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INTERNATIONAL WORKSHOP ON ALPHA-FETOPROTEIN EW TRENDS AND PERSPECTIVES

Villa Marigola - San Terenzo di Lerici (La Spezia)
October 20-21, 1989

Editors

F. PECCHIO, M. RAPELLINO, G. C. TORRE

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EDITORIAL

Fifteen Years of Alpha-Fetoprotein

G. MARIANI*

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As we all know Alpha-Fetoprotein (AFP) was identified earlier than 15 years ago, therefore the title above cannot refer to the initial event of its discovery. It refere instead to my personal interest in the biological and clinical significance of this somewath intriguing protein, an interest that is now rekindled by the publication, in this Supplement to "The Journal of Nuclear Medicine and Allied Sciences", *of a collection of papers entirely focused on AFP.*

When I started my sabbatical year at the Metabolism Branch of the National Cancer Institute (National Institutes of Health; Bethesda, Meryland, USA), my task was that of developing a reliable method for the determination of AFP metabolism in monkeys; these animals constituted in fact an experimental model thereby hepatocellular carcinoma was induced by chronic administration of a known carcinogenic compound (by the way, the onset and development of tumor disease was being monitored by sequential measurements of the AFP serum levels, using on immunological-based assay system specifically set up for simian AFP). The idea was that of ultimately determining the tumor cell burden in the intact living animals, by combining the results of in vivo *AFP turnover experiments with those of* in vitro *AFP synthesis measurements performed with hepatocarcinoma specimens obtained by percutaneous biopsy.*

In the mid-70's, each nowly published piece of information on AFP fueled a chain-reaction interest in the various chemical, biological and clinical aspects of this protein, that came to be "the" prototype of an entire class of proteins designated as "onco-developmental antigens". From the clinical point of view, interest in AFP resides, even today, in its utilization as a tumor marker as well as a marker of fetal abnormalities such as the neural tube defects (or as a marker of simple anomalies such as multiple pregnancies). From the chemical and biological points of view, excitement arose when AFP was taken under scrutiny in relation to studies on ontogenesis (AFP as a fetal precursor of albumin with hormone binding parameters, particularly for steroid hormones, more suited to intra-uterine life) and to the possible immunomodulation activities of AFP.

As concerns AFP as a tumor marker specific for hepatocellular carcinoma, it soon became obvious that this protein is not specific

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particular cancer, nor is it the sole marker for it. After all, this has been common story for virtually all known tumor markers which, as clinical data accumulate, evolve from the concept of specific indicators to be used for differential diagnosis to the concept of markers to be used, in conjunction with other markers of other types of test, for staging purposes and for monitoring the course of tumor disease following treatment.

Particularly exciting have been for some time speculations on the possible role of AFP as a modular of the immune system, particularly as a suppressor of the immune response to antigenic stimulation. In this regard, it was emphasized that AFP circulating in the body fluids (as also other onco-developmental proteins, such as the Carcino-Embryonic Antigen) happens to be increased under two circumstances that, even though dramatically different at first sight, do share some biological similarities: pregnancy and cancer. In fact, in both circumstances immunological surveillance is not able to prevent the growth in the organism of a complex of cells tissues that may be antigenically largely different from the host. In this respect, early experiments tentatively identified AFP as the immunosuppressant factor of the amniotic fluid. Moreover, observations on the increased AFP serum levels in ataxia-telangectasia, a complex disease where severe immunological abnormalities constitute one of the main landmarks, lent some additional support to the hypothesis of AFP as a potent immunosuppressant factor. However, as intriguing as such speculations might have been, the reports on the suppression of immune response exerted by AFP were not subsequently confirmed.

From the point of view of molecular biology events, AFP represents an important marker related to normal cell maturation (switching from AFP top albumin synthesis in the evolution from fetal to adult parenchymal liver cells), as well as of investigational tool for probing the mistery of tumor biology per se *(switching back from albumin to AFP synthesis during carcinogenesis).*

More recently, AFP in tumor cells has been selected as the target of specific immunoglobulins (either polyclonal antisera of monoclonal antibodies) aimed at achieving a somewhat efficient treatment (if not the cure) of hepatocellular carcinoma by means of radioimmunotherapy (besides the applications for tumor imaging by means of radioimmunoscintigraphy).

All the above considerations explain continuing expansion of clinical and experimental studies on AFP. The reports that follows are mostly focused on the application of AFP assay in various clinical conditions; very appropriately so, emphasis is given in this collection of studies to the need for simplification and standardization of the AFP assay, for easier comparison of the results obtained by different groups now that the AFP assay can be considered a routine procedure in various fields of medical practice.

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INTRODUCTION

AFP: A Tumor Marker in Progress

F. PECCHIO, M. RAPELLINO, G. C. TORRE

In 1963 Abelev demonstrated AFP in the serum of neonatal mice and of adult mice with a transplantable hepatoma and for the first time he associated this fetal serum protein with a malignancy.

In 1964 Tatarinov determined AFP in the serum of patients with primary hepatocellular carcinoma.

Among tumor markers AFP was the first to be studied to any great extent. After the data observed by Abelev and Tatarinov, elevated levels of AFP were detected in the serum of patients with germinal tumors of the ovary and of the testis. Subsequent data indicated for the first time that a tumor marker can be used for the screening of high risk populations. The use of AFP as a tool for the screening of patients with germ cell and hepatocellular carcinoma is limited, although measurement of AFP has been shown to have utility in initial staging and follow-up evaluations.

Although the pretreatment levels do not appear predictive for stage or histology, AFP was the first tumor marker used with the significance we presently have with all the other newly identified tumor markers: the possibility of controlling the lesion in the follow-up and in the monitoring of the disease.

AFP presents a characteristic of a tumor marker in progress both for the development of the methods of determination and for the other fields different from oncology where applicable. Obstetrics is another field of use of AFP, where AFP is able to detect neural tube defects and the new data show a possible use for prenatal diagnosis of Down's Syndrome.

After 25 years from the detection of AFP in the serum of human patients with primary hepatocellular carcinoma it was our intention to summarise the situation of this tumor marker in this workshop. The presence of doctor Tatarinov and the group that in Europe and in Italy are working on this tumor marker will be very useful for the comprehension of AFP history.

RELATIONS

The Past and the Future for Cancer Testing by Alpha-Fetoprotein

A review

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The morphological relationship between malignant and embryonal cells was revealed about 100 years ago at least. As is known, at the early stage of the development of embryonal and malignant cellular populations they grow swiftly and with a certain autonomy. Besides, embryonic and malignant cells have alternating stages of cell differentiation and division. By ultramicroscopic method it was shown that both embryonic cells, in particular at the earlier period of embryogenesis, and malignant adult cells have many similar morphological properties, which are absent in normal adult cellular populations. In addition, there are many indistinguishable metabolic qualitative properties.

"Although the idea of correlating embryonic and cancer phenomena has been considered over a period of 100 years, the independent discoveries of Abelev and Tatarinov in 1963 of alpha-fetoprotein (AFP) in hepatomas and fetal liver of mouse and humans and its absence in the adult liver marked the beginning of the era of modern oncodevelopmental biology".[1] Really, AFP as an embryonic protein was the first tumour marker to be discovered in mouse chemically-induced hepatomas [2] and in human hepatocellular carcinoma or primary cancer of the liver.[3]

The phenomenon of AFP reappearance in malignant cells was considered to be an embryonic reversion in adult tissues. As for the biosynthesis of embryonic products by neoplastic cells, it was named an oncodevelopmental process. The products, which are synthesized both in malignant and embryonal tissues at present are indicated as oncofetal, carcinoembryonic or oncodevelopmental proteins.

First steps of cancer testing by AFP

In 1963, the presence of AFP in the serum of two patients was first associated with hepatocellular carcinoma and it was suggested subsequently to use immunodiffusion AFP test for differential diagnosis of primary cancer of the liver and secondary liver cancer.[3] AFP could not be found normally in any pathological and cancerous condition, including cholangiocellular liver carcinoma. Its findings in adult patients was considered as the diagnosis of hepatocellular carcinoma.[4 5] In 1966-1968, the first confirmations of the above-mentioned clinical results were reported on by four laboratories at least (Table I).

As shown in Table I, during the first 5 years of AFP application 152 patients

TABLE I.—*First steps of cancer testing by immunodiffusion analysis of AFP.*

Author and country	Year and reference	Umber of AFP-positive samples in/out of			
		Hepato-cellular carcinomas	Cholangio-cellular carcinomas	Other than liver cancer	Non-cancer liver diseases
Tatarinov, USSR	1963 (3)	2/2	0/1	0/8	0/38
Tatarinov e.a., USSR	1964 (4)	3/3	0/2	0/13	1/12*
Tatarinov e.a., USSR	1965 (5)	5/5	0/3	0/19	0/79
Kithier e.a., CSSR	1966 (6)	1/0	—	—	—
Abelev e.a., USSR	1967 (7)	19/24	0/6	13/226**	0/68
Uriel e.a., France	1967 (8)	37/47	—	0/60	0/284
Tatarinov e.a., USSR	1967 (9)	12/14	0/5	0/21	—
Alpert e.a., Uganda	1968 (10)	20/40	—	—	2/128***
Total	5 years	99/135	0/17	13/347	3/609

* Acute yellow liver atrophy after viral hepatitis. ** Embryonal teratoblastomas. *** Hepatitis, cirrhosis.

suffering from primary cancer of the liver, 347 patients with a variety non-liver tumours, and 609 patients who had different non-malignant liver disorders were investigated. Of 135 patients with biopsy-documented diagnosis of hepatocellular carcinoma, 99 patients (73,3%) had initial elevated serum AFP levels, which were detectable by immunodiffusion, while control serum samples from normal adults and from patients with malignant and benign diseases were, as a rule, AFP-negative.

Only three of 609 non-malignant cases had a positive AFP-test and these patients had viral hepatitis or cirrhosis. Among the 347 cases of non-hepatic tumours, 13 so-called false-positive cases were observed and all patients presented embryonal teratoblastomas of the testis.

Thus, the immunodiffusion AFP-test revealed about 80% of patients suffering from hepatocellular carcinoma and it was also possible to differentiate between hepato- and cholangio-carcinomas. In addition, some embryonal teratocarcinomas of the testis were able to produce AFP in the blood circulation.

In principle, analogous results were obtained in a variety of geographical areas with the percentages of AFP-positive cases with hepatocellular carcinoma ranging from 42% to 87% (Table II).

Although there were differences in the percentage of AFP-positive hepatomas between Asiatic-African and Caucasian countries, it was obvious that the worldwide application of the AFP-test became absolutely necessary for the diagnosis of hepatocellular carcinoma. The specificity of the AFP-test for hepatocellular carcinoma appears to be very high and not affected by racial, geographic or environmental factors. The geographical and ethnic differences of positive test on AFP in hepatocellular carcinoma could be explained by differences in age, sex, cancer size and sensitivity of AFP immunodiffusion detection.[22]

Some Authors thinck,[23 24] that it is not always possible to differentiate strictly hepato- and cholangiocellular cancers from each other. There are convincing proofs, that no matter what elements of the liver (liver cells of the cells of biliary ducts) primary cancer of the liver derives from, one can see structures of both hepato- and cholangiocellular cancer. This is due to the genetic relation between liver cells and the epithelium of biliary ducts. Taking into account these

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TABLE II.—*Presence of AFP in serum of patients with hepatocellular carcinoma measured in different countries by immunodiffusion test of AFP.*

Country	No. of patients examined	Rate of positive cases (%)	Reference
Indonesia	100	87	11
Hong Kong	42	64	12
Singapore	29	72	13
Japan	227	78	15
Senegal	44	80	13
Mozambique	37	68	16
Uganda	40	50	10
France	30	60	17
Grece	35	51	17
Spain	17	42	18
England	41	43	19
U.S.A.	56	70	20
U.S.S.R.	112	77	21

data one can suppose that the discrepancy in the amount of AFP-positive and AFP-negative hepatocellular carcinomas could be explained by inaccuracy of the pathohistological diagnosis.[9]

Immunofluorescent study [25] has shown that AFP is produced by only a part of tumour cells, and serum AFP level can be correlated with the number of AFP-producing cells in tumours. No correlation was found with any clinical parameter investigated, or with a histological subtype or degree of differentiation of liver cancer.[13]

Embryonal germ tumors

In 1967 the relationship between AFP and embryonal teratocarcinomas of the testis was first found by the immunodiffusion test.[7] The cellular localization of AFP synthesis by these tumours was clarified in earlier investigations, in which it was shown that AFP is produced by human yolk sac.[26 27] On this basis all groups of tumours with germ-cell origin have been classified.[28-30] In accordance with the histological classification suggested by Teilum (Fig. 1), the differentiated forms of embryonal carcinomas may be divided into three histologic types of (1) endodermal sinus carcinoma or yolk sac tumour, (2) choriocarcinoma, and (3) teratoma. In embryonal carcinomas, probably, there is a variety of combinations of the three different cell types. However, the cells which are responsible for AFP synthesis in embryonal carcinomas are the epithelial cells of the yolk sac endoderm which are of endodermal sinus origin. This vitelline component which is producing AFP is also seen to produce AFP when present in the fetal yolk sac or endodermal sinus in early embryogenesis. In addition, an elevated serum AFP level has been demonstrated in patients suffering from extragonadal endodermal sinus tumours.[31 32] As one can see in Figure 2 the elevated AFP levels were demonstrated in germ cell tumours with different localization and all cases had endodermal sinus structural elements in various combinations. Since all embryonal carcinomas which have endodermal sinus elements are associated with the initial increased serum AFP levels, the measurement of AFP may be used for clinical diagnosis and for the estimation of prognosis. Moreover, the AFP level may also help in the monitoring of surgical, chemotherapeutic and radiotherapeutic treatment of germ cell carcinomas.

Gastrointestinal tumours

The first finding of AFP in the serum of patients with other tumours than hepatocellular carcinoma or embryonal teratoma was considered as a false-positive reaction for AFP.[13] However, further studies [33-35] have shown that several tumours having non-hepatic or non-endodermal sinus origin are associated with elevated serum AFP levels. Most often the increased AFP concentrations are found in patients with gastric, pan-

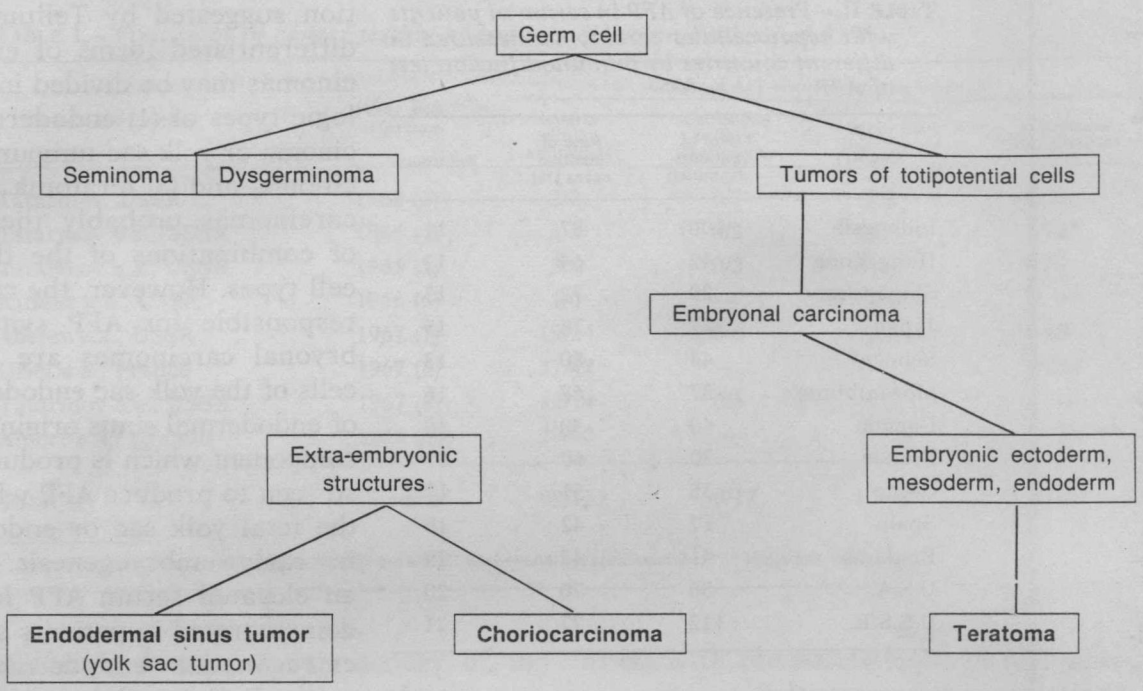

Fig. 1.—Histogenesis and interrelationship of ovarian and testicular tumors of germ cell origin.[30]

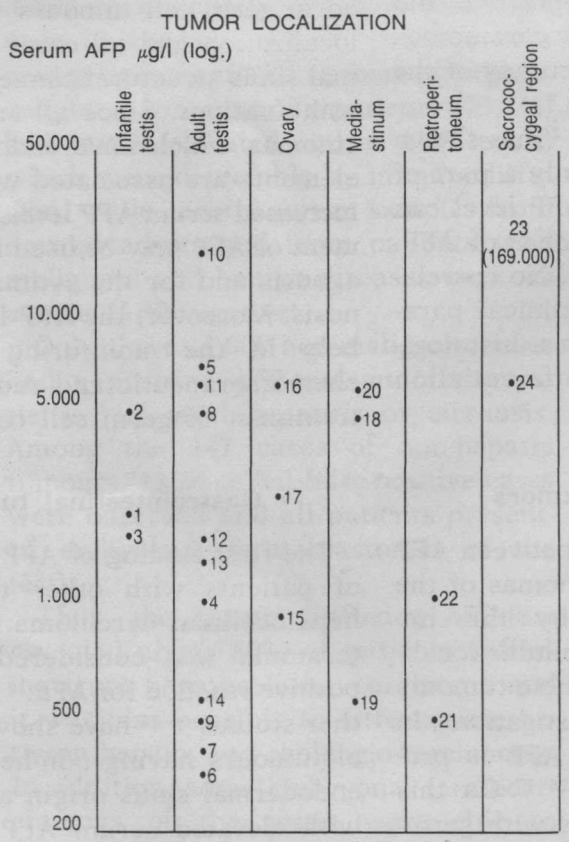

Fig. 2.—Serum alpha-fetoprotein (AFP) concentration in germ cell tumors with different localization.[32]

creatic and biliary tract tumours (Table III). It is very important that AFP could be detected not only by radioimmunoassay, but also in a small percentage of tumour cases by immunodiffusion.[35 36]

It could be postulated that tumour cells from these AFP-producing malignancies themselves possess the ability to produce AFP, because some gastrointestinal tract cells in human earlier embryogenesis can produce AFP.[26]

Although it is not possible to use the AFP-test for the early diagnosis of gastrointestinal tract malignancies, serial quantification of serum AFP levels in AFP-producing tumours is important for evaluation of the effectiveness of surgery and/or chemotherapy, as AFP concentration is an indicator of the amount of tumour present.

The present and the future in cancer testing by AFP

As is known, AFP which is produced both in embryogenesis and in different oncological situations is immunologically

TABLE III.—*Occurrence of elevated AFP levels in patients with gastrointestinal tumours*[36].

Primary tumor site	Number of patients examined	Positive patients			
		Immunodiffusion		Radioimmunoassay	
		No.	%	No.	%
Stomach	95	2	2.1	14	14.7
Biliary tract	8	0	0	2	25
Pancreas	45	1	2.3	11	24.4
Esophagus	4	0	0	0	0
Small bowel	10	0	0	0	0
Colon-rectum	191	1	0.5	5	2.6
Total	353	4	1.1	32	9.0

indistinguishable, but heterogeneity of AFP may be demonstrated by starch gel electrophoresis and especially by isoelectric focusing.[37] [38] In addition, AFP microheterogeneity can be revealed in its reaction with lectins.[39-41]

At present, we have reliable data concerning the biochemical structure of AFP and especially the structure of carbohydrate chains, which include a lot of many different glycoproteins. Because the sugar chains are not coded by gene(s) during the translation of the molecular structure of all glycoproteins it may be supposed that all modifications are synthesized in the endoplasmic reticulum and in the Golgi apparatus of embryonal and malignant cells. Apparently, as the composition of the above-mentioned cells presents differences, AFP can be produced in different variants in both embryonal and malignant cells. Such variants can be revealed by modern qualitative and quantitative methods. Although the relationship between different lectins is widely studied for clinical application in the screening and diagnosis of AFP-producing tumours, at the same time for the present we do not have available a laboratory AFP-test to distinguish AFP variants.

It was proposed that determination of AFP microheterogeneity can be used for the differential diagnosis of cancer. It was reported,[42] that AFP-producing embryonal carcinomas with yolk sac origin and gastrointestinal tract cancer are rich in LCA-lectin AFP, but AFP produced by hepatocellular carcinoma contains very few AFP components bound with LCA-lectin. Moreover, AFP reacting with Con A is present in higher concentration in the sera of patients with embryonal carcinomas originating from yolk sac cells, than in patients suffering from hepatocellular carcinoma and gastrointestinal tract tumours.[43]. These data were confirmed in recent investigations and there was included a very important result, which tells that changes in the reaction of AFP with lectins must be the sign of malignant transformation.[44] Clinical application of the AFP-test combined with lectin-AFP reactions remains to be studied, as the data obtained by different Authors cannot be compared due to differences in the techniques, precise nomenclature, reliability of the lectins used. Evidently, we should prefer affinity electrophoresis, as the results obtained by it lately present real clinical interest for the differential diagnosis of primary and metastasis cancer of liver.[45] [46]

One should seek the approaches to obtain monoclonal antibodies, which will distinguish between AFP variants and will possess high affinity to AFP, produced by different types of tumours.

Conclusion

AFP is a typical protein associated with oncogenic expression, but biochemical mechanism of this phenomenon remains to be investigated. During the last 26 years, the AFP-test was being extensively studied both in the diagnosis and monitoring of primary cancer of liver and embryonal carcinomas. At present AFP-testing is performed worldwide for cancer testing and for the diagnosis of maternal and fetal disorders.[47] Moreover, the AFP immunodiffusion test was used for the screening of hepatoma in Senegal[48] and China.[49]

The normal serum AFP level is not more than 20 ng/ml. Elevated AFP level in hepatitis and cirrhosis is between 100-400 ng/ml. We observed [50] a patient with post-necrotic viral cirrhosis, who had periodical and short increased of AFP between 1500-2000 ng/ml during five years, and after this period hepatocellular carcinoma developed, i.e. the screening of the group at risk has great significance in the early diagnosis of AFP-producing hepatoma.

The ways of therapeutic use of antibodies against AFP are in prospect. Hirai is a pioneer in the treatment of patients with hepatocellular carcinoma by monospecific antisera against human AFP.[51] Apparently, in the near future monoclonal anti-AFP will be obtained, associated with radio- and chemopreparations.

AFP was named by Fishman and Hirai [1] as oncodevelopmental protein. In 1970 the WHO group put forward some postulates for AFP designation as oncofetal protein,[52] although AFP Odyssey started in 1963 by Abelev [2] and Tatarinov.[3]

In the very near future AFP will be combined with a variety of immunochemical tests, such as placental alkaline phosphatase (PAP), acid placental phosphatase (APP), carcinoembryonic antigen (CEA), trophoblast-specific β-glycoprotein (TSG or SP-1) and other oncodevelopmental proteins, which will be used for the diagnosis and screening of several tumors. This will probably make for better clinical approaches for chemotherapy and immunotherapy of tumours.

After 15-years discussion, whether AFP possesses immunosuppressive activity or not, it seems we have convincing evidence, that a small amount of AFP molecules are strong immunosuppressors. It gives a wonderful opportunity for real immunocorrection of AFP-producing malignancies.

In the problem of oncodevelopmental proteins only the first page is open, and I hope very much and shall be happy to write in this book at least one line.

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The Physiological Role of Alpha-Fetoprotein in Cell Growth and Differentiation

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Alpha-fetoprotein (AFP) has been extensively studied since 1963 when Abelev and his coworkers demonstrated the association of this protein with primary liver cancer in the adult.[1] Attention has also been largely paid to its physiological role in embryo-fetal life (reviewed in ref. 2) particularly regarding a possible, although controversed, immunoregulatory activity. The aim of the present contribution is to outline the most recent representative data leading to conclude that the main biological function of AFP seems to be the regulation, through an AFP/AFP-receptor autocrine pathway, of fatty acids entry into cells and of their availability for metabolic processing. This autocrine pathway may be operational not only during ontogenic development but also in expanding and renewing tissues of the adult.

Alpha-fetoprotein uptake by growing and differentiating cells

Alpha-fetoprotein, a dominant globulin in the embryonic serum of mammals and other vertebrates, is mainly synthesized by the liver and/or the yolk sac. The synthesis of AFP practically arrests in adult liver and its serum concentration drops to values extremely low (less than 10^{-10} M in human adult serum). AFP has been localized by immunocytochemical techniques in fetal hepatocytes but also within the cytoplasm of many other fetal cells of ecto- meso- and endodermal origin. The protein was present transitorely during the process of cell differentiation and was absent from either undifferentiated or fully differentiated elements.[3]

The question arosed, then, on the origin of such intracytoplasmic AFP. Several authors, using dot blod and Northern blot analysis, as well as *in situ* hybridization techniques, have found significant transcripts of AFP mRNAs in several non hepatic fetal tissues including brain, lung, pancreas, heart and kidney.[4,5] Other *in vitro* and *in vivo* studies on the uptake of exogenous AFP by cells and tissues have concluded that, although the local synthesis of AFP by fetal tissues other than the liver can not be excluded, the intracytoplasmic presence of AFP in these tissues is for the most part due to the uptake of the protein from extracellular sources.[6] Moreover the ability to internalize AFP characteristic of developing tissues and lost in mature, resting cells may be resumed by neoplastic cells growing *in vitro*[7] or *in vivo*.[8]

AFP receptors in normal and neoplastic cells

Preliminary morphological observations on two malignant cell lines, a rat rhabdomyosarcoma and a human breast carcinoma suggested that the uptake of AFP by these cells was protein-mediated.

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