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Problems and Perspectives in Diagnosis and Prevention of Ovarian Tumor Diseases

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Review Article

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ABSTRACT

A set of embryonic proteins - potential markers for ovarian tumors is presented. More than ten new embryonic proteins have been tested, but no one strictly specific protein marker for diagnosis of ovarian tumors has been revealed. SOVA-1 is the most perspective marker for today. The special attention is given to peculiarities of evolution and mechanisms of early distribution of the tumor process. The role of pregnancy and "pregnancy specific glycoprotein"- PSG as a way of the ovary tumor disease prevention is discussed. An attempt to realize sources and logic of the disease is undertaken in the present work.

Keywords: Ovarian tumor - peculiarities of evolution and progress; embryonic proteins- perspectives of immunodiagnostics; pregnancy specific glycoprotein (PSG); pregnancy as prevention measure in case of ovarian tumor disease;

1. INTRODUCTION

High mortality rate from ovarian cancer evidences that the problem of the ovarian tumors is one of the most difficult to solve in the modern oncology. First attempts to study ovarian

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tumor diseases were made in the first half XIX century. In 1848 R. Wirchow suggested to consider ovarian tumors as cystomas (Wirchow, 1848). Further, bright scientists like N. Anichkov, R. Meyer, E. Novak, V. Mikhailov, M. Glazunov, M. Fathalla, I. Nechaeva, V. Vinokurov, K.I. Zhordania, H. Tanimoto and many others tried to understand the mechanisms of the disease (Prokopenko and Terentiev, 2009).

However, there is, as previously, no optimism among many famous oncologists regarding results of the ovarian cancer treatment: "it is necessary to acknowledge regarding results of the ovarian cancer treatment that at the present time the limit for improvement of results has been reached" (Zhordania, 1992), but at the same time the ovarian cancer is the "killer number 1 among benign diseases of genitals" (Tanimoto et al., 2001). Here it is necessary to emphasize the age of patients with ovarian cancer: Borisenko el al. conducted a study with 192 patients and among them 62.5% were younger than 60 years old , 20.2% were younger than 45 years old and 9.8% were younger than 40 years old (Borisenko el al., 2004).

2. TUMOR MARKERS FOR OVARIAN CANCER

2.1 Antigen CA 125

Since 1970 relatively intensive efforts have been made to reveal markers for ovarian cancer and tens of proteins have been identified but no one did attract attention as a marker (Knauf and Urbach, 1974; Borisenko, 1977; Bast et al., 1981; Bhattacharya et al., 1987; Prokopenko et al., 2001). In 1981 "a specific marker for ovarian cancer" was described and named" the antigen CA125 - CA125 (Bast et al., 1981, 1985; Afrikyan and Zhordania, 1990); other authors named it as "marker of ascites of different origin" (Bergmann et al., 1987; Molina and Filella, 1991). Later, it was established that CA125 is identical to IgG-like glycoferroprotein (IgG-GFP) from donor serum (Prokopenko et al., 2002, 2003, 2007, 2010abc; Prokopenko and Terentiev, 2009; Borisenko et al., 2007)

By biochemical characteristics IgG-GFP does not differ from the "CA125 antigen". In the serum it exists as a complex of 3 proteins: IgG, albumin and unknown "thermostable protein coupled with albumin - TPC.A". The final product of IgG-GFP dissociation is a double thermostable complex "TPC.A-Albumin" with molecular weight 55 kDa and represents a stem structure serving as a basis for reconstruction of all supercomplexes "CA125" (Prokopenko et al., 2010). "TPC.A-Albumin" is such a stable complex that it is not possible to isolate one protein from the other: after boiling during 3 hours the complex preserves its immunoreactivity and the double structure. Denaturated by boiling albumin after renaturation recovered its immunoreactivity and double structure with MW 55kDa as well as its ability to increase molecular weight (Prokopenko and Terentiev, 2010).

IgG-like glycoferroprotein (MW~470 kDa) was many times revealed in tumor tissue, ascite, serum and different names were assigned to this structure: "alpha-2H-globulin" (Druet and Burtin, 1967), alpha-2H-glycoferroprotein" (Buffe and Rimbaut, 1975), "serum macromolecular ferroprotein" (Prokopenko and Terentiev, 1975), "albumin-IgG complex" (Scharma et al., 1981), "serum macromolecular glycoprotein" (Prokopenko, 1982), "tumor-associated IgG" (Silburn et al., 1984), "IgG-like structure" (Prokopenko et al., 2006), "glycoferroprotein with peroxidase activity" (Prokopenko et al., 2010a,b,c). However, its precise structure is still unknown.

On the basis of the stem structure “TPC.A-Albumin” (MW 55 kDa) protein complexes of different molecular weight are formed in ascites up to giant supercomplexes with MW 2700 kDa (Prokopenko et al., 2010b). All the complexes demonstrate unusual adhesive properties (bind Fe ions, oligosaccharides, heme, dyes, dextrans) and, possibly, inactivate toxic cell products formed in different diseases (sanitary function). Especially, the complexes were detected in ascites of patients with ovarian cancer. Probably, due to this ability the ascite is a barrier for penetration of toxic products to the blood and serves as a depot of toxins. For example, in case of patient B. CA125 concentration in the ascite (volume ~10 l) was equal to 9700 E/ml (Prokopenko et al., 2003), and 287 E/ml in the serum of this female patient (Borisenko et.al., 2007).

Since 1970 an intensive work on searching for tumor markers has been carried out by authors of the present work. A whole set of 26 proteins was revealed, studied and characterized (Borisenko, 1975; Tatarinov et al., 1975; Borisenko et al., 1975; 1983; 2003; 2004; 2007; Gryaznova et al., 1984; 1990; Prokopenko et al., 1990; 1991ab; 2001; 2002; 2009; 2010 a,b,c). More than 10 different proteins were tested to be used in OC diagnostics, including CEA (Tatarinov et al., 1975), CCA, OMA-8, PSG, ferritin, CA125 and SOVA-1, using RIA and ELISA methods (Gryaznova et al., 1984; Prokopenko et al., 1990; Prokopenko et al., 1991a; Gryaznova et al., 1990).

2.2 Embryonic Proteins in Ovarian Tumors

However, no one protein, with exception of SOVA-1, demonstrated proper specificity as a marker for OC (Prokopenko et al., 2002). Out of 26 revealed proteins 7 were organ specific for kidney, brain and spleen. 17 proteins were revealed only in amniotic fluid and embryonic tissues and are embryonic ones.

Seven embryonic proteins were identified in serum of OC patients by reaction of immunoprecipitation (see Table 1) (Prokopenko et al., 2002), and this indicates their high concentration in the blood of patients with ovarian tumors. At the same time, on our opinion it is impossible to discover the strictly specific marker usage of which will allow to solve the problem of immunodiagnostics of ovarian tumors. According to Glazunov (Glazunov, 1961), it is necessary to consider a number of alternative sources of the protein origin.

SOVA-1 (OVA12, Table 1), the “serum oncoovarian alpha-1-globulin” is the most perspective embryonic protein for immunodiagnostics of ovarian tumors at present time (Prokopenko et al., 2002). The serum level of SOVA-1 in healthy people (female and male) do not exceed 0,05 mg/ml. In the serum of OC patients its concentration reaches values of 1 to10 mg/ml in 75-85 % of cases. SOVA-1 also is revealed in 12-25 % of cases in patients with benign ovarian tumors and in cancer of other organs (uterus, stomach, intestine). High level of SOVA-1 in part of patients with benign ovarian tumors, a priori, allows to expect its level elevation during the tumorigenesis dynamics in the ovary. Immunoenzyme method of determination for SOVA-1 is under development.

Table 1. Revealing of ovarian antigens (OVA) in tissues and biological fluids by immunochemical testing (sensitivity of the method is 1 mg/ml)

№ OVA	MW: kDa	Adult tissues	Embryonic organs	Biological fluids			Blood serum (% of detection)		
				AF	LF	ASF	HD	BOT	OC
1	600	kidney	kidney	-	-	-	-	-	-
2	110	kidney	kidney	-	-	-	-	-	-
3	60	kidney	kidney	-	-	-	-	-	-
4	115	spleen	spleen	+	+	-	-	+(40)	+(50)
5	22	spleen	spleen	-	+	+	-	+(24)	+(38)
6	130	brain	brain, GIT	+	+	-	-	-	-
7	24	brain	brain, kidney	+	+	+	-	-	-
8	35	placenta		+	-	-	-	-	-
9	57	-	GIT	+	+	+	-	+(55)	+(58)
10	55	-	IT	-	-	-	-	-	-
11	14	-	-	+	-	-	-	-	-
12	36	- (SOVA-1)	-	+	+	-	-	+(25)	+(75)
13	68	-	GIT	+	+	+	-	+(17)	+(41)
14	55	-	-	+	-	-	-	+(22)	+(33)
15	32	-	GIT	+	-	-	-	-	-
16	50	-	-	+	+	-	-	-	-
17	21	-	-	+	-	-	-	-	-
18	32	-	-	+	-	-	-	-	-
19	12	-	-	+	-	+	-	-	-
20	100	-	-	+	-	-	-	-	-
21	105	- (PSG) placenta		+	-	-	-	-	-
22	200	- (CEA)	GIT	-	x	-	-	-	-
23	40	- (PBT-40)	-	+	x	-	+(25)	+(98)	-
24	477	+(Ferritin)	+	-	-	+	-	+(25)	+(38)
25	55	+(CA125)	+	+	x	+	+(100 for all groups)		
26	23	-(EPA)	+	+	x	-	-	-	-

Note. AF: amniotic fluid (10-27 week gestation); ASF: ascitic fluid from patients with ovarian cancer; LF: lymphatic fluid from patients with ovarian cancer; HD: healthy donors; BOT: benign ovarian tumors; OC: ovarian cancer; GIT: gastrointestinal tract; IT: intestinal tract; CCA: cancerocerebral antigen; PSG: pregnancy-specific glycoprotein; CEA: carcinoembryonic antigen; PBT: protein of benign tumors; EPA: embryonic prealbumin; (+): revealed; (-): not revealed; (x): no data

It is necessary to note that the protein of benign tumors (PBT-40), which we revealed in serum of "healthy" female donors in 25% of cases, was also detected in serum of all patients with benign tumors, but was not detected in ovarian cancer (Table 1). High level of such proteins in benign ovarian tumors may reflect the degree of proliferating activity of the tumor cells and they may serve as markers of the benign process. Decreasing of its level in the blood in OC is in concordance with a suggestion that “cancer cells are spreading ..., eliminating pre-existing epithelium”, or this epithelium (of benign tumors) “undergoes dystrophic changes and exfoliates (Glazunov, 1961). Increased level of PBT-40 in the blood of “healthy” females is due to long absence of pregnancy, when high proliferating activity of ESC of the integumentary epithelium of the ovary become permanent (Fathalla,1971) or is provided by presence of benign tumor in a woman.

3. PECULARITIES OF OVARIAN TUMORS EVOLUTION

According to Glazunov, there are up to ten such sources: covering epithelium of their ovary, products of germ egg differentiation, epooforon, paraoforon, medulary gubernaculum shifted to the surface of the Fallopian tube epithelium and implants of tube and uterus epithelium on the ovary.

Peculiarities of ovarian tumors evolution compose the core idea of unique monograph work by M.F. Glazunov (1896-1967) - "Tumors of ovary" (Glazunov, 1961). To present time, taking into account his deep insight into the problem, this book is the most fundamental work on ovary tumors in the world scientific literature. There are answers for the most difficult issues of oncology in the monograph but it remains unrealized by modern oncologists.

Glazunov classified ovarian tumors to benign (*cystadenoma and proliferating cystadenoma*) and malignant (*related tumor and ovarian cancer*). He outlined 4 stages of the whole continuous process- the process of serous ovarian tumors evolution: 1. *benign cystadenoma,* 2. *benign proliferating cystadenoma*, 3. *related* tumor or "*initial stages of cancer development*" and 4. *ovarian cancer* completes the *evolution* (Glazunov, 1961).

Successive continuous character of the tumor process in ovary was evidently demonstrated by Glazunov at different cell generations and in brief it may be described as follows. At the crest of the 1-st wave of proliferation a 1-st generation of tumor cells is formed- one-layer epithelium of benign tumor covering the internal surface of the cyst (*cystadenoma*).

In some cases the process will be completed at this stage and the cyst will be permanent and the epithelium completely disappeared. In other cases centers of next wave of proliferation lead to formation of tumor cells of 2-nd generation which, in turn, form papillary projections, epithelium of which "*actively proliferates*" (*proliferating cystadenoma*). Such papillary projections "appear at the external surface of the cyst and also they can inseminate the largest or smallest part of peritoneum".

The 3-rd generation of tumor cells is characterized by Glazunov as "transitional" or "initial stages of cancer development", which are formed at the crest of the next, more high, wave of proliferation: "Simultaneously with changes of cytophysiological character the covering epithelium of papillaries demonstrates *distinct features of proliferation"*. Evidently, only the 3-rd generation of tumor cells undergo malignization and it is formed at the surface of the 2-nd cells generation. But at the early stages of malignization like the first 2 generations of cells it possesses exophyte/non-invasive growth. Next stage of the related tumor development – maturation of clone of cells capable to endophyte/invasive growth: simultaneously with exophyte growth the epithelium, incorporated into walls and bases of papillae, forms new cysts which are increased in a volume and covered by new papillae. Thus, the picture of the cancer is arised, in other words the 4-th stage – ovarian cancer completes evolution of the tumor process.

4. EARLY DISSEMINATION OF THE TUMOR PROCESS

Analysis of failures in searching for specific markers and reasons of non-effective treatment of OC allowed us to reveal the unique feature of metastasis: *dissemination of ovarian tumor cells takes place long before the malignant cell formation* (Borisenko et al., 2004). It is known that in the case of ovarian tumors the process proceeds predominantly by mode of

implantation (Glazunov, 1961; Vinokurov and Kolosov, 1980; Nechaeva and Vinokurov, 1987).

According to data of different authors epithelial implants of ovarian tumor cells at peritoneum were observed in the following benign tumor stages: in cystadenomas in 8.4% (Bychkov et al., 1969; Selezneva and Zheleznov, 1982) and in papillary *proliferating cystadenomas* in 13% and 29% of cases (Glazunov, 1961). As for related tumors the dissemination was detected in 52% of cases *in solid cystic* forms and in 81% of cases in papillary forms of the tumor (Vinokurov et al., 1983; Nechaeva and Vinokurov, 1987). In OC the dissemination process was detected in 96.9% in primary patients, and in 97% of cases by autopsy data (Vinokurov and Kolosov, 1980). Seemingly, so-called "finger structures" facilitate implantation of tumor cells (Kolosov, Mkrtchyan, 1986).

So, there are almost no early stages of OC (only 3% of patients). In other cases the process is greatly disseminated. K.I. Zhordania also concluded that there are only two stages of OC: the real 1-st one in which the process is only localized in the ovary, and the II-nd stage, in which the process acquires a systemic character (Zhordania, 1992). This is also confirmed by other authors who described false positive diagnosis of early stages of OC and this is supported by late backset of the disease (Novak's Gynecology, 1996). The data of Antoneeva indicates full absence of the 1-st stage of OC on FIGO: life expectancy after diagnosis is 21,84 months for patients in the 1-st stage of ovarian cancer. In other words, the process was disseminated in all the patients (Antoneeva, 2007).

Correspondingly, the viability of cell implants in autonomic conditions is increased. After resection of the center of benign cystadenoma (ovaryectomia) existing implants at peritoneum do not induce the disease backset (Selezneva and Zheleznov, 1982). In papillary *proliferating cystadenomas* position and an amount of implants across peritoneum vary in a wide range. According to Glazunov, *for many years they may stay permanent and do not lead to the disease backset, but in some cases hundreds of them inseminate the peritoneum's surface (Glazunov, 1961).*

In related tumors the list and topography of implants are sufficiently expanded (Vinokurov and Kolosov, 1980; Nechaeva and Vinokurov, 1987). Using the frequency of cases of mortality from the disease backset the invasive and non-invasive forms of the transition tumor are differed greatly. According to data of different authors (without discrimination of the disease stages) 0%, 4.7%, 6% and 15% of patients with non-invasive metastasis and 23%, 34%, 66.6% and 100% of patients with invasive metastasis died from the disease re-occurrence (Novac's gynecology, 1996). It may be concluded that only non-invasive form of the related tumor may be considered as the early stage of the cancer development, while the invasive form does not differ from ovarian cancer by clinical symptoms. In NII (Research Institute) of Oncology (Sankt-Petersburg) all patients with ovarian cancer die in 3 years from the disease backset and life expectance in case of diploid tumors is 20,8 months and in case of uneuploid tumors - 11,8 months (Vinokurov, 2003).

In European part of the Russia (Ul'yanovsk oblast) the life expectance of 374 patients is, in average, 9, 44 months. According to FIGO stages and life expectance of patients with ovarian cancer is represented as follows: I stage (19) - 21,84, II stage (6) - 14,71, III stage (127) – 13,78 and IY stage (222 patients) - 5 77 months (Antoneeva, 2007).

The data regarding life expectance of patients with ovarian cancer evidences the total expansion of resistant cancer cells maturating in the presence of the ovary damaged by the

tumor. Earlier authors named the ovarian cancer as “peritoneum disease”, underlining its wide spreading (Nechaeva and Vinokurov, 1987). So, longer tumor cells develop under neurohormonal control of the ovary damaged by the tumor, then more resistant these cells to treatment. Due to wide dissemination and multicenter malignization of implants (Glazunov, 1961), tumor cells acquire high resistance to treatment.

Increase of middle age of the patients also demonstrates a consistency in the development of the ovarian tumor disease. According to data of Nechaeva, the middle age of patients with cystadenoma is 43,6 years old, proliferating cystadenoma – 47,7 years old, related tumors – 48,9 years old and ovarian cancer – 56 years old (Nechaeva and Vinokurov, 1987).

5. EMBRYONIC CELLS- SOURCES OF OVARIAN TUMORS

One of the probable sources of origin of serous tumors of ovary are embryonic stem cells (ESC), originating from integumental epithelium of the ovary, inserted among mature cells of mesothelium (Glazunov, 1961; Fathalla, 1971). ESC is an organ for urgent reparation of tissue in the case of its damage, for cell homeostasis control, replacement of “old” cells and elimination of mutant cells. Their content is not more than 0,01- 0,1 % of all mature cells of the organ, but they possess a high potential ability to proliferation and high efficiency in reparation of the damaged surface. Therefore, elevation of concentration of embryonic proteins in the serum may be linked not only with the tumor development and then not to be a specific event for tumors only. Elevation reflects the degree of activity of proliferation processes taking place at any damages of the tissue, which needs restoration of the cell homeostasis.

Trophoblast and amniotic fluid antigens, detecting in the cancer tissue (Table 1), may be products of differentiation of totipotent ESC – zygote. Till the stage of morula formation, the zygote is capable to differentiate into any line of specialized cells, including trophoblast and placenta (Glazunov, 1961). Biological readiness of oocyte for differentiation is so high, that its partogenetic development become possible, in which only trophoblast is formed completely. However, different forms not only of teratoid tumors represent the terminal product of non-impregnated oocyte. For example, trophoblast – type morphological structures (trophoblastic nest) with intracellular synthesis and PSG secretion into the blood of the female patient are revealed in the tissue of “serous cystadenocarcinoma of ovary with sectors of granulose cell tumor” (Prokopenko et al., 1990).

Interrelationships between embryonic and tumor cells are under discussion more than 100 years and are concluded “not in the vicious character of the tumor source, but in the capability of this source – sex/embryonic cell – in pathological conditions to grow and differentiate in characteristic to it directions, undergoing or not undergoing malignization” (Glazunov, 1961).

We observe this in evolution of embryonic kidney rudiment in the ovarian tumors. Rudiments of the primary kidney – epooforon and paraoforon – preserved in the female ovary throughout her life, but kidney-specific proteins were not detected. However, in the tumor tissue in ovarian cancer high concentration (up to 10 mg/ml) of kidney-specific proteins was determined (Prokopenko et al., 2001; Borisenko et al., 2004). This may serve as evidence of proliferating activity of ESC of kidney in the tumors. But mature kidney cells have never been detected in the ovarian tumors. Consequently, the differentiation does not lead to kidney definitive cell formation.

However, epithelial mesonephroid light-cell ovarian tumors are well known, which demonstrate obvious cytomorphological similarity with the hypernephroid cancer of kidney. This is reflected in one of synonyms of this tumor- “ovary hypernephroid” (Glazunov, 1961). It is obvious, that the differentiation vector oriented at the mature cell reproduction deviates in pathological conditions of alien microenvironment and the kidney cell undergoes malignization, but still continues to synthesize organ-specific proteins of the kidney (Prokopenko et al., 2001). These results represent the clear demonstration of the genetic memory of the tumor cell about the progenitor cell, because kidney-specific proteins arising in the tumor tissue in ovarian cancer can only origin from embryonic kidney rudiments presented in the adult ovaries.

5.1 Other Endogenic Sources of Tumor Cells

Origin of the ovarian tumor disease and biological meaning of early tumor implants dissemination, possibly, are grounded in anatomic and physiological features of women. In absence of pregnancy the system of reparation of wound surface of integumentary epithelium of the ovary is hardworking and this leads to premature exhaustion of potential of the system of reparation of ovarian integumentary epithelium (theory of permanent ovulation). This is very probable mechanism, but it requires some additions.

Main (endogenic) sources of benign ovarian tumors, according to Glazunov, are embryonic cells of the integumentary epithelium of the ovary and cells of rejecting tube (between menstruation) and uterus (during menstruation) epithelia locating at the surface of the ovary (Glazunov, 1961; Zhordania, 1964). In the absence of pregnancy, permanent and cyclic (2 times in a month), there is a possibility of retrograde throw of epithelia into abdominal cavity. Likely, this is a “normal” physiology of a woman in the absence of pregnancy. So, spreading of implants proceeds without symptoms, because in the case of pregnancy woman, probably, will become clear of implants. By topography the fallopian tube is oriented to the ovary and embraced it by fimbria.

So, the first “target” of epithelial attack at the abdominal cavity is always the ovary. Ovarian integumentary epithelium break takes place 1 time in a month. As a result, a cavity with diameter up to 1 cm is formed, which is filled by the blood with flowing into it adhesive surfaces of broken ovarian surface epithelium. Restoration of its integrity should be completed up to the time of next ovulation due to active proliferation and differentiation of young forms – embryonic stem cells of the ovarian integumentary epithelium. This mechanism is also sufficiently effective in the process of elimination of mutant cells arising at the stages of active differentiation (Fathalla, 1971).

6. PREGNANCY AS PREVENTION MEASURE FOR OVARIAN TUMORS?

Physiological pregnancy and breast – feeding of a child has huge, if not decisive, significance for prevention of ovarian tumor diseases. In our study out of 192 patients with ovarian cancer 2,6 % were in the age from 17 to 22 years old, no patients were in the age of 23-29 years old (this is an active child-bearing age). Then a number of patients is increased: 30-40 years old – 7,2 % and 40-45 years old – 10,4% (Borisenko et al., 2004). The pregnancy interrupts penetration of implants into abdominal cavity, corrects immune system and assimilates existing implants. “Ability of trophoblast to melt subject tissues” before the

embryo implantation is well known (Zhordania, 1962; 1964; Gynecology by ten teachers, 2000).

6.1 Pregnancy - Specific Glycoprotein: Description of Bioactive Structure

The most representative structure of the trophoblast, associated with pregnancy, is a trophoblast-specific glycoprotein/pregnancy-specific glycoprotein (TSG/PSG) (Tatarinov and Masyukevich, 1970; Terentiev et al., 2010). The main function of PSG is protection of the embryo from premature rejection and this protein is considered as female-associated protein. Its family comprising more than 30 proteins is a part of immunoglobulin (Ig) superfamily, coding by 11 genes located at chromosome 19.

Typical molecule of PSG represents a single polypeptide chain composed of 5 domains: (L)N-A1-F2-B2-C, where L- leading sequence (34 amino acid – aa); N- Ig-like variable domain (109 aa); A1-A2 – Ig-like repeating constant domains (each 93 aa); B2 – Ig-like constant domain (85 aa); C – short variable domain. Degree of glycosylation, absence of A-domains (one or two) in some members of the protein family and functioning in the association with heavy chains of IgG and albumin (or their fragments) determine endless diversity of intra- and intercomplex interactions of separate representatives of PSG family. Molecular weight of polypeptide chain backbones (by aa) of practically all the members of PSG family are in the range from 25 to 50 kDa (Shmagel and Chereshnev, 2003).

After 40 years since PSG discovery in 1970 (Tatarinov and Masyukevich, 1970) nobody could isolate biologically active preparation of this protein in a form free of IgG heavy chains and albumin in commercial as well as analytical amounts (Prokopenko and Terentiev, 2009). Recombinant form of bioactive PSG have not also been prepared in commercial purposes. PSG functions in the blood of pregnant women only in the complex with IgG heavy chains and albumin in unknown proportions. Maximum concentration of PSG in the serum (0,65%) is reached at 40 week of gestation (Shmagel and Cherechnev, 2003). In a laboratory, as a rule, a biologically active preparation containing 3% of PSG is obtained and it represents a complex of PSG, IgG/HC and albumin in the proportion of ~1:30:4 (Prokopenko and Terentiev, 2009). Final product yield is equal to 10% and this is considered as a “good” result. However, after maximum release of PSG from heavy chains of IgG and albumin the resulting preparation of PSG loses immunological activity and reacts only with anti-IgG and anti-albumin.

Seemingly, this provides an adequacy of our own results on immunoenzyme determination of PSG in the serum if using only highly purified by immunoaffinity chromatography antibodies against PSG. PSG preparations used for immunoenzyme analysis are represented in SDS-polyacrylamide gel electrophoresis in reducing conditions by two protein bands (Prokopenko et al., 1990): major band with MW 60 kDa (heavy chains of IgG) and minor band with MW 42 kDa (PSG). Our results on determination of PSGs in the blood serum using immunoenzyme method were coincided practically with pioneer and then classical results of Sokolov, who used radioimmunological method (Sokolov, 1977; Tatarinov and Sokolov, 1977).

Data of group of Avendano may cardinally change the idea about sex origin of PSG. It was shown that sperm of fertile man contains a ready template of PSG-mRNA, which is absent in oocytes. Authors did not detect PSG as antigen in the extract of sperm cells. However, mRNA of PSG and products of its polymerase chain reaction (PCR) were revealed in

oocytes in 3 hours after spermatozoa injection and their amount were increased during 24 hours (Avendano et al., 2009). PSG-mRNA was also revealed in testicles of male rats (Shmagel and Cherechnev, 2003).

From this follows, that a female has no reliable mechanisms for protection of the embryo from own immune attack and rejects the alien embryo. But a male "possesses primary knowledge" about this situation and "provides a guard" for his posterity? Authors did not reveal PSG in the sperm and they consider that PSG is not necessary protein for these cells. However, we suppose that intracellular PSG synthesized de novo is represented by immunologically inactive peptide backbone. At the moment its antigenic determinant is not available yet for antibodies, because only the complex of PSG (with IgG heavy chains, albumin and oligosaccaharides) forms immune puzzle for antibodies (Prokopenko and Terentiev, 2009; Shmagel and Chereshnev, 2003). Namely, in such a form it is presented in the blood of pregnant women and placenta. Basic protein profile in the electrophoresis picture is represented by bands with molecular weight from 25 to 50 kDa (Fig. 2a) and this molecular weight range is typical practically for all types of PSG family (SwissProt). We in full share the authors' opinion that a great need in PSG in early embryogenesis is to provide the embryo implantation, which takes place at 3-5-th day after impregnation. This is supported by high rate of PSG mRNA replication in oocytes in first hours after sperm injection (Avendano et al., 2009).

6.2 PSG in the Human Serum

At present time we think that impossibility to obtain "artificially" a pure and biologically active PSG from the serum is not occasional. This confirms inefficiency of all modern technologies used for this purpose. We suppose that this fact demonstrates people's inability to solve the problem, which determines the main role of PSG – providing and control of reproduction of life. Physiological pregnancy is a bright confirmation of this: up to 1,5 g of biologically active PSG in primordial harmony of optimal proportions (Borisenko et al., 2004; Prokopenko and Terentiev, 2009) are circulated only in the blood of pregnant women, that exceeds the PSG level in the blood of non-pregnant women by factor of 100,000 and more. For example, to prepare 1,5 g of PSG it is necessary to process 600/250 l of retroplacentary the blood/serum.

However, determination of PSG concentration in the blood serum of virgins (data not available), may lead only to increasing the differences, because, according to our data, concentrations of PSG in the blood of men and 90% of women do not exceed 2 ng/ml (Prokopenko P.G. et al., 1990). Extremely interesting results with usage of radioimmunoassay were obtained by A. Sokolov (1939-2002) - one of the most strong and honorary researchers of modern time. PSG was detected in 2 of 17 healthy men (Russian cosmonauts) and its concentration was equal to 0,4 and 0,6 ng/ml. In one man (Lion, France) it was 4 ng/ml and in other 2 men (Bethesda, USA) - 10 and 11 ng/ml. Concentration of PSG in cases of testicular cancer reached levels from 360 to 600 ng/ml (Sokolov, 1977).

6.3 Sex Identity of PSG

According to Glazunov, seminoma of testisticle/ovary (synonyms: cancer, disgerminoma, sarcoma, embryonic carcinoma and etc.) "… is significantly more likely (95% of all tumours of the testis) to arise in male gonade"; in the ovary (up to 30% of tumors) it is localized in

"remainders of the male part of the ovary underwent differentiation" and "originates from sex cells of male part of the ovary". Some authors consider tumors of male testicles to be "trophoblastic by nature" end for the detection of the relevant morphological structures – cyto- and cyncytiotrophoblast (Glazunov, 1961). From this follows that in males this is a primary tumor (testicle), and in the ovary it originates from ovary rudiments like "hypernephroma of ovary" which originates from rudiments of primary kidney (Prokopenko and Terentiev, 2009).

The first sign morphological structure of early embryogenesis is cytotrophoblast and which product – PSG originates from one source – "germ cells of male gonads". The template for PSG – mRNA is brought to oocyte by spermatozoa. This also evidences for male origin of PSG (Glazunov, 1961; Avendano, 2009).

Cytotrophoblast and PSG – is it the property of men? Entrusted with protection of the fetus? Rudiments of male gonads in the ovaries are the "accidentally forgotten remains" or they represent the most important strategic reserve, which functions during pregnancy? Is the PSG level in the virgins lower than those in the cosmonauts? Could the Sokolov's test be the test for innocence? Data of Sokolov and Avendano allow us to give a restricted answer for these questions.

6.4 Role of Pregnancy and Breast-Feeding of a Child

It is impossible to overestimate the role of pregnancy in supporting health of a woman. Only one case of pregnancy and child-birth decreases by factor of 2 the risk of ovarian tumor development, 2-3 child-births decreases the risk by 7,7 times, 4 and more child births by 10,8 times (Nechaeva and Vinokurov, 1987; Serov and Kudryavtseva, 2001). Among patients with fallopian tube cancer 45 % of women did not give birth to child and 71% of women are infertile (Gynecology by ten teachers, 2000). These observations evidence the correctness of the woman health formula: "propagate and breed".

From this follows that PSG, seemingly, not only protects the embryo from its rejection, but melts the tumor implants as well as melts the uterus epithelium located above the place of the embryo implantation and clearing and making healthier a woman who carries an embryo.

Breast-feeding has also not lesser meaning for health of mother and child: risk of ovarian cancer decreased almost 2 times in women with breast-feeding in comparison with women who gave birth to child, but were not a suckling mother (Scheider, 1987). Breast-feeding elongates unovulation period and the time necessary to restore the embryonic reparation system. Virologists paid attention at the decisive meaning of the milk for programming of health of posterity. Feeding of newborn mice of the line with high risk of cancer by female mice belonging to the line with low risk of cancer practically transformed the posterity with high risk of cancer to those with low risk of cancer and vise versa. This phenomenon obviously was linked to the milk of feeding mother and received a name: "milk factor" (Zilber, 1946). Evidently, that biological control of health of mother and embryo does not completed after birth of a child, but continues over duration of breast-feeding. This control is greatly important for health of posterity. With the milk of mother the immune system of a child is "learning" and improving and biological cycle and quality of life of the newborn individual is programming.

In perspective compilation and use of different combinations of proteins (Table 1) for diagnostics purposes may allow to determine not only the presence, quality and origin of the tumor, but, in case of intellectual approach, and the evolution stage, on which it will be enough to recommend only one remedy – pregnancy.

7. EXOGENIC FACTORS

This mechanism is provided by muscular activity of fallopian tubes (Glazunov, 1961; Zhordania, 1962; 1964). This mechanism is justified also for any material particles from the environment (viruses, spermatozoa, talcum powder, asbestos, dust, etc.), which, while penetrating into genitals, may be drawn in abdomen and implanted into ovarian integumentary epithelium and peritoneum (Woodruff, 1979; Rosenblatt and Thomas, 1996). For example, there are up to 500 mln of spermatozoa in one ejaculate (Zhordania, 1964), and nuclear products of "alien" spermatozoa decay - protamines, are suspected by oncologists for carcinogene properties (Bokhman, 1989).

The demonstrative one is the data regarding mortality rate from ovarian cancer among women working as bookbinders in printing-house: 12 out of 525 women died (Il'ichova et al., 2001). For comparison: 10-16 death cases on 100, 000 women; this is 2,9 in Japan (Nechaeva and Vinokurov, 1987; Borisenko et al., 2004).

8. CONCLUSIONS

On the basis of 150 year experience of oncologists and our own results we also tried to interpret the origins and logic of this disease and to draw some conclusions, which, may be, help find right steps to resolve the problem.

Clinical observations of the last 50 years have demonstrated that the ovarian tumor disease is likely to perceive in accordance with Glazunov as the whole and sequential process, including: Benign Tumor, proliferating Benign Tumor, Related Tumor and ovarian cancer – the final stage of the evolution.

Metastasizing of tumor implants begins long before the cancer cell maturation: in 8,4% to 29% of cases in patients with Benign Tumor and up to 81% in patients with Related Tumor. In OC metastasis are revealed practically in all patients.

Implants existing at the stages of benign tumor development lead to backset of the disease. So, it is necessary to master how to discover the tumorigenesis at these stages.

Close relationships and wide potential of genitals epithelium to similar re-constructions in pathology exclude the possibility of existence of proteins with strict specificity regarding ovarian tumors.

Cancer cell is a degrading structure, where "all are lost, nothing is created": all the known proteins of the cancer cell have an embryonic origin.

Refusal of a woman from pregnancy hides high risk to be eliminated out of the human population due to uselessness for reproduction: "the vine not producing a fruit is subjected to be cut out".

The pregnancy cleans a woman out of implants, makes her healthier and is a reliable preventive measure against ovarian tumor disease.

Some epithelia of genitals mature only to 20 years. So, early sexual contacts carry high risk of tumor development. The lowest mortality rate from OC is observed in Japan – the country of chastity and traditions and the country where the time of majority is 20 years old.

Chastity, traditional family and reproduction of healthy posterity in the term determined by the Nature – the basis for health of mother, child and society.

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