STAR and RUTH trials there will be additional prospective data to support, or refute, claims for raloxifene as a multifunctional drug.

The future for selective oestrogen receptor modulators looks promising, but what can be said now for the practitioner? In the United States tamoxifen is approved for treating and preventing breast cancer. It has been tested prospectively for 25 years.[12] Raloxifene is approved for preventing osteoporosis, but now there is evidence that it may reduce the incidence of breast cancer in the older population. A risk reduction for breast cancer contrasts with the effect of hormone replacement therapy, but it must be emphasised that neither tamoxifen nor raloxifene ameliorates menopausal symptoms so they are not substitutes for hormone replacement therapy. Most importantly, although raloxifene is a chemical cousin of tamoxifen, it has not been tested as a breast cancer treatment so there is no evidence to suggest that a switch from tamoxifen to raloxifene would be wise. In fact it may be dangerous, as there is also no information about what dose to use. What can be said is that raloxifene's efficacy as an osteoporosis agent is documented, and proof of multifunctionality must await the results of ongoing trials. Nevertheless, it is clear that a new era of preventive therapeutics has arrived, and through the clinical trials process a range of novel multifunctional drugs will become a reality within the next decade.

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Cell adhesion molecules

Sticky moments in the clinic

Cell adhesion molecules were first identified through their ability to allow cells to adhere to each other and to the extracellular matrix. We now know, however, that this group of cell surface receptors not only promotes adhesion but also allows cells to interact and communicate with each other and their environment and, in doing so, regulates a range of cell functions, including proliferation, gene expression, differentiation, apoptosis, and migration. A theme issue of *Molecular Pathology*, published this month, provides an opportunity to review work on cell adhesion, including its application to clinical practice.

There are at least five groups of cell adhesion molecules: integrins, selectins, adhesion molecules belonging to the immunoglobulin superfamily, cadherins, and the CD44 family. All cell adhesion molecules bind to other cells or matrix components through their interaction with appropriate counter-structures, referred to as a ligands. In some cases the ligands are themselves adhesion molecules, as is the case with the selectin family, whose ligands are members of the immunoglobulin superfamily, and vice versa.

Cell adhesion molecules are critical to many normal physiological processes. During embryogenesis, for example, the differential expression of adhesion molecules is responsible for the selective association of embryonic cells into specific tissues, and in the immune system adhesion molecules mediate the migration and homing of lymphocytes to specific tissues. Given their widespread importance it is not surprising that cell adhesion molecules have also been implicated in many diverse pathological processes such as inflammation and wound healing, septic shock, transplant rejection, cancer, and atherosclerosis.

Recently, an understanding of the role of cell adhesion molecules in these processes has suggested their use as either diagnostic or prognostic markers, or as potential targets for therapeutic intervention. This is best exemplified in cancer. Loss of cell-cell adhesiveness contributes to the process of metastasis, whereby tumour cells can invade surrounding tissues and disseminate to distant organs. The cell adhesion system mediated by E (epithelial) cadherin has been shown to be critical to maintaining cell-cell adhesion and is often inactivated in epithelial cancers. This inactivation may result from mutations that directly affect the genes for E-cadherin or may occur in those genes that code for the catenins, a group of molecules that connect cadherins to actin filaments and establish firm cell-cell adhesion. In fact, loss of E-cadherin expression is an adverse

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prognostic indicator in several carcinomas, including those of the colon, stomach, prostate, and breast.[1] In some situations, as in the development of oesophageal cancer, temporal changes in adhesion molecule expression correlate with tumour progression.[2]

Abnormalities in the CD44 cell adhesion molecules have also been intensively investigated in many types of cancer. Variants of the CD44 protein may be created by a process known as alternative splicing. Expression of certain CD44 variants (CD44v) by cancer cells is associated with the ability of these cells to metastasise and with a poor prognosis.[3] Also, soluble forms of CD44 (sCD44) may be detected in the serum of patients with cancer and in some settings correlate with clinical markers of disease. In non-Hodgkin's lymphomas, for example, high serum levels of sCD44 at diagnosis are associated with a high international prognostic index score, poor response to treatment, and an unfavourable outcome.[4]

The possible use of CD44 as a diagnostic marker is emphasised by the detection of CD44 variants in exfoliated cells in urine, which correlates with the presence of urogenital malignancies,[5] and in faecal samples from patients with colorectal cancer.[6] Furthermore, animal experiments have shown that injection of reagents interfering with CD44-ligand interaction (for example CD44v specific antibodies) inhibits local tumour growth and metastatic spread.[7] Recently, Dall et al described a novel approach to target CD44 in cervical cancer: cytotoxic T lymphocytes were genetically modified to express a recognition site for a CD44v form often detected in cervical cancer but absent from normal cervical epithelium.[8] Target cells expressing this CD44v were killed by these cytotoxic T lymphocytes, but control cells were not. Clearly, although still experimental, these approaches offer promise as potential therapies for metastatic cancers in which CD44 variants are expressed.

One of the most important events in the reaction to all forms of injury is the adhesion of leucocytes to endothelium, which precedes their emigration to the tissues and is central to the processes of inflammation and immune reaction. Leucocyte adhesion to the endothelium is mediated by adhesion molecule pairs, principally the selectins (E, L, and P), members of the immunoglobulin superfamily (ICAM-1 and VCAM-1), and the integrins. The importance of these adhesion molecules in lymphocyte recruitment has been shown in several pathological processes, including transplant rejection, septic shock, atherosclerosis, and late phase hypersensitivity and in reperfusion injury.

For example, in acute stroke it is postulated that the presence of adhesion molecules on the surface of glial cells facilitates the post-ischaemic migration of leucocytes through the brain parenchyma. The relevance of adhesion molecules to the pathogenesis of ischaemic brain damage has been corroborated by studies showing that, compared with normal controls, ICAM-1 deficient mice show a significant reduction in cerebral infarction size after transient middle cerebral artery occlusion.[9] One observation with potential clinical relevance is that the expression of adhesion molecules caused by cytokines is higher in endothelial cells from hypertensive rats than in those from normotensive rats, suggesting that ischaemic injury may have more severe consequences in hypertensive individuals.[10] Up regulation of adhesion molecules has also been documented in people with stroke. Leucocytes from patients having an ischaemic stroke or transient ischaemic attack showed higher integrin (CD11a) expression within 72 hours of the onset of symptoms than in controls matched for age and risk factors.[11]

The potential for intervention to prevent lymphocyte recruitment in many pathological processes is suggested by recent studies in which antisense oligonucleotides to ICAM-1 prevented ischaemic reperfusion injury and delayed graft rejection in experimental renal transplantation.[12] It is possible to envisage how such approaches may be applied to treating or preventing other conditions in which adhesion molecules have a pathogenic role. Recently, for example, antibodies to ICAM-1 have been shown to reverse atherogenesis in hypercholesterolaemic rats.[13] The detection of raised levels of ICAM-1 and VCAM-1 in patients with stable angina pectoris who develop myocardial infarction suggests that similar approaches may be useful in preventing cardiovascular disease in humans.[14]

Although the diagnostic and therapeutic usefulness of adhesion molecules remains largely untapped, an increasing awareness of their roles in disease states suggests greater opportunities for their clinical application. For example, new knowledge of the role of adhesion molecules in the pathogenesis of infectious diseases may enable new approaches to treating resistant infections.[15] In future, the development of treatments for inflammatory diseases may depend on the selective inhibition of lymphocyte recruitment to a particular tissue without preventing normal recruitment elsewhere. Alternatively, lymphocytes could be programmed in vitro to express receptors that would target specific tissues.

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Lessons from a cyclist

Doctors should do more to promote physical activity

One hundred years ago the *BMJ* reported that "In France the bicycle has done wonders, as those who remember Paris, Fontainebleau, and the intervening districts thirty years ago can bear witness if they once more revisit that pleasant part of the world."[1] For three weeks in July the bicycle in France was, once again, the source of wonderment, as Lance Armstrong won the world's premier cycling race, the Tour de France. Armstrong's quest for victory during the gruelling event not only captured the attention of sports enthusiasts but also that of the media and the public at large, because just three years ago Armstrong was diagnosed with metastatic testicular cancer. He began his racing comeback early in 1998 after four rounds of chemotherapy and two operations. Acknowledging the role of modern medicine in his achievement, Armstrong noted that "Fifteen or 20 years ago, I wouldn't be alive, much less riding a bike or winning the Tour de France." Beyond this remarkable story of determination and courage, the Tour de France reminds us of the health benefits of exercise and physical activity.

Although the effects of physical activity on testicular cancer have not been reported, physical activity reduces the risk of cancer of the breast[2] and colon,[3] diabetes, coronary heart disease, and several other diseases.[3 4] Participants in the Tour de France engaged in vigorous activity for several hours each day, but increasing evidence suggests that health benefits can occur with activity of much lesser intensity. The US Surgeon General's report on physical activity recommended 30 minutes of moderate physical activity on most, if not all, days of the week.[4] Lifestyle activities such as walking or working in the garden seem as beneficial to health as more structured exercise, at least for sedentary middle aged people.[5 6]

Achieving the Surgeon General's recommendations for the population will be as challenging as winning the Tour de France. More than 60% of Americans do not engage in regular physical activity, and 25% are sedentary.[4] Despite the beneficial effects of physical activity, only 20% of US physicians advise their patients about physical activity.[7] However, doctors can play an important part in preventing chronic disease, as shown by observations that more counselling by doctors about physical activity increased physical activity levels among sedentary adults in Australia[8] and New Zealand.[9]

Doctors represent only one part of the solution of how to raise physical activity levels. Community structure may directly affect daily physical activity. For example, in the Netherlands 30% of all trips are by bicycle and 18% are by walking.[10] Comparable figures for England and Wales are 8% by bicycle and 12% by walking, and for the United States 1% by bicycle and 9% by walking. Lack of community infrastructure that supports physical activity, like sidewalks or bicycle trails, as well as cultural norms that favour car use over physical activity as part of daily living, probably account for some of these differences. Improved design of communities to include sidewalks and bicycle trails represents an important environmental intervention to promote physical activity. Such changes will also foster the development of future generations of athletes like Lance Armstrong.

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