for two to three years as this is when they are at the greatest risk of relapse.

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Adhesion and the cancer jigsaw

May help explain metastasis

In 1889 Paget asked "What is it that decides what organs shall suffer in a case of disseminated cancer?"[1] More than a century later this question remains unanswered despite intensive investigation into tumorigenesis and metastasis. New research, however, is improving our understanding of the molecular basis of neoplastic behaviour. Such work may provide better variables to assess tumour cell biology, which may, in turn, form the basis of new modalities in the treatment of cancer.

The concept of adhesive forces holding tumour cells together and the decrease in this adhesion allowing them to spread is not new. Fifty years after it was first proposed,[2] cellular adhesion (and the molecules that are responsible) is attracting increasing attention. This has been facilitated largely by the production of monoclonal antibodies directed against these cell adhesion molecules and the ability to introduce alterations into the genetic make up of a cell in order to study changes in subsequent protein expression.

Two sorts of receptors mediate cellular adhesion—those that play a part in intercellular interactions and those that mediate interactions between cells and their surrounding extracellular matrix (a scaffold of glycoproteins and collagens supporting the cells). The main receptors responsible are integrins, cadherins, selectins, and members of the immunoglobulin superfamily.[3] Integrins are the prime mediators of cell-matrix interactions and cadherins of intercellular interactions. Apart from being implicated in tumour invasion and metastasis they have also been implicated in wound healing, inflammation, coagulation, and embryogenesis.[4]

Neoplastic transformation results from the loss of normal controls over the growth and differentiation of cells[5]; once transformed, the cells require a reduction in adhesiveness to detach themselves. For migration to occur the affinity between cells and endothelium or lymphatic channels needs to change. For a cell to attach in a particular target organ further changes in receptor expression, at both the target and the invading cell, are necessary. A prerequisite for these cells to form a metastasis is an increase or re-expression of intercellular adhesion receptors coupled with a capacity to grow independently.[6,7]

Thus, theoretically, at any stage the malignant process may be interfered with and arrested by modulating adhesion. Several laboratories have reported experiments in which dissemination of intravenously injected tumour cells in mouse tissues has been inhibited by a simultaneous injection of a peptide containing the protein sequence recognised by many integrin receptors as their ligand. The loss of adhesion resulting from the peptide injection may deny the cells anchorage and traction for growth and migration.[8] In vitro and in vivo studies have shown that in many human tumours there is a widespread deregulated expression of cell adhesion molecules,[9-11] and this has implications for the behaviour of these neoplasms.

Evidence is now emerging that these molecules not only are important in adhesion but also transduce signals into cells that control morphological differentiation, gene expression, and cell motility.[3] The control of cellular morphology through linkage of the receptor tail to the cytoskeleton has provoked much interest. As an inverse relation exists between growth of the tumour and morphological differentiation in many human cancers[12] induction of a differentiated phenotype by the promotion of the activity of cell adhesion molecules has been proposed as a mode of treatment.[13] This would probably limit the growth potential of a developing tumour. Modulation of the expression of integrins and cadherins either by blocking with monoclonal antibodies[14] or by genetic manipulation with full length cDNAs or antisense RNAs has produced dramatic results on the differentiation of tumour cells. Other workers have found that the invasive and metastatic potential of neoplastic cells falls when they are subjected to these treatments.[15,16]

Such findings provide another perspective on the metastatic cascade. The process is, however, much more complex, and other modifiers of biological responses such as soluble growth factors and cytokines clearly have some degree of interplay with adhesion molecules.[17]

Clinically, cell adhesion molecules may serve as selective markers for some tumours. This could be useful for either diagnosis or prognosis. The location of these molecules (or their neoplastic isoforms) on the surface may facilitate the use of specific monoclonal antibodies coupled with drugs or radioactive markers in tumour imaging and delivery of drugs.[18] The possibility of altering adhesiveness through genetic transfection in vivo, however, remains to be explored.

Advances in our understanding of how the function of adhesion molecules is controlled may lead to their future incorporation into treatment. The recent cloning and characterisation of a gene located on chromosome 16q that

regulates cell adhesion[19] provide further experimental evidence that the pieces in this puzzle are finally beginning to come together.

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Searching for gastrinomas

Visceral angiography is improving detection

The three main causes of peptic ulceration are infection with *Helicobacter pylori*, ingestion of non-steroidal anti-inflammatory drugs, and the gastrinoma (Zollinger-Ellison) syndrome. Effective treatment now exists for the first two conditions: antibiotics, especially in the presence of effective acid inhibition, cure most ulcers related to *H pylori* infection. Coadministration of antisecretory agents and misoprostol may prevent damage induced by non-steroidal anti-inflammatory drugs.

Patients with the gastrinoma syndrome, once the syndrome has been diagnosed, can be treated with high dose proton pump inhibitors such as omeprazole. These patients remain at risk, however, of considerable morbidity and mortality from gastrinoma metastases. Thus it is important to identify the one in 1000 patients with peptic ulceration who has a gastrinoma and to remove it.

What increases the likelihood that a patient will have a gastrinoma? Such patients have a history of severe ulcer disease refractory to medical treatment, often occurring in atypical sites such as the oesophagus and jejunum. Complications, such as stricture or haemorrhage, occur frequently, and patients may have acid driven severe watery diarrhoea, sometimes antedating the ulceration. To diagnose the condition a raised gastrin concentration should be found in a plasma sample taken from the fasting patient. Treatment with omeprazole must be stopped two weeks, and H_2 blockers three days, before sampling. The commonest confounding cause of a raised gastrin concentration is relative hypochlorhydria, even in patients with active peptic ulcer disease. Chronic renal failure or hypercalcaemia may cause hypergastrinaemia in patients with common peptic ulcer disease.

To distinguish between these conditions basal gastric acid output must be measured. Only in the gastrinoma syndrome is a high gastrin concentration associated with an increased acid output. A basal output of 10-15 mmol of hydrochloric acid per hour is suspicious of the diagnosis and an output greater than 15 mmol/hour is characteristic. Measuring acid output after stimulation with pentagastrin does not improve diagnostic accuracy.

The intravenous secretin test has been advocated as an alternative to measuring gastric acid output. This test relies on the fact that the autonomous gastrinoma increases gastrin secretion in response to secretin. In patients with ulcers but without gastrinomas a balance exists between stimulation of the gastrin secreting G-cells by secretin and inhibition by local factors, such as somatostatin, so that gastrin concentrations rise to a much lesser extent, if at all.[1,2] The best criteria for diagnosing the gastrinoma syndrome with the secretin test are based on the absolute rise in gastrin concentration and so must be standardised for individual assay laboratories.

Regrettably, a significant rise in plasma gastrin concentration has also been found in some patients with hypergastrinaemia related to achlorhydria[3] and also in patients with peptic ulcer disease but without a gastrinoma.[4,5] Adjusting the criteria to minimise the rate of false positive results reduces the sensitivity of the secretin test to about 80%. Thus it should be reserved for those patients who have equivocally raised acid output or plasma gastrin concentration or who are unable to stop taking omeprazole because of rapidly recurring severe ulceration.

Once a gastrinoma has been diagnosed it must be localised. Nine out of 10 sporadic gastrinomas occur in the gastrinoma triangle, bounded by the third part of the duodenum, the neck of the pancreas, and the porta hepatis; up to 40% of these are in the duodenum.[7,8] Pancreatic gastrinomas have already metastasised to the liver in over half of cases, but duodenal gastrinomas have been reported to be clinically less malignant, with only 10% associated with hepatic metastases. Yet metastasis to local lymph node occurs in as many as 70% of duodenal gastrinomas less than 0·5 cm in diameter (microgastrinomas). All gastrinomas must therefore be regarded as possibly malignant, and curative surgery should be performed whenever possible.[6,7]

Some 60% of gastrinomas are greater than 1 cm in diameter, often with associated hepatic metastases, and these can almost always be identified with transabdominal ultrasonography and abdominal computed tomography. Magnetic resonance imaging, with present technology, does not seem to improve the sensitivity of these techniques.[8] The remaining 40% of gastrinomas represent the major clinical problem as these tumours are likely to be amenable to curative resection and yet their localisation by conventional imaging is poor.

Highly selective angiography improves localisation, with angiographic detection rates from specialist referral centres