Recently Defined Onco-Fetal Antigens and Their Potential Application in Clinical Medicine

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ABSTRACT

It has been shown that in human embryos there are heretofore undescribed embryonic antigens, which induce antibodies cross reacting with a wide range of malignant neoplasms. A simple screening method of sera for human malignant neoplasms is suggested.

A hypothetical model of protein synthesis over the entire life span of an organism is presented depicting the relationship of embryonic and adult proteins.

Introduction

The present experimental evidence in cancer research clearly indicates that there is an unpredictably disturbed regulatory process of protein synthesis involving repression and derepression. However, it is impossible to formulate any hypothesis of carcinogenesis until the normal regulatory processes in protein synthesis of animal cells are understood.

Recently, there has been much interest in relating the embryonic appearance of malignant neoplastic cells by biochemical means to normal embryonic cells. It is now well established that in malignant neoplasms there is reappearance of components, which are normally present in corresponding tissue types during the embryonic period. However, all of these antigens, after further investigations, have been found in either components of normal, in regenerating or in diseased non-cancerous tissues.

If it were possible to demonstrate exclusively in malignant neoplasms embryonic components, then malignant neoplasia could be diagnosed on this basis, applying biochemical analysis. Indeed, it would facilitate the detection of malignant neoplasia if the transformed cells would possess a universal embryonic component.

Theoretical Considerations

In an approach to a search for a universally present embryonic component in malignant neoplasms, several theoretical con-
considerations can be made. The synthesis of all proteins consist of two phases—the synthesis of embryonic proteins and that of the adult type proteins. These two phases from the beginning of embryogenesis to the end of the life span of an organism, can be demonstrated graphically (figure 1). Four general patterns could be operative in this overall process. In model A (figure 1A) are shown predominantly embryonic types of proteins at the earliest period which gradually and continuously decrease until the end of the entire life span. Only small amounts of adult proteins are synthesized at the beginning, but they would gradually and continuously increase, while concomitantly the synthesis of the embryonic proteins would be repressed.

As shown in model B (figure 1B) during an initial period, only the embryonic proteins are synthesized. After this initial period, the adult type proteins would appear. The relationships of the two types of proteins by the end of the life span are similar to those shown in model A.

As shown in model C (figure 1C), initially the protein relationships are the same as shown in model A except that at some period of the life span there would be a complete cessation of the synthesis of embryonic proteins. Consequently, for a certain final period of time during the adult life, only the adult type of proteins would be synthesized.

In model D (figure 1D) is shown a combination of the relationships among the embryonic and adult proteins as depicted in models B and C. Initially, only embryonic proteins are apparent and, finally, by the end of the life span only the adult type of proteins are synthesized.

The present experimental evidence does not firmly establish any one of the four alternates. However, it would seem that for

**Figure 1.** Graphic demonstration of embryonic and adult type protein synthesis. On the X axis, \( t \) is life span of an organism. On the Y axis, Prot. is the amount of protein. A. Initial predominance of embryonic proteins, which decrease until the end of the entire life span with a concomitant reciprocal increase of adult type of proteins. B. Initial period of embryonic protein synthesis, followed by the appearance of adult type of proteins. The relationships of these proteins by the end of the entire life span are similar to those in model A. C. The relationships of the two types of proteins initially are similar to those depicted in model A. The synthesis of embryonic proteins ceases completely at some period of the adult life.

D. Combinations of models B and C. Initially, only embryonic and finally only the adult type of proteins are synthesized.
the hypothesis to find a specific universal embryonic protein in malignant neoplasms, the models C or D would be the most advantageous. According to the models A and B, small amounts of embryonic proteins still could be found in normal tissues, even at the end of the entire life span. Therefore, on the basis of embryonic protein presence alone, the malignant neoplasms could not be differentiated from normal adult tissues. On the other hand, if, in the adult life, certain kinds of embryonic proteins are not present, as in models C or D, and they reappear only in malignant neoplasms, such proteins then would be specific indicators of malignant neoplasia.

The hypothetical model D is supported by a few experimental observations. Many enzymes are not found in embryonic liver. On the other hand, there is evidence that a cellular antigen which is tumor specific, but not of viral origin and therefore probably represents one of the embryonic components, is not present in normal adult tissues. In adult fowl, the embryonic red blood cell antigens disappear completely.

Model D would also be compatible with well established observations of the tumor differentiation as judged by their morphology and behavior, dividing the various tumors in well differentiated, moderately differentiated, and poorly or undifferentiated malignant neoplasms (figure 2). In a well differentiated state, the tumor cells would synthesize predominantly the adult type proteins and only a few embryonic components. The moderately differentiated situation would be the one in which both embryonic and adult proteins are synthesized about equally by the cell.

A poorly differentiated or undifferentiated malignant neoplasm would be represented by the kind of protein synthesis where mostly embryonic proteins and only a few or none of adult proteins are present. The application of model D could well be extended further to benign neoplasms where no embryonic proteins are synthesized and only the adult type proteins are present. According to this hypothetical assumption, the authors investigated to find out whether or not there would be a specific embryonic component universally present in different types of human malignant neoplasms.

Another approach to establish a quantitatively and qualitatively measurable specificity of malignant neoplasia could be the determination of the deletion from neoplastic tissues of certain components which are present in normal tissues, such as, the HL-A and the ABH antigens. However, this approach appears limited. The antigens, like ABH, are present only in epithelial types of tissues, and the disappearance of the HL-A antigens has been reported only in isolated cases. For the recognition...
of malignant neoplasia, a positive component identification would appear to be more advantageous.

Embryonic Antigens

The probability of finding a specific universal embryonic antigen in human malignant neoplasms was suggested by experimental evidence of such embryonic antigens universally present in various kinds of mice cancers. The preliminary studies indicated that universal embryonic antigens could be present in all kinds of human malignant neoplasms. An aqueous extract of six to seven weeks old intact human fetus was used as the antigen. Ouchterlony double diffusion technique was applied to determine the reactivity. The rabbit immune serum against this human fetal embryonic antigen, after appropriate absorption with normal adult tissues, reacted with malignant neoplasms derived from all three types of germ layers.

Subsequently, the effects of the placenta on the induction of antibodies which could conceivably cross react with antigens in human malignant neoplasms were examined. The antiserum in a rabbit was raised with the placenta from a 3.5 cm fetus. The reactivity of this immune serum was limited to fewer malignant neoplasms. Only adenocarcinomas of pancreas and colon, as well as squamous cell carcinoma of esophagus, reacted with this antiserum. The placental antigen was partially purified by Sephadex G-200 gel filtration. There were two distinct immunologically active areas. One, with the higher molecular weight, revealed alkaline phosphatase activity, conceivably representing Regan isoenzyme. When the active fractions were pooled and subjected to cellulose acetate electrophoresis, two larger fractions appeared (figure 3).

From these preliminary studies, it appears as if the total embryonic extract contains a wider range of antigens than the placenta, inducing antibodies against all malignant human neoplasms. However, it is possible that a more potent immune serum against the placenta could conceivably react with a wider range of malignant neoplasms.

Using immunofluorescence microscopy, the present evidence indicates that the antigens in malignant neoplasms are localized predominantly in the periphery of the cells. It is possible that they are present in the cell membranes. Future studies, using ferritin labeled antibodies and observing with electron microscope, will reveal precisely the antigenic sites.

Up to the present time, using the Ouchterlony double diffusion technique, 31 carcinomas have been examined; all reacted with the rabbit immune serum raised against human embryonic tissues. A wide variety of non-malignant tissues such as adenomatous polyp of rectum, fibroadenoma of breast, ulcerative colitis, diverticulitis and microfollicular adenoma of thyroid have been examined and did not reveal positive results. Preliminary data indicate that only sera from patients with malignant neoplasms give a precipitin band with antifetal antibodies.

Discussion

At the present time, it is not possible to comment with certainty that the antiser
which has been induced with human embryonic extracts will cross react specifically with malignant neoplasms. This will become apparent only with more extensive future work.

Further experiments, using antiembryo antiserum, revealed that the cross reacting antigens in malignant neoplasms are not the carcinoembryonic antigens (CEA). CEA elicited no reaction with the immune serum (figure 4). This observation does not exclude the presence of a low titer of anti-CEA antibodies.

At the present time it is not known whether or not the immune serum contains a universal antibody against some embryonic and malignant tissue components or if there is a wide range of different antibodies which react correspondingly with a wide range of human neoplasms. For practical purposes, the technique of applying rabbit immune sera raised by fetal tissues in diagnosis of human malignant neoplasms may be highly significant. This can be performed by using the Ouchterlony immunoprecipitation method.

In the preliminary stage of applying this technique as a screening procedure, it was found among 13 known cancer patients that there were seven positive sera for oncofetal antigens. No positive sera have been found among 15 healthy individuals.

References


