MEETING REPORT

UNDERSTANDING WHAT 'OUT OF CONTROL' MEANS

ATLANTA—How do protooncogenes and their oncogenic alleles regulate growth? Although this question remains incompletely answered, the relationship between oncogenes and growth factors in promoting uncontrolled cellular growth is becoming clearer: cellular oncogenes are not only capable of inducing growth factor synthesis, but in some cases they have been shown to be growth factors themselves.

Ray Erikson (Harvard University, Cambridge, MA), in a session devoted to oncogenes and growth control at the 25th meeting of the American Society for Cell Biology held here in November, said that 25 to 40 oncogenes have now been identified. When these oncogenes are grouped on the basis of their effect on cell phenotype, however, only a few classes of oncogene-encoded proteins emerge. Data suggest that, in the cytoplasm, these proteins probably regulate levels of second messenger molecules; in the nucleus, they may modulate transcriptional events. Many of the gene products are also involved in pathways that determine the cell's response to growth factors.

A fundamental trait of tumor cells is a decreased dependence on growth factors. Oncogenes can confer growth factor autonomy on cells by an autocrine mechanism: a tumor cell can secrete growth factors into the medium; these then readsorb to growth factor receptors on the same cell that has just released them, creating a positive feedback loop.

Transforming growth factors (TGFs), for instance, probably function in this manner. Anita Roberts (National Institutes of Health, Bethesda, MD) reported that TGFs are actually bifunctional regulators of cell growth, for they can both stimulate and inhibit. TGFs—which are identified by their ability to promote anchorage-independent cell growth—are polypeptides that produce a reversible transformed phenotype in non-neoplastic cells. Two distinct types of TGFs have been identified. The TGF-alphas are single chain polypeptides of 50 to 53 amino acids, linked by three disulfide bonds. TGF-alpha is found in neoplastic tissues, while epidermal growth factor (EGF, also of the TGF-alpha class) is found in the salivary gland, the kidney, and the liver. TGF-alpha is functionally analogous to EGF and competes with EGF for binding to its receptor.

TGF-beta, on the other hand, does not bind to EGF/TGF-alpha receptors, but to its own highly-specific ones. TGF-beta is composed of two amino acid chains (112 residues each) held together by disulfide bonds. The monomers are inactive. Interestingly, the presence of TGF-beta is not restricted to transformed cells: TGF-beta has been isolated from kidney, placenta, and platelets. In fact, it has been demonstrated in all tissues examined to date. Moreover, all cell types that have been examined so far have receptors for TGF-beta. TGF-beta can both stimulate and inhibit proliferation of fibroblasts and tumor cells in soft agar; it also inhibits the proliferation of many cells in monolayer tissue culture. In many cases, TGF-beta acts synergistically with other growth factors; cells transfected with the *ras* oncogene exhibit increased expression of TGF-alpha, TGF-beta, and platelet-derived growth factor (PDGF).

While transforming growth factors appear to interact with receptors, a more direct autocrine route is used by the *sis* oncogene. In this instance a gene encoding the structure of a growth factor becomes deregulated and converted into an active oncogene. According to Stuart Aaronson (National Cancer Institute, Bethesda, MD) the *sis* oncogene codes for PDGF. *Sis* is an altered deregulated version of the normal cellular gene specifying PDGF. The processed *sis* gene forms a PDGF-like dimer with biological activity. The *sis* transforming function is mediated by the PDGF receptor: in fact, partially purified *sis* proteins compete with PDGF for binding to the PDGF receptor. The coding information in the normal PDGF sequence has the ability to become a transforming element. If the gene is activated in a cell such as a fibroblast, it can lead towards neoplasia. If activated in other cells, it may aid in wound healing.

Even cells transformed by the oncogenes *src* and *ras* release growth-stimulatory factors into the culture medium. It is now clear that these oncogenes do not themselves encode the growth factors, but instead indirectly stimulate growth factor genes. The *ras* oncogenes, according to Erikson, code for nucleotide-binding proteins which play a role in regulating adenylate cyclase. *Ras* proteins are in large part bound to the plasma membrane, where they bind GTP and GDP. The protein coded by the oncogenic *ras* allele hydrolyzes GTP much less efficiently than does the normal *ras* allele; it is thought that this reduction in GTPase activity is the event that activates the protooncogene.

The *src* gene codes for a protein kinase activity specific for tyrosine residues. Mutations in the *src* gene that inactivate the kinase activity invariably eliminate the transforming potential of the protein. Although a number of cellular proteins are modified by the kinase activity, none of them have been directly linked with malignant conversion. It is thought that the *src* protooncogene is activated when its protein acquires a foreign, physiologically unresponsive subunit.

Since cellular protooncogenes are highly conserved, they must play key roles in the growth control of normal cells. Many of the normal genes and their gene products must pass growth stimulatory signals from upstream in a regulatory pathway to one or more targets downstream. The identification of these normal roles for protooncogenes has just begun.

—Jennifer Van Brunt

Studies on the activation of ribosomal protein S6 may illuminate the functional changes in enzyme activity that affect cell proliferation.