TRANSITIONAL MUCOSA OF THE COLON AND TUMOR GROWTH FACTORS

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ABSTRACT

Transitional mucosa of the colon is the tissue immediately adjacent to a cancer, which has histochemical and ultrastructural features similar to those seen in neoplasia. Therefore, it has been hypothesized in the past that this tissue represents the premalignant antecedent to colonic adenocarcinoma. Other investigators have disputed this explanation because similar changes are found adjacent to colonic lesions other than adenocarcinoma.

The hypothesis offered here suggests that transitional mucosa may result from the paracrine influence of tumor growth factors released by the tumor. Candidate peptide hormones known to be produced by tumors are proposed, and a framework is outlined to explain the occurrence of transitional mucosa adjacent to non-neoplastic lesions. Transitional mucosa may be both a genuine reflection of the transformed phenotype and yet a "reactive" phenomenon secondary to the presence of the adjacent tumor.

TRANSITIONAL MUCOSA AND COLONIC NEOPLASIA

Transitional mucosa in the colon is epithelium immediately adjacent to a cancer, usually confined to a zone no larger than 2 cm from the morphological border of the tumor. In 1969, it was first reported by Filipe that this mucosa has abnormal histochemical properties (1,2). Although there was a sharp change in the pathological appearance between the cancer and non-malignant mucosa, a decrease in the

normally expressed sulfomucins accompanied by a replacement with sialomucins was noted in this tissue. Since neoplastic colonic lesions contained a heterogeneous mixture of neutral and other non-sulfated mucins compared with the predominantly sulfated mucins in normal colonic mucosa, Filipe suggested that transitional mucosa was epithelium at an early stage in carcinogenesis (2).

In 1977, Saffos and Rhatigan (3) examined transitional mucosa in detail using light microscopy and reported an increase in the length of crypts, frequent distention and branching of the crypts, and an increase in the number of goblet cells per crypt. However, cytological atypia was not observed and mitotic activity remained confined to the bottom half of the crypt. When these changes were sought in randomly located specimens of grossly normal colon distant from the cancers, significant deviations from the normal histological pattern were seen in only 1 of 20, leading to the conclusion that these changes were generally confined to the rim around the tumor.

The ultrastructural characteristics of transitional mucosa were described by Dawson and Filipe in 1976 (4), and Riddell and Levin in 1977 (5). They reported an increase in the numbers of mature goblet cells in the lower half of the crypt and an increase in immature goblet cells and "intermediate cells" in the upper half of the crypts. The crypts were shown to be larger in diameter and composed of larger cells with larger nuclei than seen in normal colon. Similar changes were described adjacent to a sessile cecal adenoma that was free of cancer.

Therefore, the epithelium appeared to be under the influence of a substance (or substances) that stimulates cell growth and proliferation. This was consistent with the hypothesis that transitional mucosa might be premalignant, although the investigators admitted that it was not possible to conclude whether these were early neoplastic changes or nonspecific reactive phenomena.

Other groups have subsequently described additional changes in the mucin of transitional mucosa such as the appearance of the fetal-type M-1 antigen (6,7). A unique type of carbohydrate structure, that which binds peanut lectin, was found in the mucins of carcinoma as well as transitional mucosa, but not normal colon (8,9). This observation has been confirmed using polyclonal and monoclonal antibodies to the structure recognized by peanut lectin, the T (Thomsen-Friedenreich) antigen (10).

Meanwhile, other laboratories have demonstrated that the morphological or histochemical changes seen in transitional mucosa may be seen adjacent to squamous cell carcinoma of the anus (11,12), a variety of sarcomas in the colon (12,13), endometriosis (13,15) and colonic

inflammation due to diverticulosis and ischemic necrosis (15). These observations have suggested that the morphological and histochemical changes in this mucosa may be reactive rather than a primary premalignant lesion.

HYPOTHESIS

How can these differing explanations be resolved? In part, both may be correct. Transitional mucosa may be a genuine reflection of the neoplastic phenotype, but one which may occur secondary to the paracrine influence of tumor growth factors released by the tumor.
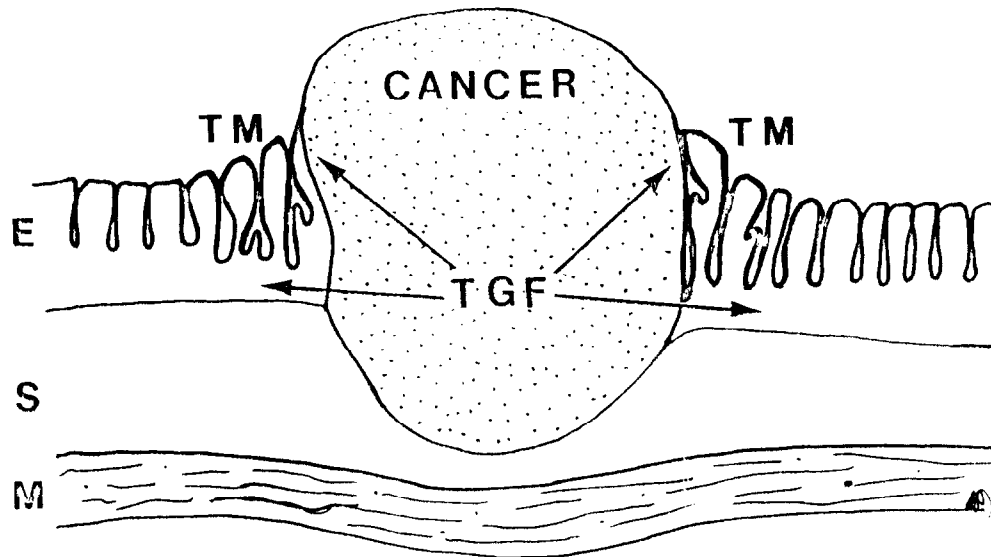

Fig. 1. Schematic representation of transitional mucosa. E = epithelium, S = submucosa, M = Muscularis propria, TM = transitional mucosa, TGF = tumor growth factors.

What evidence may be brought to bear on this hypothesis? First, Filipe reported that the width of the zone of transitional mucosa was related to the size of the tumor, e.g., 1.3 cm in stage A tumors, 2.7 cm in stage B tumors, and 3.5 cm in stage C tumors(2). If transitional mucosa were the premalignant antecedent to cancer, one might expect to find diffuse changes throughout the colon, and the focal changes that preceded a neoplastic lesion would tend to be overgrown by an expanding tumor. In this case, the size of the zone of transitional mucosa would be inversely related to the size of associated tumor, and foci might be found around adenomas and in flat mucosa, which is not commonly the case. An alternative explanation is that "growth factors" produced in the tumor may be released into the interstitial

fluid and diffuse into adjacent tissues, producing the changes seen in transitional mucosa (Fig. 1).

What evidence is there for the existence of diffusible growth factors in tumors? Cancer cells from solid tumors may produce a variety of peptide hormones capable of producing a reversible neoplastic phenotype in non-transformed cells (16-18). These peptides are released from cultured tumor cells into the culture medium, and are theoretically capable of stimulating proliferation and phenotypic changes in adjacent normal tissue by a paracrine mechanism (19).

Two candidate peptides known to be produced by tumor cells are epidermal growth factor (EGF) (20) and platelet derived growth factor (21). Chemical transformation of anchorage-dependent (i.e., non-malignant) cells results in the production of a low molecular weight peptide that interacts with the EGF receptor and promotes the growth of previously anchorage-dependent cells in soft agar. In short, the peptide confers the malignant phenotype to non-transformed cells (22).

A low molecular weight peptide that promotes mitogenesis may therefore be produced by and released from tumor cells, where it may serve an autocrine function. If produced in excess, this peptide may diffuse through the interstitial fluid and influence the adjacent colonic epithelium (i.e., as a paracrine effect). Under the influence of a tumor growth factor, the "transitional epithelium" would be (perhaps reversibly) stimulated to hypertrophy and proliferate. The mechanism by which proliferation is stimulated is not entirely clear, however, it has been observed that EGF binds to a membrane receptor, activates a tyrosine kinase (20,23), and stimulates ornithine decarboxylase activity (24). The amino acid sequences of platelet derived growth factor are highly homologous with the gene product of the simian sarcoma virus (20,25,26). In addition, the C-sis oncogene directs the synthesis of a functional platelet-derived growth factor subunit, and several other oncogenes appear to encode for functional components of the growth-regulating cascade (27).

The zone of transitional mucosa might be a variable function of the relative amounts of tumor growth factors produced by the cancer, both in terms of the intrinsic ability of the tumor to synthesize these peptides per unit of tumor mass, and the total size of the tumor. Thus, it would not be likely to find isolated nests of "transitional mucosa" distant from tumors, and the size of the zone of ultrastructurally and histochemically abnormal epithelium would be related to the ability of the tumors to generate and release these substances. This would explain the presence of transitional mucosa adjacent to metastatic tumors and other non-carcinomatous malignancies in the colon, since the presence of transitional mucosa would be a function of the ability of any tumor to release growth factors. It is

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tempting to speculate that some of the epithelial changes adjacent to large cancers, which have been classically interpreted as residual tissue from a preexisting adenoma, may actually represent previously normal colonic tissue under the influence of stimulation by a tumor growth factor.

It still remains to be explained why the histochemical properties of transitional mucosa are seen adjacent to non-neoplastic disease such as the solitary rectal ulcer or in an inflamed colon. Tissue injury is followed by cellular proliferation and repair, and this may require the activation of cellular genes that produce changes in morphology and glycoprotein biosynthesis that mimic those seen in neoplasia. This process may be mediated in part by platelet derived growth factor , as platelets are sequestered in the usual inflammatory response (21). Again, there is a similarity between the actions of this peptide hormone and the gene product of a well characterized oncogene (21). The difference between repair and neoplasia lies in the autonomy of proliferation achieved in cancer. The difficulty in morphologically distinguishing brisk repair from early neoplasia is known to every pathologist. The explanation may be that both processes share common peptide hormones that stimulate changes in the biology of the epithelial cell critical for repair on the one hand (when regulated) and characteristic of neoplasia on the other (when out of control).

CONCLUSION

Thus, authors on both side of the issue may be correct concerning transitional mucosa. This tissue may appear fundamentally neoplastic in nature because of the paracrine influence of tumor growth factors produced by the adjacent tumor. The tissue is not premalignant under this conceptual framework, since it would not antedate the tumor, and the transformation may be reversible. This would account for the observation that "transitional mucosa-like" colonic epithelium may be found adjacent to other malignancies by virtue of the release of tumor growth factors, and non-neoplastic colonic diseases by virtue of the appearance of platelet derived growth factor involved in the response to injury and repair.

ACKNOWLEDGEMENTS

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