Landscaper seeks remunerative position


Abstract
Juvenile polyposis syndrome (JPS) is an inherited genetic defect resulting in production of multiple hamartomas, some of which subsequently develop into carcinomas. About 30% of these patients are known to have a heterozygotic defect in the SMAD4 gene that codes for a mediator of transforming growth factor beta signalling. The loss of one of the two normal SMAD4 alleles is not thought to be sufficient to induce hamartomas but requires the additional loss of the residual normal allele as a secondary event. In patients with JPS, the hamartomas were thought to result from loss of the second normal allele in stem cells that produced stromal cells and equally importantly, that the overlying epithelium continued to have one copy of the normal allele. On this basis, the subsequent development of carcinoma of the epithelium was considered to be due to the epithelial cells being positioned in a highly abnormal microenvironment ("soil", hence landscaper theory). In this paper, Woodford-Richens et al used fluorescence in situ hybridisation (FISH) directed against the SMAD4 gene to probe individual cells of the polyps to determine which had lost both copies of SMAD4. They found that cells of the stroma and epithelium, but not the inflammatory infiltrate, had lost both alleles. A complicated theory involving "cross talk" between a normal overlying epithelium and an abnormal stroma does, therefore, not have to be invoked to explain why the epithelial cells subsequently undergo malignant transformation. In addition, the finding of identical secondary genetic defects in both the epithelium and stroma of the hamartomas suggests that they originate from the same stem cells and not from distinct lineages as previously thought.

Comment
In 1998, Kinzlker and Vogelstein proposed a hypothesis that expanded the limited data available from known specific genetic defects into a general mechanistic process underlying malignant transformation of the gastrointestinal tract. In this model, classic tumour suppressor genes such as APC function as "gatekeepers", preventing, in the case of APC, the translocation of β-catenin to the nucleus where it complexes with Tcf- 4 and induces, inter alia, expression of c-myc, with ensuing increased cell proliferation and selection. Secondly, DNA repair proteins such as MLH1 and MSH2 act as "caretakers" of the genome, correcting mismatches in potentially important genes and thus preventing their inappropriate expression. Finally, in a series of diseases as disparate as inherited polyposis syndromes such as juvenile polyposis syndrome (JPS), and acquired conditions such as ulcerative colitis, changes in the stromal component of the lesions—the clonal stromal component of the hamartomas of JPS and the inflammatory infiltrate in ulcerative colitis—result in an altered terrain for epithelial cell growth which increases cancer susceptibility (the "landscaper" hypothesis or effect). In this model, it is envisaged that mutations in the stroma of the hamartomas in some way modulate epithelial cell proliferation through epithelial:mesenchymal interactions or epithelial damage (fig 1) while the cocktail of cytokines secreted by the inflammatory infiltrate have similar effects on the colonic epithelium in ulcerative colitis. The detailed molecular processes underlying this epithelial:mesenchymal “cross talk” remain to be elucidated although several examples have now been demonstrated. For example, large...
fold gastritis is a premalignant gastric condition that involves *Helicobacter pylori* colonisation causing an increase in cytokine (interleukin 1β) production by the inflammatory infiltrate. This in turn stimulates hepatocyte growth factor production and release by mesenchymal cells, resulting in increased epithelial proliferation due to the released hepatocyte growth factor binding to c-met receptors on epithelial cells. In conditions such as these, a general stimulation of proliferation may allow subpopulations of cells with genetic defects to expand. Alternatively, the constituents of the inflammatory cocktail, such as nitric oxide, free radicals, and the cytokines themselves, may result in direct genetic injury. In addition, modulation of cytokine and growth factor production might influence cell growth and cell-cell interactions via mechanisms such as E-cadherin downregulation and β-catenin signalling.

While the jobs of the “caretaker” and “gatekeeper” appear safe, at least for the moment, a recent paper by Woodford-Richens and colleagues has made the position of the “landscaper” if not redundant at least tenuous. Epithelial malignancies are increased in incidence in both JPS and ulcerative colitis. The “landscaper” effect was coined to explain the apparent paradox of a stromal lesion—the hamartomas of JPS—predisposing to an epithelial malignancy: the abnormal stromal environment affects the development and growth of epithelial cells. JPS is one of several hamartomatous polyposis syndromes which include Peutz-Jeghers syndrome and Cowden’s syndrome, all of which show multiple polyps in the gastrointestinal mucosa, with cystically dilated glands and a cellular stroma composed of smooth muscle, fibroblasts, and myofibroblasts. The spectrum of organ specific malignancies in these syndromes is wider, with Peutz-Jeghers syndrome predisposing to breast, cervix, and gastrointestinal cancers, Cowden’s syndrome to thyroid and gastrointestinal tumours, and JPS to carcinomas occurring in the intestine and stomach.

The molecular pathology of these lesions is now being studied: in Peutz-Jeghers syndrome, the polyph epithelium shows clonal allelic loss at the LKB1/STK11 locus (encoding a serine-threonine kinase) on chromosome 19p13.4, and carcinomas arising in Peutz-Jeghers syndrome show loss of this wild-type allele, strongly favouring evolution from hamartomas to carcinoma. Moreover, hamartomas, and both adenomas and carcinomas in Cowden’s syndrome, show loss of heterozygosity at the PTEN/MMAC1 locus on chromosome 10q23.3, indicating that further loss of the hamartoma with occasional progression to carcinoma, in the classical tumour suppressor gene mode.

In JPS, germline mutations in the SMAD4, or DPC4 gene on chromosome 18q21.1, are seen in a proportion of cases. Most SMAD4 mutations produce a truncated protein that inactivates its function as a cytoplasmic mediator in the transforming growth factor β signalling pathway. SMAD4 appears to act as a classical tumour suppressor (gene) in the colon and pancreas, and importantly, a high incidence of colorectal cancer has been reported in a large JPS kindred, linked to 18q21.1, with mutation in SMAD4, further suggesting that SMAD4 acts as a tumour suppressor gene in JPS.

Using microsatellites, Woodford-Richens and colleagues have demonstrated that JPS polyps containing a constitutively mutant fraction often lose the wild-type SMAD4 allele, strongly suggesting that somatic loss of this allele is the first somatic mutation, inducing the growth of the hamartoma. Thus hamartomas in JPS resemble colonic *adenomas*, rather than primarily stromal lesions as previously thought. Moreover, FISH showed loss of SMAD4, not only in epithelial cells but also in stromal fibroblasts and pericytial myofibroblasts, but not in lymphocytes.

These findings indicate that the epithelium in JPS polyps is clonal and somewhat surprisingly, this clonality is shared by a component of the stroma, suggesting that the precursors of these lesions are laid down very early in development, before epithelial/mesenchymal differentiation in the intestinal anlage, with later clonal expansion. Alternatively, the mutation could occur later in life as a stem cell with plasticity of a greater degree than is usually considered. Certainly other neoplasms with multiple lineages, such as hamartomas in tuberous sclerosis and mixed mullerian tumours which contain both epithelial and mesenchymal elements, appear clonal.

This brings the epithelium into sharp focus in the formation of the hamartoma and its progression to carcinoma. Thus in JPS, and also possibly in other hamartomatous lesions such as Cowden’s syndrome and Cowden’s syndrome, the development of epithelial malignancy is likely to be due to direct progression of the epithelial component. Therefore, although the previous suggestion of complex epithelial/mesenchymal interactions remains a possibility in the causality of malignant development of JPS, invocation of Occam’s razor dictates that the most “straightforward” mechanism (involving the minimum number of assumptions) should be considered to be the most likely. There is no need therefore to incriminate the “landscaper” hypothesis: in these lesions, job flexibility or retraining to the “gatekeeper” career pathway seems more appropriate. Whether or not openings are available for landcapers in other territories, such as the elderly and colored patients with ulcerative colitis, remains to be seen.

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