Onco-Developmental Gene Expression

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ONCO-DEVELOPMENTAL GENE EXPRESSION: A PREVIEW

A justification of a conference such as this is that it has obliged its organizers to evaluate the spectrum of this jumbled research activity and to decide where it is now and what to call it. However, the reader is at a disadvantage unless the organizers share their perspectives and concerns with him in advance. This is the purpose of the present preview which is at the same time both retrospective and prospective. It is our hope that from the following the reader will be better equipped to understand the reasons why certain investigations have been carried out and to judge independently the potential significance of the results of each paper in terms of the major questions which are confronted. In this rapidly evolving field of endeavor, we should expect that to a variable extent what appeared to be settled and agreed upon yesterday may become unsettled and confused today and vice versa.

What is onco-developmental gene expression?

"Gene expression" is viewed as the process by which information coded in DNA is transcribed into messenger RNA and the latter translated into gene products which are specific proteins. The precise mechanism by which DNA transcription and translation is initiated and the whole process of the regulation of gene expression is the subject of intense activity among molecular biologists.

"Onco-developmental" is an adjective which refers to substances which are produced in both developmental and neoplastic tissues. "Gene products" then refer to proteins, enzymes or polypeptide hormones without the requirement that they be macromolecules or immunogenic in other species or in the host (i.e., antigens).

In approaching onco-developmental gene expression, we are focusing on the process which regulates the production of substances by neoplastic cells which are products of genes active in normal development and we are searching for the significance of this phenomenon in neoplastic transformation. Many of the characteristics of malignant cells are also found in cells at early stages of development and the study of onco-developmental gene expression is probably leading to a more precise understanding of the nature of cancer.

The present definition does not require that developmental proteins be lacking from adult tissues as there are more and more examples of persistently activated developmental genes. For example, neural crest cells begin making calcitonin

in the embryo at six weeks of life and the progeny of such cells in the adult, thyroid C-cells, continue to produce calcitonin. Also, extensive work on the isoenzymes of several of the glycolytic enzymes demonstrates the coexistence of their fetal and adult forms in adult rat liver; alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) are present in small amounts in normal adults. An immunologic response of the host to an onco-developmental protein may be anticipated when that particular protein is not made in adult tissues.

Onco-developmental gene products: a history of their discovery.

In this section, we are choosing to review these products under the Conference headings of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), isoenzymes and isoproteins (including polypeptide hormones). Each of these is the subject of busy workshops devoted to methodologic discussions as well as appearing in papers of Plenary Sessions devoted to conceptual advances. Alpha-Fetoprotein: This is the first alpha-globulin to appear during development. It was found by Gitlin to be made by fetal liver and by the antecedent yolk sac. Later in gestation (human or rat) and postpartum, the rate of alpha-fetoprotein production declines. In the adult the corresponding gene is expressed by only trace production of the protein. Abelev's key discovery in 1963 that alpha-fetoprotein appeared in the sera of mice with hepatoma (liver tumors) was instrumental in opening up the modern phase of onco-developmental research. He recognized the significance of this finding; that a fetal gene was reexpressed in neoplasia. Up to that time, concepts suggesting that cancer was the product of the activity of undifferentiated embryonal cells which had persisted in adult as "rests" were far overshadowed by theories of viral etiology of cancer and chemical carcinogenesis. Later, alpha-fetoprotein was found in teratocarcinoma, an embryonal tumor, when these tumors contain "endodermal sinus" tissue believed to be of yolk sac origin. These results suggest that a particular developmental gene can become activated in neoplastic cells.

The circumstance that alpha-fetoprotein was produced by hepatoma tissue was fortunate because investigators already possessed the ability to study the events of carcinogen-induced hepatomas. Thus, when an appropriate chemical carcinogen is incorporated into a basal diet in subcarcinogenic amounts, alpha-fetoprotein appears as early as one week after feeding, in every animal, without any histologic evidence of abnormality and alpha-fetoprotein synthesis persists even though administration of the carcinogen is discontinued. Since tumors do not appear until after 16-20 weeks of feeding in some cases, AFP production occurs well before morphological evidence of neoplastic transformation. The session on *gene expression in carcinogenesis and experimental injury* includes a variety of papers highly relevant to this subject.

The extension of Abelev's finding to human hepatoma and teratocarcinoma has provided a serodiagnostic test for these two types of human cancer. The realm of diagnosis also includes fetal abnormalities such as anencephaly and spina bifida, fetal conditions which enrich the amniotic fluid and subsequently the serum with

alpha-fetoprotein. Accordingly, alpha-fetoprotein qualifies as an onco-developmental gene product with diagnostic potential in neoplasia and in development.

A current report suggests that AFP may influence immune reactivity and therefore may be biologically active in preventing immune rejection of fetal tissue during pregnancy. This subject has not previously been examined thoroughly but will be a major subject of the conference. Thus, AFP serves as a marker for abnormal development, liver regeneration following toxic liver injury and for neoplastic transformation and tumor growth. Of particular interest are studies directed toward understanding the biological function of AFP. The rapid advances in these areas, reported at this conference, are particularly timely.

CEA: This "Carcinoembryonic Antigen" discovered by Gold and Freedman in 1965 is a perchloric acid soluble glycoprotein present in cell membranes of epithelial cells of fetal intestine and of adenocarcinoma of the colon. It has become evident in time that the CEA of Gold and Freedman was one of a family of closely associated glycoproteins which are expressed in a large variety of tumors and in nonmalignant cell proliferative conditions. Some of these latter circumstances predispose to cancer.

Although CEA has not performed as specifically as alpha-fetoprotein in the clinic, it is turning out to be valuable in studies of "marker" profiles in human cancer and in experimental studies in carcinogenesis.

The absence of universally available standardized, pure preparations of CEA and of standard preparations of monospecific antisera has led to difficulties in evaluating clinical results from different laboratories. Nevertheless, the literature on CEA has continued to expand which promises to clarify some of these uncertainties.

Isoenzymes: In 1963, Schapira and her coworkers found a fetal type of aldolase in a human hepatoma which they attributed to the resurgence of fetal aldolase at the expense of adult liver aldolase. Weinhouse found a common pattern of expression of fetal glucose-ATP phosphotransferases, aldolases, pyruvate kinases and glycogen phosphorylases in experimental hepatoma. The Regan isoenzyme, a *placental* rather than fetal alkaline phosphatase, was found by Fishman et al. at Tufts Cancer Research Center, to be widely distributed in human neoplasms. It was the first of several tumor phosphatases discovered later which have their counterparts in development.

These gene products not only are as antigenic as alpha-fetoprotein and CEA but possess a distinct catalytic activity. It has been the ability to probe the differences in the catalytic sites of isoenzymes with specific amino acid inhibitors that has led to their resolution rather than by the direct immunologic approach. For example, the common placental F, FS and S phenotypes, as distinguished by electrophoresis, are expressed in cancer cells as well as the rare D-variant phenotype and are resolved also by their differing sensitivity to L-leucine. Furthermore, chorion and amnion (FL) alkaline phosphatases are identifiable by distinctive profiles of sensitivity to biochemical and immunologic reagents. Thus, what was simply referred to as tumor alkaline phosphatase can now be resolved into at least six

different proteins, each being onco-developmental. Thus, the work on the onco-developmental alkaline phosphatases has illustrated the effectiveness of combining the techniques of isoenzymology and immunology.

Interest in model systems is centered around two HeLa sublines, each of which is monophenotypic for Regan and non-Regan alkaline phosphatases. Cell cycle studies of the Regan isoenzyme-producing cell line (TCRC-1) demonstrate that prednisolone not only extends the G_1 period but also blocks cells in this compartment.

In the area of isoenzymes, new basic findings and interpretations are reported in the sessions on *gene expression in development and newly recognized onco-developmental gene products.*

Isoproteins: Since Richter's studies in 1964 reporting an acidic isoferritin in cultured cancer cells, there have been numerous reports on the degree of tumor specificity of proteins of the ferritin class. These proteins have also been found in fetal liver and placenta, which qualifies them as onco-developmental gene products. The substance, α_2H, differs from ferritin in molecular size and sugar content but is immunologically identical.

It is known that variable amounts of iron may be sequestered within the multimeric protein shell of apoferritin. Additional variability in the composition of ferritin is inherent in its subunits which are unlike and exist together in different proportions. The association of hyperferritinemia with a wide range of human neoplasms and their activity is now well known.

Isohormones (polypeptide hormones): In the clinical literature, ectopic polypeptide hormone production is widely reported as a concomitant of neoplasia, although unless the levels are abnormal, these hormones are not necessarily associated with particular clinical symptoms.

In the case of human chorionic gonadotrophin, its expression, aside from choriocarcinoma, is most frequent in carcinoma of the ovary, testis and pancreas. The recognition of the immunologically unique β-subunit of HCG has made it possible to distinguish HCG from pituitary gonadotrophin and LH. The α-subunit of HCG which lacks biological activity is also secreted by tumors sometimes independently and at other times in association with whole HCG or with β-subunits. Instances of the co-expression with HCG of chorionic somatomammotrophin and placental alkaline phosphatase suggest that a whole set of trophoblast genes coding for polypeptide hormones and enzymes may be activated in some cases of neoplasia.

Comment on onco-developmental gene products.

From the foregoing, it may be pointed out that with the possible exception of α-fetoprotein, each onco-developmental gene product is expressed as a family of proteins, probably of variable subunit construction and which can be distinguished from each other by a combination of electrophoretic, immunologic and catalytic site techniques. The assembly and processing of these entities into cytoplasmic constituents and cell membranes may be under progressively restricted control in

the course of development. If one had to rank the relevance of classes of genes to onco-developmental gene expression, perhaps processing genes would be followed by regulatory genes and then by structural genes.

Newly discovered gene products described in the last session of the conference include antigens, polypeptide substances and enzymes. The interest in onco-developmental proteins has heightened the attention of many more investigators to the events in development which mark the appearance of such proteins. An example is the expression of α-fetoprotein by yolk sac. Yolk sac tumors that produce AFP also contain yolk sac (endodermal sinus) structures.

Of the different types of cancer, teratocarcinoma represents one condition which bridges development and neoplasia. In particular, the stem cells of teratocarcinoma carry a number of cell surface antigens of embryonic cells and also, the differentiation of these totipotent cells into a number of cell lineages can be studied at the point of its initiation as Pierce has demonstrated in the mouse tumor.

Finally, in Markert's view, cancer is a developmental disease. When this statement is translated into the framework of the Conference, cancer can be regarded as a disorder in the regulation of gene expression.

Epidemiologists now accept the view that there is a higher incidence of neoplasms in infants with genetic and birth defects. This fits in with the idea that fetal anomalies and neoplasia are entities on the same spectrum. A picture of current advances in these areas can be obtained by the papers given in the session on *diagnostic implications.*

The cell cycle, its control and gene expression.

It has become important to fix the time of expression of a particular gene in the cell cycle which is defined as the events of DNA synthesis (S) and mitosis (M) separated by G_1 and G_2 phases. For example, the initiation of synthesis of α-fetoprotein is believed to take place during G_1 and the synthesis of Regan isoenzyme is initiated in the middle of the G_1 period. If cells are blocked by chemical agents at these particular points in the cell cycle, the investigator is in a better position to study the mechanism of expression of the particular gene which codes for the onco-developmental product since the latter will accumulate in much larger amounts.

The session on *gene expression and cell cycle control* therefore is addressed mainly to the study of phenomena in gene expression and its regulation in continually cycling cells.

Diagnostic implications of onco-developmental gene products.

The thrust of the pioneer observations of Abelev and Gold has been the diagnostic and clinical implications of serum α-fetoprotein and CEA, respectively. In addition to the monitoring of tumors by measuring these products individually, several papers deal, for the first time, with the assembly of profiles of these gene products in the study of human cancer. The investigators at this meeting are expected to take a conservative view as to clinical utility of any one