. According to these findings, CTZ seems to be a variant of the Müllerian vaginal epithelial differentiation. It is not of uterine Müllerian origin resulting of a variable position of the original SCJ that, in cases of vaginal adenosis, is located in the area of the vaginal fornices. The results by Fritsch et al. [32] are consistent with the clinical fact that (pre)cancer of a CTZ occurs as often as a precancer of the original squamous epithelium of the cervix (vaginal Müllerian epithelium). Because CTZ originates from uterine Müllerian epithelium, one would expect that (pre)cancer of a CTZ would occur as often as (pre)cancer of the cervical TZ. However, this is not the case.

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