

Keratin profiling studies in differential diagnosis of carcinomas.

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encountered the terms “gobbledygook” and “poppycock.” Nevertheless, the monograph does not integrate scientific knowledge with a histopathologic diagnostic paradigm that accurately reflects the totality of atypical melanocytic lesions encountered by dermatopathologists.—John T. Seykora, MD, PhD, *Department of Dermatology, University of Pennsylvania Medical School, Philadelphia, PA*

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Letter to the editor:

To the Editor,

We read the paper by Carrilho et al [1] with great interest. This publication is well timed in that the last few years have seen a revival of interest in keratin profiling studies in the differential diagnosis of carcinomas. We have, however, frequently noted that many of the recent studies, including this one, are duplications of studies that appeared years ago [2]. This and the fact that a reappraisal of the results of Carrilho et al [1] is necessary, in light of the incorrect approach to cervical carcinogenesis, have prompted our response.

The authors state that increased expression of keratins 8 and 17 and decreased expression of keratins 10 and 13 are indicators for malignant transformation in the cervix. The expression of these keratins is compared to a reference epithelium. For keratin 8, endocervical columnar cells serve as the reference, whereas for keratins 10 and 13, it is the ectocervical squamous epithelium, and for keratin 17, the authors correctly choose reserve cells as a reference epithelium. Unfortunately, they go on to compare keratin 17 expression of cervical intraepithelial neoplasia (CIN) III and cervical squamous cell carcinoma with ectocervical squamous epithelium.

In our opinion, the choice of a reference epithelium is not correct. It is a well-known fact that cervical squamous cell carcinoma does not develop from endocervical epithelium, the reference epithelium for keratin 8, and that few, if any, cervical carcinomas will develop from ectocervical non-keratinizing epithelium, the reference epithelium for keratins 10, 13, and 17. The choice of epithelium should have been the reserve cells in the squamocolumnar junction. These cells are thought to be the progenitor cells of practically all CIN lesions and cervical carcinomas, including adenocarcinomas. Reserve cells in the squamocolumnar junction proliferate and develop into mature metaplastic squamous epithelium via an intermediate state of immature squamous metaplastic epithelium. If at some point the differentiating reserve cells are infected with oncogenic human papillomavirus (HPV), a major prerequisite has been fulfilled for possible transformation to CIN. Even after infection, transformation is a rare event, and progression to cervical carcinoma is even rarer.

This hierarchical relationship between the stem cell (reserve cell) and cervical carcinoma means that the choice of reference epithelia cannot be arbitrarily chosen.

Against this background, the results of Carrilho et al [1] must be reconsidered. Reserve cells contain, among others, keratins 8 and 17 but no keratins 10 and 13. In our studies, we showed that approximately 50% of CIN III contained these reserve cell keratins [3]. Other keratins, such as keratins 10 and 13, were found in some CIN lesions but usually only in case of squamoid maturation. Cervical carcinomas contained all the reserve cell keratins and often differentiation-related keratins [4]. This prompted our conclusion that the presence of reserve cell keratins in a CIN lesion indicates its potential to develop into a cervical carcinoma, if not treated. On the other hand, the absence of the reserve cell keratin phenotype indicates that a CIN lesion is not progressive and will regress, transforming into a mature squamous metaplastic epithelium. We had legitimate reasons for this perhaps very speculative conclusion. First, the high fidelity of keratin expression is a well-known phenomenon. Basically, this means that the keratins identified in a carcinoma are normally also found in the carcinoma progenitor cell. Second, the percentage (50%) of CIN III expressing the reserve cell keratin phenotype approximated estimates of the fraction of CIN III with a malignant potential.

We reported a reserve cell keratin phenotype in all cervical carcinomas further supporting the high-fidelity rule. This percentage is higher than that reported by Carrilho et al [1]. As they correctly state, this difference is attributable to the fact that our initial studies were applied to fresh frozen tissue specimens [4]. Because we realized the consequence of the hypothesis that reserve cell keratins may well indicate the potential of CIN III to progress to cervical carcinoma, we repeated the studies with a comprehensive panel of keratin antibodies on archival formalin-fixed paraffin-embedded material. Our results of a decade ago were similar to those of Carrilho et al [1,2].

We do agree with the authors' conclusion that application of keratin antibodies could be valuable in the subclassification of cervical carcinoma, an observation we published many years ago [2,4]. Time has not stood still for the cervix since we preformed the studies summarized above. It is encouraging to see that our results are reproducible but saddening to conclude that the model for cervical carcinogenesis is so loosely adhered to. We have modified the position we had 12 years ago, and this influences our interpretation also with regard to keratin expression in the cervix. Progression rates of 50% for CIN II/III to cervical carcinoma are exaggerated; based on literature, 20% would seem more realistic. We furthermore underestimated the role of HPV at the time and now think that integration of HPV in the human genome is pivotal in progression from CIN III to cervical carcinoma [5]. Keratin phenotyping in relation to viral status would therefore seem the logical step forward.

References

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Reply

To the Editor,

We thank Smedts et al for their interest in the study we published in *HUMAN PATHOLOGY* [1]. These authors criticize our choice of ectocervical squamous epithelium as a reference for comparative purposes on keratin staining patterns. The criticism stems from the fact that, for example, keratin 17 stains reserve cells, and therefore these cells should be used as a reference. Although we agree that strictu sensu the term “reference epithelium” may be

misleading, we are confident the readers will understand our rationale of comparing the keratin expression profiles of squamous carcinomas (invasive carcinomas and cervical intraepithelial neoplasia lesions) with those of ectocervix epithelium. Both in cytology and in biopsy specimens, the diagnostic problems are centered on the features of squamous cells. It was not our aim to approach cervical carcinogenesis using keratin markers—so we disagree that our approach was incorrect. We simply did not approach that issue. Regarding the actual problem we were interested in, to evaluate the usefulness of keratin markers for diagnostic purposes, our data confirm those published by the group of Smedts et al, and we have explicitly acknowledged this fact. We think it is important to confirm previous studies performed in several laboratories before the conclusions are used for diagnostic purposes. In conclusion, the issue raised in the last paragraph of the letter regarding comparison of keratin phenotyping in relation to viral status has been addressed, and the results will be published soon.

Reference

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