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Sydney Brenner's epigram 'genes make DNA, make proteins, make money' explains the phenomenally fast progress in structural genomics and bioinformatics that has made it possible accurately to predict the structure of a protein from its genetic sequence. Armed with this knowledge, drug companies can set about the synthesis of novel medicinal substances that excite or block specific cell-surface proteins. With such knowledge, the pharmaceutical companies are on the threshold of changing global disease patterns and potentially of making vast profits. But, as is usually the case, there is another side to the coin: for example, triclosan, an antiseptic additive found in many household products, has the same target as isoniazid; this raises the spectre of losing control of tuberculosis altogether.

New proteins, new names

Coagulation proteins

The complexity of the human coagulation cascade is likely to have had some survival value for the species as well as for the individual. Elucidating the structure of the proteins involved and their genomic evolution will increase our knowledge of how these proteins control and direct the coagulation process and, with it, our ability to influence the occurrence of thrombotic episodes.

Pentraxin proteins

This superfamily of proteins contains the well-known C-reactive (CRP) human protein and the serum amyloid P component (SAP). The latter is involved in maintaining and stabilising amyloid fibrils.

Clinical studies have shown that amyloid deposits regress if SAP production is inhibited by disease-modifying drugs. Resolution of the protein structure of SAP led to the development of a novel inhibitor, CPHPC, a palindromic molecule that dimerises SAP, which is rapidly cleared from the blood by the liver. Clinical trials of CPHPC appear promising. This drug is the first example of the 'knockout' of a plasma protein by a small molecular agent, and may be a prototype of similar drugs that dimerise other pentraxin proteins, such as CRP, with clinical benefit.

Polycystin and polycystic kidney disease

What causes the cysts in polycystic kidney disease? The answer lies in mutations of the PKD1 or PKD2 gene, encoding for polycystin-1 or polycystin-2, respectively. The majority of clinical cases are related to PKD1 defects. The interaction of polycystin-1 and polycystin-2 on the cell surface produces an ion channel, which affects the concentration of intracellular calcium. The PKD1 gene is expressed not only in the kidney but also in smooth muscle of arteries and embryonic cartilage; this may help explain some of the other associated clinical manifestations.

Serpins and serpinopathy

What links severe emphysema with Alzheimer's disease? Both are the end result of an abnormal polymerisation of proteins. In emphysema, the enzyme alpha-1 antitrypsin is absent, which allows the abnormal gene product to be deposited in cells as an insoluble polymer. Moreover, the proteolytic enzymes are allowed free rein, and destroy cell membranes. On the other hand, if too much of the polymer is deposited in tissues such as the liver or brain, their function is severely impaired. Members of the serpin family include C1 inhibitor, neuroserpin and antithrombin; any of these can produce a puzzling clinical picture. It may be possible for specific drugs to reduce or reverse polymer deposition.

Recent advances in vascular disease

Unstable angina and inflammation

It has become fashionable to attribute atheromatous changes in the large blood vessels to inflammation caused by a variety of viruses or bacteria. In patients with unstable angina (UA) it is thought that the whole coronary bed is inflamed. This offers an opportunity to search for novel forms of treatment, perhaps using existing anti-inflammatory drugs.

Early work showed evidence of systemic inflammation in patients with UA without myocardial infarction, though it was unclear whether this inflammation reflected atherosclerosis, was a consequence of ischaemia, or was a cause of ischaemia.

However, increased levels of CRP in UA patients, compared with stable angina patients and unheralded myocardial-infarction patients, suggests that atherosclerosis *per se* is not the major cause of CRP elevation.

Gene therapy for vascular disease

Is gene therapy for atherosclerosis possible? Focusing on the atheromatous degeneration of saphenous vein grafts after coronary artery bypass grafting, various factors have been described as necessary for successful gene therapy. The choice of vector is all-important in transferring the gene to the nucleus, and the currently available methods have both advantages and disadvantages. The most promising approach is via adenoviral or accessory adenoviral transfection; however, viral transfer of gene(s) incurs a higher cost, and greater immunogenicity, than other methods such as liposome transduction. Assuming successful gene transfection, the candidate gene must also be effective, ie able to reduce atherosclerosis. Several possible mechanisms are currently being evaluated. One is the transfection of nitric oxide synthase to inhibit adhesion-molecule expression, macrophage infiltration and platelet activation. An alternative is the use of soluble cell-adhesion molecules as leucocyte 'decoys', resulting in less vessel-wall infiltration.

Nitric oxide in the blood vessel wall

Diabetes, hypercholesterolaemia and smoking are all associated with lower levels of nitric oxide (NO). Inhibition of NO synthase by experimental arginine analogues, such as L-NMMA, has long been known to result in vasoconstriction and hypertension. Interestingly, a naturally occurring NO synthase inhibitor, asymmetric dimethyl arginine (ADMA), is found in circulating serum. ADMA is metabolised to citrulline by a highly conserved enzyme, dimethylarginine dimethylaminohydrolase (DDAH), found in two isoforms. DDAH-1 is found predominantly in the kidney and brain; DDAH-2 occurs in the vascular system and placenta. The targeted inhibition of ADMA by novel agents, or, alternatively, increasing DDAH activity, might provide useful clinical benefits in a wide range of vascular disorders.

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