Distinguished Expert Series

The columnar epithelium hypothesis of cervical carcinogenesis

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Human papilloma virus (HPV) is the essential etiologic agent for intraepithelial and invasive squamous as well as glandular neoplasia of the cervix. Cervical carcinogenesis is regarded as the consequence of persistent high-risk HPV infection and co-factors.

It is clear that HPV infects epithelial reserve cells. These cells have a progenitor cell function. They are small cuboid cells with relatively large nuclei in basal layers of the columnar epithelium, the original squamous epithelium and metaplastic squamous epithelium (Figure 1). They are responsible for the regeneration of the epithelium and enable the metaplasia from columnar to squamous epithelium. After reserve cells are infected with HPV, they express non-structural viral proteins. If control of the viral genes in the reserve cells is lost, the dividing cell population expands and epithelial cell differentiation is delayed and is less complete.

It is widely agreed that HPV infection of the cervix is initiated when minor trauma (e.g., sexual intercourse) exposes the reserve cells of metaplastic squamous epithelium of the cervical transformation zone to the virus [1].

Squamous metaplasia is the transitioning of columnar epithelium to a stratified and more resilient squamous epithelium. Factors that induce this process include pH changes, changes in the sex steroid hormone balance, mechanical irritation, environmental conditions, and chronic inflammation.

But does the decades-old concept of microtrauma of the overlaying layers of metaplastic squamous epithelium as the point of viral entry hold up to morphological and functional scrutiny? No one has seen such epithelial defects under the microscope or colposcope [2]. From a functional point of view, it is precisely the squamous epithelium that protects the cervix from injury. Morphologically, the squamous epithelium consists of several layers. The squamous cells are very close to each other. There is little intercellular space between them and cell junctions are plentiful. While the squamous epithelium can withstand mechanical challenges, the columnar epithelium, whose function is not to provide mechanical protection but to secrete mucin, can be injured easily. The columnar epithelium is single-layered and the reserve cells less more accessible. Thus, it can be assumed that it is much easier for HPV to reach the reserve cells in this case.

The following hypothesis takes issue with the dogma of microtraumata of metaplastic squamous epithelium. It is hypothesized that the major pathway of cervical carcinogenesis starts with HPV infection of a distinct number of subcolumnar reserve cells of the columnar epithelium with and without microtraumata (Figure 1a), not with infection of the reserve cells of the metaplastic squamous epithelium.

After HPV infection the columnar epithelium of the cervix can present itself in many different ways. It can remain in its original form, be transformed into adenocarcinoma in situ (AIS), undergo normal metaplasia to become normal squamous epithelium (Figure 1b), or undergo an atypical metaplastic process producing a squamous intraepithelial lesion (SIL). More than one process may occur at the same time. With the influence of co-factors after varying lengths of latency, invasive cancer can develop.

This hypothesis provides explanations for the following findings:

1) Why do glandular, squamous and mixed lesions occur? The target cells for HPV, the subcolumnar reserve cells, can differentiate in both directions.

2) Why is malignant transformation of the original squamous epithelium of the cervix uncommon? [3]. The subcolumnar reserve cells are never located in the area of original squamous epithelium.

3) Why are recurrence rates low after excisional or destructive treatments of SIL and AIS? The predominant concentration of subcolumnar reserve cells is near the external os of the cervix [4]. This area is removed or destroyed during treatment.

4) Why are early age at first intercourse and multiparity risk factors for cervical cancer? Early age shows a physiological eversion of columnar epithelium onto the ectocervix (ectopy) and a most active transformation. Also pregnancy shows repeated eversion of columnar epithelium onto the ectocervix. Anatomically, the subcolumnar reserve cells can now be easily reached by HPV.

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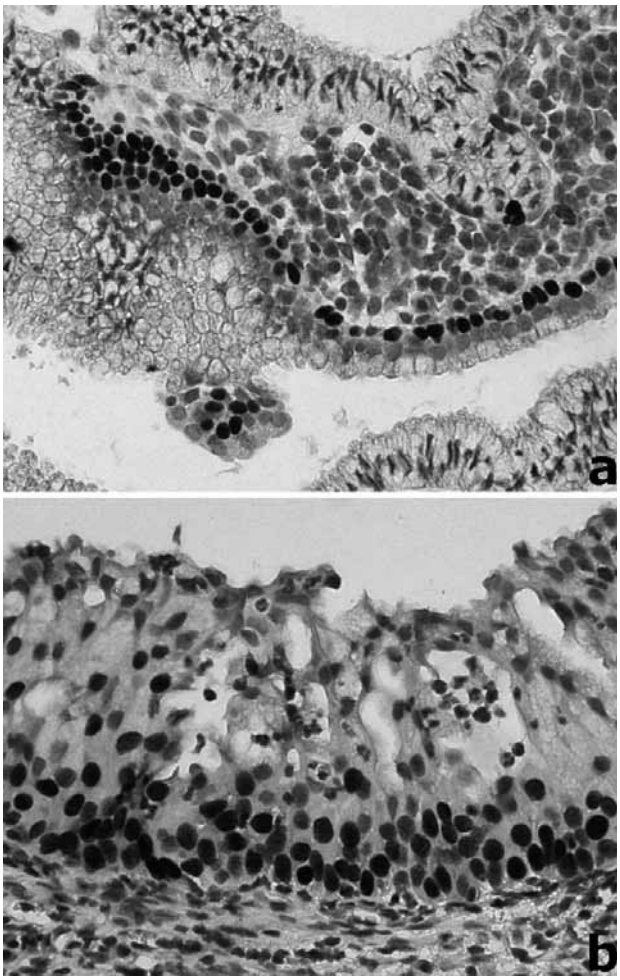

Figure 1. — a) Columnar epithelium of the cervix. Subcolumnar reserve cells express the marker p63 [6]. b) Immature squamous metaplasia. Note the expanding population of p63 positive proliferating cells. (Immunohistochemistry x 100).

Scientific theories have to be continuously verified and falsified. The present "columnar epithelium hypothesis of cervical carcinogenesis" abstains from assuming traumatic epithelium defects of the metaplastic squamous epithelium to explain HPV infection of reserve cells and thus is more compatible with objective observations. Since the integration site of the HPV genomes into the cellular DNA of the host cell is unique, mapping of integration sites in cervical mixed lesions may allow this hypothesis to be tested [5].

References

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