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Fifty Years of Discovery of Alpha-Fetoprotein as the First Tumor Marker

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SUMMARY
Alpha-fetoprotein represents the most prominent oncobiomarker, widely used in the diagnosis of hepatocellular carcinoma for monitoring of tumor progression, presence of metastasis, assessment of cancer prognosis and successful antitumor therapeutic measures. Yuri Semenovich Tatarinov is a Russian scientist who first published antigen specific for human hepatocellular carcinoma in 1963. To commemorate the 50th anniversary of the discovery of alpha-fetoprotein, 9th International Scientific-Practical Conference entitled "Achievements of fundamental science and translational medicine capabilities in solving actual problems of practical public health", was held from May 6–8th, 2013 in Astrakhan, Russia. The conference was held in memory of historical scientific work of Yuri Semenovich Tatarinov.
Keywords: alpha fetoprotein; first tumor marker; history of medicine; Yuri Semenovich Tatarinov

INTRODUCTION

Alpha-fetoprotein (AFP) is a 591 amino acid-gycoprotein (69000 Da) containing 4% carbohydrates, structurally very similar to albumin, with difference in N terminal sequence. Synthesis of AFP starts early in the fetus [1, 2, 3] and a high concentration of AFP can be also found in neonates [3, 4, 5]. During pregnancy the concentration of AFP is usually very high, with values 25-30 times above the reference values in human adults. It has been found that the gene for AFP is localized on the chromosome 4 [6]. AFP is an embryo-specific and tumor-associated protein that is additionally present in small quantities in adults in normal physiological conditions [2-7].

Modern medicine is constantly searching for new molecules that could be used as tumor markers. However, those identified so far have proven not to be perfect [8, 9, 10]. AFP is one of many tumor markers used in the clinical diagnosis [5, 7]. In combination with other proteins AFP has been also proposed to be biomarkers for the detection of human hepatocellular carcinoma (HCC) [5, 7, 11]. Although serum AFP level is obviously raised in most patients with HCC at the time of diagnosis, unexpectedly low or even normal AFP values are reported in about 10–15% of cases. Moderate increase of AFP is also detected in 15% of gastrointestinal cancer, mainly gastric especially associated with worse prognosis. The most common cause of AFP false positivity are acute or chronic liver disorders including cirrhosis, as well as hepatitis and toxic liver diseases occurring mainly after the use of paracetamol and anesthetic. In these cases the increase of AFP is usually moderate and generally under 100 ng/mL in serum. Clinical data indicates that total AFP may be an indicator of tumor mass in liver cancer. Based on this, AFP is considered as a "golden standard" among tumor-specific molecular biomarkers for HCC since the 1970s [12, 13].

Over the past decades, literature data have shown that total AFP is a collection of heterogeneous glycoproteins consisting of three different glycoforms [12, 13]. The total AFP can be separated into three fractions, AFP-L1 to AFP-L3, based on its reactivity to Lens culinaris agglutinin (LCA) on affinity electrophoresis. The AFP-L1 fraction is mostly present in chronic hepatitis and liver cirrhosis, and constitutes a majority fraction of total AFP in the non-malignant liver diseases. AFP-L3 fraction appears to be produced only by cancer cells, indicating their measurements most sensitive for tumor diagnosis [11-14].

HISTORY OF THE DISCOVERY OF ALPHA FETOPROTEIN

The history of Russian science is filled with important milestones, which determined the development of the worldwide biological and medical science. One of them is connected with the names of Harry I. Abelian and Yuri S. Tatarinov.

Scientific Tatarinov's intuition led him to cooperation with a group of scientists from the Institute of Epidemiology and Microbiology of N.F. Gamaleja Academy of Medical Sciences of the USSR (Moscow), which studied tumor tissue in the early 60's of the last century.

Harry Abelev and colleagues have identified new protein in blood of mice with experimen-

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tal liver tumor, which proved AFP in 1962 [1]. At that time Abelev announced his belief that protein could not be used in diagnosis, because a lot of murine hepatocellular carcinoma did not produce this protein. He focused the obtained results on cell proliferation under normal and pathological conditions.

The following year 1963, at the Biochemical Congress in Moscow, Yuri S. Tatarinov, Astrakhan, biochemist and head of the Department of Biochemistry of the Astrakhan Medical Institute, reported on the detection of AFP in the blood of patients with hepatoma, and suggested that it could be an immunochemical test for the diagnosis of primary liver cancer [2]. Shortly after, the discovery of AFP prompted a great interest in the clinical application of this molecule.

On the personal initiative of Tatarinov, the first international expedition to Africa and Siberia was launched, as there was a high incidence of hepatocellular carcinoma, much higher than in Europe at that time, and with the aim to analyze and establish the significance of the detected proteins in these patients. Indeed, the first announcements of increased AFP values were associated with the geographic distribution of the occurrence of hepatocellular carcinoma [3, 4, 5]. Thus, it was confirmed by the discovery of "the synthesis of embryo-specific proteins and the resumption of their production in adult animals and humans," registered in 1971 (G.I. Abelev, Yu.S.Tatarinov and other, Diploma for the discovery, № 90).

Later, studies began on the causes of hepatocellulal carcinoma and its correlation with the presence of viral infection and fewer chemical carcinogenesis.

In 1980 W. Fishman and H. Hirai, two of the founders of the International Society for Oncobiology (ISOBM), wrote in an editorial for the opening of the first issue of the Society journal (Oncodevelopmental Biology and Medicine, 1980, vol. 1, No. 1, p. 1-5): "Although the idea of the relationship between embryogenesis and carcinogenesis has been discussed in the last 100 years, but only the opening of the synthesis of alpha-fetoprotein in 1963 Abelev and Tatarinov in fetal liver in experimental hepatoma and hepatocellular cancer in humans was the beginning of a new era in oncology and medicine."

In Serbia clinical studies on the value of AFP in primary and secondary liver tumors as well as a high prevalence of infection with hepatitis B were initially conducted and published from 1979 and 1981. The data indicated the problems in the diagnosis of tumors and suggest the use of immunological methods for its detection [15, 16].

Methods for detection of AFP

Keeping in mind the first results on the values of AFP and the fact that it is not always detectable in the serum, as well as a large number of false negative analyses, the issue on the methods for the detection of the protein was raised immediately after its discovery [17].

Application sensitive methods radioimmuno identification and ELISA determination AFP demonstrated the presence of low concentrations (5-7 mg/l i.e. 10^{-10} M) of AFP in serum of healthy adults, and allowed to determine the diagnostic level of AFP in HCC patients mostly about 20 mg/l, excessive value compared to the normal level of 3-5 mg/l [17, 18]. However, increased AFP up to 20 mg/l and slightly above may also be associated with acute and chronic hepatitis, cirrhosis, tyrozinhemia, and hypoplasia of the thymus gland [18, 19, 20]. Increased concentration of AFP in adult serum is a mark of pathological conditions, primarily tumor diseases, such as primary liver cancer and teratocarcinoma. The increased AFP has been also found in some cases of stomach cancer, lung cancer and pancreatic blastoma [21-24].

Usage of highly sensitive radioimmunoessay can determine AFP in its minimum content of 0.2-1 mg/l. Improved methods of enzyme-immunodetermination reveals 0.5-3 mg/l of AFP. The limit of sensitivity of electrochemiluminescence techniques is 0.4 mg/l. The least sensitive nephelometric methods are based on immuno-agglutination assay using latex particles and can detect a value above 5 mg/l.

All of these techniques allow the determination of AFP in serum of healthy adults and are able to detect changes in the level of AFP in blood during the development of pathological process [16, 17, 21]. They are widely used for screening and monitoring HCC patients involved in a program that exist in several countries simultaneously with continuous abdominal ultrasound monitoring of patients with a long history of chronic liver disease.

Belgian researchers E.N. Debruyne and J. R. Delange [18] in the review of the development of laboratory methods for the diagnosis of hepatocellular cancer (2008) stated that "despite the promising results of new potential markers, currently they can only be recommended as additional tests and cannot even replace the test with serum AFP – the gold standard of tumor markers of hepatocellular cancer".

TATARINOV BIOGRAPHY

Professor Yuri S. Tatarinov was born in 1928. Initially, he worked in Astrakhan and then transferred to Moscow. He was the Rector of the Institute in Astrakhan, Vice-Rector of the University in Moscow and has been always the head of the Department of Biochemistry in Astrakhan and Moscow (Figure 1). He created a scientific School of Immunochemistry of embryonic and cancer tissues. In 1968, Task Laboratory for the study of embryonic and cancer tissues was organized by the Department of Biochemistry. However, it was transferred to Moscow University in 1972. In Astrakhan, he was surrounded by talented and dedicated science students and young colleagues.

Accompanied by a fellow in Astrakhan, Professor Yuri Tatarinov had his second discovery relevant to the diagnosis of pregnancy, in the early 1970s: "The phenomenon of synthesis and secretion in the blood of mammals and human protein-trophoblastic beta-globulin" (Y. S. Tatarinov, V. N. Masyukevich, Diploma for the opening number

Figure 1. Yuri Semenovich Tatarinov (1928–2012)

247, 1981). This protein was also detected in the blood of patients with trophoblastic disease that developed in rare cases after delivery, including malignant form - chorionepithelioma uterus [21].

Yuri Tatarinov with his research students holds the record in the detection of protein markers of pathological processes. His third discovery was made in Moscow and was reported under the title: "Property of the reproductive system of human tissue-specific synthesis of alpha 2-microglobulin and secrete it in biological fluids" (Yuri S. Tatarinov, D. D. Petrunin – Diploma for the opening number 29 with data from April 19th, 1996).

Professor Tatarinov was not only a research talent, fine analyst, but also a gifted teacher. More than 50 of his research students are professors and academics who work in different areas of basic and clinical science and are heads of departments, laboratories and institutes in many cities of Russia.

Yury S. Tatarinov has always tried to foster a true interest in science among young people. Since 1999, he has systematically participated in scientific conferences and workshop "Protein markers of pathological conditions", and later "Achievements of fundamental science in solving actual problems of medicine" that became a tradition in the Astrakhan State Medical Academy.

THE 9TH INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE

In September 2013, Professor Tatarinov would have been 85 years old. From May 6-8, 2013, the 9th International Scientific-Practical Conference was held in Astrahan, Russia, entitled "Achievements of fundamental science and translational medicine capabilities in solving actual problems of practical public health", dedicated to the 50th anniversary of the opening of the first tumor marker and in memory of Yuri Semenovich Tatarinov (Figure 2). The congress was composed of five sections.

The first section on the fundamental achievements of modern science involved a total of 15 lectures. A distinguished researcher from Japan, Masaki Tan held a lecture on the application of molecular medicine in the prevention of many diseases associated with aging. A group of authors from the Moscow University and prominent sci-

Figure 2. Participants of the Conference in Astrakhan, Russia, May 6-8, 2013

Figure 3. Tatarinov memory plaque at the Medical Astrakhan Academy, May 2013

entists from the Astrakhan State Academy of Russia, held a very interesting lecture on modern diagnostics based on the application of molecular medicine, including a discussion about applications of proteomics and nanotechnologies. Certainly, scientist from Russia dealing with the field of personalized medicine sparked a great interest among the audience and developed a broad discussion on the application in everyday work with patients [25]. The second section was entirely devoted to the exploration of contemporary biomarkers as the indicators of pathological conditions with special view on the implementation of new methods and clinical significance in the diagnosis of diseases, mostly based on cancer [8, 26]. The next section was entirely devoted to the exploration of contemporary biomarkers as indicators of pathological conditions and innovative technologies. A prominent scientist from California, USA, Marsall [27] gave his vision of contemporary target treatment in the implementation of drug creation in chronic and autoimmune diseases. The next section was devoted to molecular, morphological and functional pathology in various states and was largely dedicated to original results achieved by Russian researchers [28]. Certainly, no less important was the section dedicated to the medical and biological aspects of social adaptation when the issues on everyday life of patients, complications of diabetes, osteoporosis, and occupational diseases were raised.

One of the Forum events was the opening of Tatarinov memorial plaque on the building of the Academy, where he worked and where his research students still continue to further develop his scientific school (Figure 3).

CONCLUSION

The aim of this paper was to once again remind us of the great discoveries in medicine and science that have helped in the diagnosis of tumors [2, 3, 29]. The paper encourages further thinking, and also points out the possibility of finding and implementing new ideas, accompanied with new technologies and diagnostic methods for the detection of tumors, which are one of the leading causes of mortality in general.

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Педесет година од открића алфа-фетопротеина, првог туморског маркера

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КРАТАК САДРЖАЈ

Алфа-фетопротеин је најзначајнији биомаркер који се користи за рано откривање хепатоцелуларног карцинома, за праћење прогресије тумора и метастаза, те за процену прогнозе и успешност лечења. Јурij Семенович Татаринов је 1963. године први описао антиген специфичан за хумани хепатоцелуларни карцином. У знак сећања на овог руског научника, од 6. до 8. маја 2013. године одржана је 9. Међународна научнопрактична конференција достигнућа фундаменталне науке и медицине, могућности примене у решавању актуелних проблема народног здравља, посвећена педесетогодишњици открића првог туморског маркера у Астрахану, у Русији.

Кључне речи: алфа-фетопротеин; први туморски маркер; историја медицине; Јурij Семенович Татаринов

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