Emerging molecular targets

BRCA1 *gene product*

Mutations in the *BRCA1* gene are known to be responsible for most forms of sporadic breast and ovarian cancers. Now, Dr J. Holt and coworkers at Vanderbilt University Medical Center (Nashville, TN, USA) and the University of Washington Health Science Center (Seattle, WA, USA) have found that retroviral transfer of the normal, but not the mutated, *BRCA1* gene, into breast and ovarian cancer cells suppresses the growth of these cells [*Nature Genetics* (1996) 12, 298–302]. The *BRCA1* gene is quite specific in blocking only the growth of breast and ovarian cancer cells; it had no effect on colon or lung cancer cell lines or normal fibroblasts. According to Holt, this is unusual; most tumor suppressers block the growth of tumor cell lines indiscriminately. This suggests that there is a unique aspect to the growth regulation pathways in these cells that can be exploited for drug discovery.

The 190 kDa BRCA1 protein appears to belong to the granin family of proteins [Jense, R.A. *et al. Nature Genetics* (1996) 12, 303–308]. The granins are a group of little-studied proteins that undergo highly regulated secretion and proteolysis to generate biologically active peptides that regulate various cellular functions. In the case of BRCA1, the peptide(s) generated from its protein are presumed to act to inhibit the unregulated cell division that is characteristic of breast and ovarian cancer cells. Work is furiously underway to define the peptide(s) responsible for the tumor suppression activity and to identify its receptor. Both will be of immediate interest for drug discovery. In the meantime, there is an opportunity to devise screening assays to search for small molecules that act in a similar manner as the BRCA1 protein to suppress the growth of breast and ovarian cancer cells.

Chloride channels and kidney stone diseases

Mutations in the gene *CLCN5*, which is known to code for a renal chloride channel, correlate with a high incidence of inherited kidney stone diseases, according to a recent report [Lloyd S.E. *et al. Nature* (1996) 379, 445–449]. When the normal *CLCN5* gene was expressed in *Xenopus* oocytes it produced an outwardly rectifying chloride channel, but when the mutated form of the gene was expressed, the chloride current was either not present or was significantly diminished. Assuming that the mutated form of the chloride channel is expressed in the plasma membrane, a screen for compounds that would trigger the chloride channel to open may result in the discovery of compounds that will prevent the generation of familial kidney stones.

According to the authors, kidney stones affect 12% of men and 5% of women in the West. Some 45% of all kidney stones are the result of a genetic predisposition, and kidney stones account for up to 1% of all hospital admissions.

Ligand for CD44

The lymphocyte cell surface receptor CD44 is known to regulate cell attachment, lymphocyte aggregation and homing, and to bind hyaluroinc acid at its NH_2 extracellular terminus. However, CD44 has been suspected of binding other ligands involved in regulating lymphocyte function. Now Georg F. Weber and colleagues from the Dana-Farber Cancer Institute and Harvard Medical School (Boston, MA, USA) have discovered that the cytokine osteopontin (Osn), also known as Eta-1, is a protein ligand for CD44 [*Science* (1996) 271, 509–511].

The response of lymphocytes on binding Osn is different from that seen when they bind hyaluronic acid. For example, Osn triggers chemotaxis but not homotypic aggregation, whereas the reverse is true for hyaluronic acid. Osn is known to be involved in the regulation of inflammation, bone formation and angiogenesis. These functions have been attributed to its ligation to $\alpha_v\beta_3$ integrins. Now the possibility is raised that some of these functions may be mediated through its binding to CD44.

The discovery of compounds that specifically block the interaction of Osn with CD44 would play an important role in establishing the cellular functions of Osn and possibly lead to the development of new drugs.

Cyclin E-CDK2 kinase

Loss of an anchorage-dependence of cell growth is one of the clearest indicators of cell transformation and has a high correlation for *in vivo* tumorigenicity. Dr F. Fang and coworkers at the La Jolla Cancer Research Foundation and the Salk Institute for Biological Studies (La Jolla, CA, USA) report that the cyclin E-CDK2 kinase may be the key enzyme in determining whether or not a cell line exhibits anchorage-dependent growth, and, by implication, a normal or transformed phenotype [*Science* (1996) 271, 499–502].

When nontransformed fibroblasts were kept in suspension, the cyclin E-CDK2 kinase was inactive and cells were arrested in late G1 phase, the phase of the cell cycle regulated by cyclin E. Once the cells were allowed to attach to a substrate, the cyclin E-CDK2 kinase became activated and the cells began to divide. In transformed fibroblasts, however, the cyclin E-CDK2 kinase was always active, regardless of whether the cells were in suspension or on a substrate. The researchers conclude that inhibition of cyclin E-CDK2 kinase activity is likely to be responsible for anchorage-dependent growth. If this conclusion proves to be correct, cyclin E-CDK2 kinase may be an important molecular target for the discovery of compounds that can reverse the loss of anchorage-dependent cell growth and possibly block the growth of tumor cells.

Robert W. Wallace

Piezoelectric IgM immunosensor

The use of high-throughput screening in drug discovery programmes has driven the development of methods of monitoring for drug–receptor interactions without the use of radioactive substances. One such approach is the use of piezoelectric immunosensors that modulate their oscillating frequency in depending on the bound mass. Chu, X. and coworkers [*Analyst* (1995) 120, 2829–2832] describe the development of a piezoelectric immunosensor for the measurement of increases in human IgM in response to acute infections, acute and chronic hepatitis and other disease states. Goat antihuman IgM antibodies were immobilized to the surface of the crystal using a cyanogen bromide-activated 2-hydroxyethyl methacrylate / methyl methacrylate copolymer. The immunosensor was sensitive to human IgM in the concentration range of 5–93 $\mu g\ ml^{-1}$ and could be reused 20 times without loss of sensitivity.

Copyright © Elsevier Science Ltd. All rights reserved.
1359-6446/96/$15.00