Altered expression of keratin in epithelioid tumours

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Keratins are proteins of 40 to 68 kilodalton molecular weight that make up a class of intermediate filaments 8–10 nm in diameter. Expression of keratins is a common and relatively stable feature of all epithelial cells. In epithelial tumours some keratin polypeptides are either not expressed or are overexpressed. Therefore keratins have gained importance as marker proteins useful in diagnosis of tumours of epithelial origin.

ALL cells of an organism possess identical genetic information, but the reason for diversity in cell phenotype is the fact that differentiated cells express a specific part or parts of the total genome besides those parts of the genome that encode 'household' cellular functions common to all cells. Normally, the expression of a particular set of genes by a cell is a foolproof phenomenon; however, certain environmental factors, such as heat shock[1], and chemical factors, such as vitamins[2–4], hormones[5,6] and enzymes[7], may bring about variations in these patterns of expression.

The specific gene products altered in malignant transformation of cells can be used as marker substances for tumours. Tumour markers are substances that can be used for diagnosis and prognosis of a tumour and also for monitoring efficacy of treatment. Although tumour markers may not be very useful when considered solely for diagnostic purposes, because of their low specificity with respect to a particular malignancy, they serve as effective tools for monitoring progression or regression of a tumour, and have therefore gained much importance.

Classification of tumour markers

A tumour marker may be broadly defined as a biochemical substance produced by the tumour and, when present in significant amounts, indicates the presence of a cancer. They may remain as intracellular substances in the case of tissues or may be released into the circulation and appear in serum. According to Ziegenbein[8] tumour markers can be broadly classified as (i) *tumour-derived products* and (ii) *tumour-associated products.*

Tumour-derived products, or molecules produced by tumours, can be subdivided into synthesized products and metabolically active substances. There are several classes of synthesized products:

(i) *Oncofoetal antigens.* Markers like α-foetoprotein[9,10] and carcinoembryonic antigen[11,12] belong to this class. They are glycoproteins synthesized in the embryonic stage, and reach minimum level at adulthood. Only in certain specific malignancies, their level in serum is increased significantly in adults.

(ii) *Ectopic products.* The modified metabolism of tumour cells resulting from increased cell proliferation leads to increased synthesis of various enzymes compared to normal cells. Marked increase in the activity of some enzymes of glycolysis, protein biosynthesis and nucleic-acid biosynthesis are characteristic of a malignant metabolic process. However, because of the low specificity of these changes, their usefulness in tumour diagnosis is limited.

(iii) *Oncoplacental antigens.* Human chorionic gonadotropin and pregnancy-specific B-1 glycoprotein (SPI) are the best-known members of this class[13–15].

Tumour-associated products are factors accompanying the phenomenon of malignancy. Although this class of markers has low specificity as additional facultative markers they can indicate malignant disease and provide additional information during time-course monitoring. This class includes quantitatively altered serum proteins such as ferritin and β_2-microglobulin[16–18].

Epithelial cells and keratins

The epithelial cell system is highly complex and diversified, both morphologically and functionally. However, epithelial cells have several morphological features in common, the most notable of which is the presence of desmosomes and tonofilament bundles[19]. In malignancy epithelial tissues may lose these features to varying degrees, resulting in the absence of a recognizable epithelial morphology in certain anaplastic epithelium-derived tumours. To overcome the problem of changing morphology during malignant transformation and to be able to recognize the malignant condition, it is essential to have an epithelial cell marker that remains conserved while these changes occur. Expression of keratin polypeptides is a stable feature of all epthelial

carcinomas[20]. There may be variations in their expression, compared to that in normal tissue, depending on the degree of differentiation[21] of epithelial tumours. This property of keratins allows their effective use, in combination with other changes, as markers for malignant transformation in epithelioid tumours.

Keratins are remarkably diverse, highly resistant and the most conserved cytoskeletal proteins present in all types of epithelial cells. They form a major portion of the total cellular protein. The composition of keratin filaments ranges from a few polypeptides to 19 different polypeptides whose isoelectric pH varies from 5 to 8 and molecular weight from 40 to 68 kDa (ref. 22). Human epithelial keratins can be divided into acidic (type I) and basic-neutral (type II) types according to their charge, immunoreactivity, mRNA hybridization, peptide maps, amino-acid sequence and relationship to wool keratins. Acidic type I keratins include polypeptides of lower molecular weight, ranging from 40 to 57 kDa, whereas the basic-neutral type II keratins include polypeptides in the higher molecular-weight range, i.e. 52 to 68 kDa.

Epithelia can be classified according to their keratin composition. The 50-kDa and 58-kDa keratins are present in all cell layers, including the relatively undifferentiated basal cell layer of skin, cornea and other stratified epithelia, whereas the 56.5-kDa and 65–67-kDa keratins are associated only with the more differentiated cells above the basal layer. The 50-kDa and 58-kDa keratin subclasses appear to be characteristic of all stratified squamous epithelia, whereas the 56.5-kDa and 65–67-kDa classes are unique to keratinized epidermis[23,24].

Keratins as epithelial tumour markers

Recently, by diagnostic histopathology and immunohistochemistry, the molecular components that are specifically expressed in epithelial cells have been recognized. These specific components have acquired great importance in tumour biology and pathology and have been designated as 'epithelial differentiation markers'. Such markers have two main applications: (i) in distinguishing epithelial from nonepithelial tumours, and (ii) in distinguishing the type of epithelial tumour.

Importance is now attached to epithelial differentiation markers such as cancer-associated antigen (19–9) (refs. 25–27), cancer-associated antigen (12 5) (refs. 28–31), epithelial membrane antigen (EMA), tissue polypeptide antigen (TPA), keratins[20,23,32–39], squamous-cell carcinoma antigen (SCCA)[40–43] and neuron-specific enolase (NSE)[44–47].

In contrast to other epithelial markers, keratin filaments are usually uniformly distributed among carcinoma cells. The degree of stability of keratin expression in tumours is remarkably high. Therefore keratin is also a reliable marker for (i) undifferentiated and anaplastic carcinomas, (ii) disparately growing infiltrating carcinoma cells, and (iii) metastasizing single carcinoma cells in suspension. TPA. which is regarded as a marker of cell proliferation, is a mixture of proteolytic fragments containing the relatively stable α-helical rod domains of simple epithelium-type cytokeratins. These fragments are probably released during necrosis and lysis of the carcinoma cells. Thus TPA should be regarded as a broad-spectrum epithelial tumour marker and not as a specific molecular marker for epithelial neoplasms.

Expression of keratins in epithelial tumours

Keratins have been used effectively as markers for epithelial carcinomas, especially those of stratified and squamous-cell origin, e.g. lung carcinomas[48–51], breast carcinomas[52–54], urinary bladder carcinomas[55], thymomas[56] and cervical carcinomas[21,57]. Since the gastrointestinal-tract lining, from the buccal cavity to the rectum, including the pancreas and gall bladder, is of epithelial origin, keratin serves as a useful marker for gastrointestinal tumours[39,58].

Nelson *et al.*[33] and Osborn[59] showed that keratin polypeptides can actually be used as cell type-specific molecular markers for tumours of epithelial, stratified or squamous-cell origin. Moll *et al.*[20] studied patterns of expression of keratin polypeptides in certain human carcinomas by immunoblotting and 2D gel electrophoresis. Keratin has been used as a differential marker in thyroid, gastrointestinal, prostate, lung and breast tumours.

Thyroid tumours

On the basis of the presence of keratin in various types of thyroid tumours Miettinen *et al.*[60] concluded that papillary and follicular thyroid carcinomas originate from different types of epithelia. Lodewijk *et al.*[61] also distinguished papillary, follicular carcinoma and follicular thyroid adenoma from each other on the basis of the pattern of expression of keratin 19.

Prostate tumours

Keratins have been widely used as markers in prostatic tumours[62,63]. Svanholm *et al.*[64] observed expression of keratin polypeptides 8, 18 and 19 in prostatic carcinomas and also variable expression of polypeptides 7 and 9. In comparison with benign prostatic hyperplasia, they showed that only the luminal

cells are stained with antibodies against keratin polypeptides 8, 18 and 19.

Lung carcinomas

In lung cancers keratin polypeptides 14, 5 and 15 are generally expressed. Sun *et al.*[65] and Schlegel *et al.*[66] found squamous-cell lung carcinomas to be strongly positive for keratin polypeptides 14, 15 and 5; adenocarcinomas are weakly positive, and undifferentiated and carcinoid tumours are negative for these polypeptides.

Breast tumours

Keratin polypeptide 19 is the major polypeptide expressed in mammary carcinomas. Bartek *et al.*[52] and Schlegel *et al.*[66] found ductal adenocarcinomas to be strongly positive, fibroadenomas to be weakly positive, and cystosarcoma phyllodes and lobular adenocarcinomas to be negative for keratin 19.

Gastrointestinal carcinomas

Buccal carcinomas. Oral cancers are mostly (90%) of squamous-epithelial origin, and hence keratins are the best possible histological as well as biochemical markers for these tumours[67,68]. Vaidya *et al.*[68] found that normal buccal squamosal mucosa expresses mainly polypeptides 4, 5, 13 and 14 and well-differentiated buccal squamosal carcinomas aberrantly express keratins 1 and 16, whereas expression of keratins 18 and 19 is by and large a constant feature. Hence polypeptides 1 and 16 can be used as marker proteins for well-differentiated buccal mucosal squamous carcinomas.

Oesophageal tumours. Schlegel and Harris[69] found that the normal tissue expresses keratins 4, 5, and 8, whereas in oesophageal carcinomas keratin 8 is absent or markedly reduced, and 4 and 5 are present in reduced amounts.

Colorectal adenocarcinomas. Fisher *et al.*[70] observed the reactivity of various keratin antibodies with their particular keratin expressed in gastrointestinal adenocarcinomas and found that normal colorectal tissue expresses keratins 7, 18 and 19 whereas malignant tissue from the same part expresses keratins 18 and 19 but not 7. Thus, in colorectal carcinomas, keratin polypeptide 7 can be used as a marker (Figures 1 and 2).

Pancreas, stomach, gall bladder. The study of Fischer *et al.*[70] has been further extended to the pancreas, stomach and gall bladder. In these organs the normal

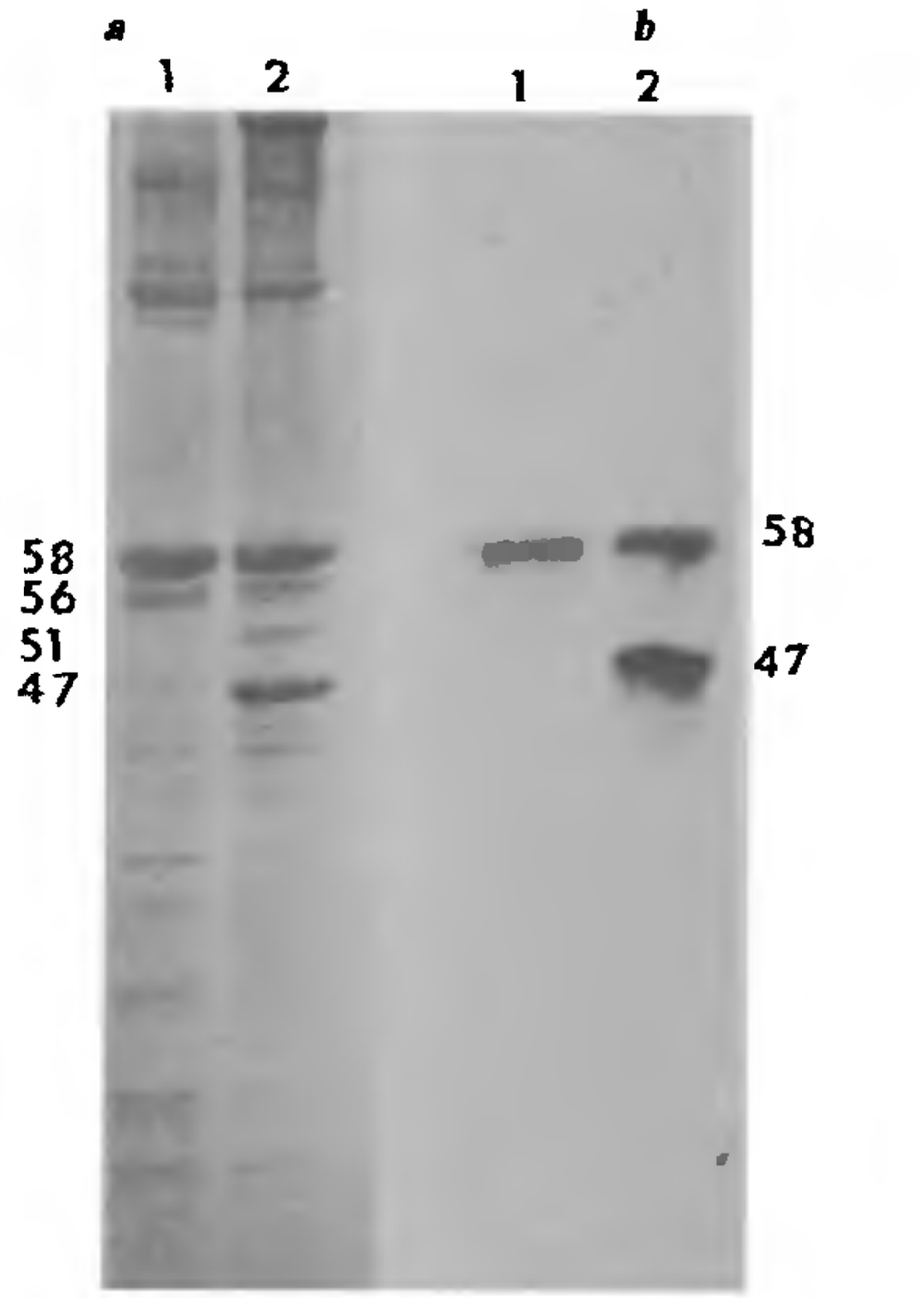

Figure 1. *a*, SDS-PAGE of total homogenate of human rectal adenocarcinoma (lane 1) and normal tissue of rectum (lane 2). Note the four keratin polypeptide bands of 47, 51, 56 and 58 k Da in lane 2; in lane 1 the polypeptide of 47 k Da is markedly reduced and 51 is totally absent. *b*, Western-blot analysis of *a*. Two polypeptide bands are visible in lane 2 (normal tissue) while in lane 1 (adenocarcinoma) only one bands is visible.

epithelia express keratins 8, 14, 18 and 19, whereas malignant epithelia from these organs express keratins 8 and 18 but not 14 and 19. Osborn *et al.*[39] also support this observation. Depending on the organ and the degree of differentiation, there are certain differences in the pattern of keratin expression that can be effectively used to specify the keratin polypeptide which can be used as a marker in a particular type of carcinoma.

Conclusion and future prospects

Studies on expression of keratin in various epithelioid tumours revealed that keratin polypeptide synthesis is regulated by the degree of malignancy and the type of epithelial cells involved[21,71–73]. There may be either up-regulation or down-regulation of keratin polypeptides during malignant transformation; this also depends on the stimulus given and the target tissue involved. The up-regulation of keratin polypeptides in oestradiol target tissue has been studied extensively by histological[19,74], biochemical[5,75] and molecular-biological

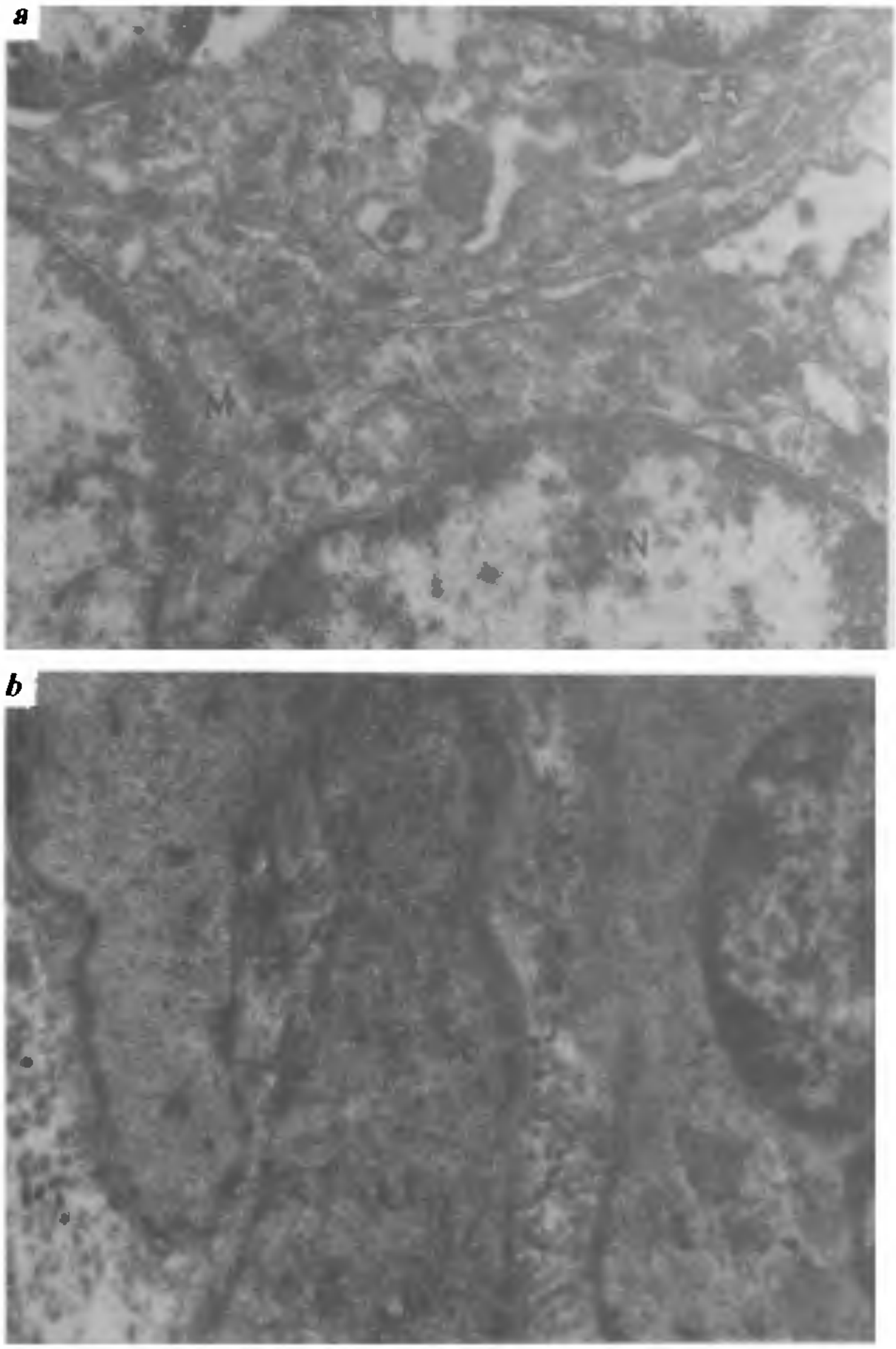

Figure 2. *a*, Transmission electron micrograph of human rectal adenocarcinoma showing various cytoplasmic structures. Note total absence of tonofilament bundles in the cytoplasm (×22,000). *b*, TEM of normal human rectal epithelial cells showing tonofilament bundles in the cytoplasm (×22,000) (N, Nucleus; *ER*, endoplasmic reticulum, *R*, polyribosomes, *M*, mitochondria, Tb, tonofilament bundles)

techniques[76]. Various factors that down-regulate keratin polypeptide expression have not been investigated in detail, although there are a few reports that mention the involvement of retinoic acid in the down-regulation of these polypeptides[77,78]. The mechanism of down-regulation of keratin polypeptides is not fully understood.

It has been generally observed that keratin expression is markedly reduced or the expression of certain polypeptides may be totally inhibited during malignant transformation. This suggests that some inhibitory substance may be produced during malignant transformation that inhibits expression of keratin polypeptides at the transcriptional or translational level, or both. There may be another possibility, in which

keratin polypeptides are incapable of being phosphorylated[79], and, in turn, cannot be cross-linked by transglutaminase[80]. Thus some of the polypeptides synthesized may be degraded to an extent where they are not detected or are present in low quantities. Since the mechanism of down-regulation of keratin polypeptides during malignant transformation is not yet clear, it opens up new avenues of research where the suggested hypotheses can be tested.

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RESEARCH ARTICLES

Parallelization of molecular electronic-structure calculation

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Electronic-structure calculations are useful for understanding atomic and molecular processes. Here we present a parallel *ab initio* algorithm developed for the preliminary electronic-structure program with special emphasis on four-index transformation for the transputers at the Centre for Development of Advanced Computing (C-DAC) in Pune. We also present results obtained on a four-node machine.

DEVELOPMENTS in computational quantum chemistry have therefore been linked with advances in computer hardware and software[1]. We have been developing an accurate electronic-structure package for parallel computing. The simplest *ab initio* Hartree–Fock (HF) or self-consistent field (SCF) electronic-structure calculations can be very time-consuming for large systems, and scale as N^4 (N is 2-5 times the number of electrons). Further, calculations. that incorporate electron correlation like the coupled cluster (CC) calculations, are even more expensive[2] and scale as N^6-N^7. Even the first cut in correlated theory, like second-order many-body perturbation theory (MBPT 2), scales as N^5, primarily owing to the necessity of transforming the integrals from atomic-orbital (AO) basis to molecular-orbital (MO) basis. Bender Shavitt's algorithm[3-5] provides us with the best of the required algorithm. For a system of reasonable size, meaningful *ab initio* computation is not possible without high-speed integrated circuits. While the development of high-speed chips and cheaper computer hardware is opening new avenues, an attractive alternative lies in parallel computation.

Much work has already been done on parallelization of the SCF code[5-7]. However, comparatively less attention has been paid on parallelization of correlation calculations as well as on the four-index transformation preceding these[8,9]. We focus primarily on this aspect in this paper. The parallelization of four-index transformation attempted earlier was based mainly on the algorithm of two two-index transformations. However, this involves an extra sorting at the beginning and at the end of the first two-index transformation. In addition, it requires more memory. In view of the limited memory available on our hardware, we found it useful to parallelize Bender's original algorithm. We highlight the merits of the strategy used to achieve this and discuss the specific problems that can arise. We also mention parallelization of the SCF code, including the one on evaluation of the two-electron integrals. We discuss our experience with the significant parts of this code and present preliminary results on a four-node transputer machine.