Proliferation in the normal cervix and in preinvasive cervical lesions

A number of recent studies describe the expression of Ki-67 and proliferating cell nuclear antigen (PCNA) in normal, metaplastic and abnormal cervixes, as detected immunohistochemically. These antigens, which permit the calculation of a labelling index and provide an assessment of the proliferation state, together with the presence of nuclear labelling, can be detected in routinely fixed and processed tissue and can be adopted for use in most diagnostic laboratories.

Cellular proliferation is assessed most frequently in the cervix by histopathologists who use the numbers and location of mitotic figures in the diagnosis and grading of cervical intraepithelial neoplasia (CIN). Although more sophisticated techniques such as [3H]thymidine and bromodeoxyuridine labelling and the quantitation of cellular DNA permit assessment of the proliferation rate, they require either in vitro or in vivo rearing of tissue prior to fixation or access to specialised, and often expensive, image analysis equipment, thereby limiting their use in routine diagnostic practice.

Ki-67 has been immunolocalised to the parabasal and basal layers in the normal and metaplastic ectocervix. Variations during the menstrual cycle have been described, with the number of cycling cells increasing in association with increases in progesterone receptor expression in the luteal phase of the cycle and during pregnancy. Atrophic epithelium is associated either with no staining or with staining confined to the parabasal layers. The development of a CIN lesion is associated with the identification of Ki-67 positive cells in the intermediate and superficial layers of the squamous epithelium, the percentage of positive cells and the height above the basement membrane at which they are located, increasing as the grade of CIN increases. The presence of a few scattered immunoreactive cells in the apparently maturing epithelium and at higher levels than the most superficially placed mitotic figures lends weight to the view that some degree of cellular abnormality involves the entire thickness of the squamous epithelium in these lesions. In cervixes which are infected with human papillomavirus, the viral subtype usually associated with high grade CIN lesions show a higher percentage of cells immunopositive for Ki-67, than those which are usually associated with low grade lesions.

Findings similar to those for Ki-67 have been described with PCNA, with the reactive cells confined to the basal layers in non-neoplastic ectocervix and only scattered positive cells in the superficial layers of immature metaplastic epithelium. In CIN lesions the proportion of the height of the epithelium at which immunoreactive cells are identified increases with the grade of the lesion.

In glandular lesions, although statistically significant differences in the Ki-67 and MIB-1 labelling indexes between benign endocervical lesions and glandular intraepithelial neoplasia of the cervix have been identified, it is unlikely that, given the degree of overlap between the groups, these will find a diagnostic application.

Rowlands was unable to identify a statistically significant difference in the number of AgNORs in normal squamous epithelium and epithelium showing CIN I and CIN II lesions. There was a small but significant increase in the number of AgNORs in the CIN III group.

Can any of these findings be applied to routine diagnostic practice? As Ki-67 and PCNA immunoreactivities are largely confined to the basal and parabasal layers in normal epithelium, with only occasional scattered positive cells in the intermediate and superficial layers in metaplastic and virally infected epithelium, the major practical application of these studies seems to be to exclude or confirm the presence of a CIN lesion in problematic cases. The technique would seem to be of particular value where the atrophic epithelium, encountered occasionally in hysterectomy specimens from post-menopausal women, bears a resemblance to a CIN III lesion. The finding of Ki-67 confined to the parabasal layers will save much time in consultation with colleagues and in the processing and examination of additional blocks.

CIN is graded according to the third of the epithelium (lower, middle, upper) in which basaloide cells appear. In most of these studies the CIN lesions would have been overgraded had the highest third of the epithelium in which MIB-1/PCNA positive cells were situated been used to grade these lesions. Bulten et al have developed a technique, utilising the 90th percentile of the relative distances of MIB-1 positive nuclei from the basement membrane, which allowed all the cases in their small series to be classified correctly. This required the use of specialised image analysis equipment, however, compromising the potential for more general use of a simple antibody technique.

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