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Review

Immunomodulation of carcinogens-induced steroids-dependent human diseases

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ABSTRACT

The experimental and clinical data about antibodies against environmental chemical carcinogens and endogenous steroids are represented. The conception of immunomodulation of carcinogens- and steroids-dependent human diseases is proposed. It is postulated that antibodies to polycyclic aromatic hydrocarbons and heterocyclic amines in cooperation with antibodies to cholesterol, sex hormones, mineralo- and glucocorticoids stimulate or inhibit cancer, malformation, cardiovascular and autoimmune diseases depending on their personal combination. It is recommended to use immunoassay of these antibodies for the human diseases prediction. The alternative approaches for prevention using the probiotics transformed by anti-carcinogen antibodies are substantiated.

Contents

Abbreviations: Cg, chemical carcinogens; PAH, polycyclic aromatic hydrocarbons; S, steroids; PE, phytoestrogens; Bp, benzo[a]pyrene; ER, estrogen receptors; Abs, antibodies; Es, estradiol; Pg, progesterone; PR, progesterone receptors; LC, lung cancer; BC, breast cancer; LCP, lung cancer patients; BCP, breast cancer patients; MW, women with malformation; HW, healthy women; ER+, estrogen receptors positive; ER−, estrogen receptors negative; PR+, progesterone receptors positive; PR−, progesterone receptors negative; cAhR, cytoplasmic; mAhR, membrane aril hydrocarbon receptors; *CYP*, cytochrome P-450.

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1. Introduction

The environmental chemical carcinogens (Cg), such as polycyclic aromatic hydrocarbons (PAH), being mutagens induce human malignant tumors, malformations and fetal disorders (Rengarajan et al., 2015; Igwe and Ukaogo, 2015; Abdel-Shafy and Mansour, 2016). These compounds take part in pathogenesis of inflammation and autoimmunity diseases (Boeckler et al., 2009; Alshaarawy et al., 2013; Rengarajan et al., 2015; Abdel-Shafy and Mansour, 2016), atherosclerosis (Marinković et al., 2013; Alshaarawy et al., 2016) and arterial hypertension (Delfino et al., 2010; Guo et al., 2010). All these diseases are dependent on various endogenous steroids (S) (Watson and Gametchu, 2001; Bouman et al., 2005; Bhupathy et al., 2010; Villablanca et al., 2010; Marquez-Garban et al., 2011; Nagao et al., 2011; Cunningham and Gilkeson, 2011; Kulungowski et al., 2012; Mohammed et al., 2015). Evidently exogenous phytoestrogens (PE) play important role in endocrine disruptions (Patisaul and Jefferson, 2010; Albini et al., 2014).

It is known, that monohydroxy derivatives of PAH (i.e. benzo[a] pyrene, Bp) bind to estrogen receptors (ER), and several of them have estrogenic or anti-estrogenic activity (Charles et al., 2000; Hirose et al., 2001). Another Cg, heterocyclic amines, bind to the ER and activate or inhibit estrogenic response in human cells (Bennion et al., 2005). On the other hand, estrogens promote Bp-induced carcinogenesis (Chen et al., 2011; Lin et al., 2012) and act as a mitogens for cell in vitro and in vivo (Kreuzer et al., 2003). One of the possible ways of interaction between exogenous Cg and S is induction of steroid receptors mutation as it was revealed for ER mutation in breast cancer (Toy et al., 2013; Alluri et al., 2014).

At the time the experimental investigations show that antibodies (Abs) specific to Cg and S modulate their biological effects [see below]. Here the supposed mechanisms of immunomodulation of Cg-induced S-dependent human diseases are discussed.

2. Antibodies against chemical carcinogens and steroids

2.1. Antibodies against chemical carcinogens in experiments

Abs against PAH-DNA adducts were revealed in the serum of mice chronically exposed to PAH (Lee and Strickland, 1993). Immunization of animals by PAH conjugated with proteins induced Abs binding a variety structurally closed Cg (Černohorská et al., 2012). There were revealed the anti-idiotypic Abs2 presumably modifying the action of corresponding Abs1 specific to Bp after immunization of mice with Bp-protein conjugate (Ustinov et al., 2013).

Mucosal Abs inhibited the transport of Cg into and through respiratory and intestinal epithelium in vivo (Moolten et al., 1978a; Silbart and Keren, 1989; Rasmussen and Silbart, 1998), as well as mucosal-like monoclonal Abs in the model experiments in vitro with dialysis membrane (Silbart et al., 1996) or epithelium cell monolayers (De Buck et al., 2005, 2010). The monoclonal mucosal-like Abs reduced the amount of Cg genotoxic metabolites and inhibited the Cg-induced cells proliferation in vitro (De Buck et al., 2005, 2010). In contrast serum-like model Abs increased the penetration of Cg through membrane or cell monolayers and its metabolic activation (Silbart et al., 1996; De Buck et al., 2005).

Serum Abs levels positively correlated with the levels of Cg in the blood and liver in immunized animals (Grova et al., 2009). On the other experimental conditions Abs produced by immunization were effective in reducing the amount of Cg-DNA adducts in mouse livers after intraperitoneal exposure to Cg (Galati et al., 2000; Černohorská et al., 2012). After immunization Abs reversed the suppressed effect of Cg on the proliferation of T- and B lymphocytes and immunotoxic action of Cg on cytokines production as well as inhibited the induction of *CYP1A1* in lymphocytes and *CYP1B1* in the liver by Cg (Schellenberger et al., 2009). Anti-Cg Abs protected non-lymphoid cells from toxicity and mutagenicity in vitro (Moolten et al., 1978b; Tompa et al., 1979).

Only one experiment has shown that active immunization against Cg conjugated to a foreign protein significantly increased tumor formation when the animals were treated with Cg (Curtis et al., 1978). In the other hands immunization against carcinogens inhibited Cg-induced tumors (Peck and Peck, 1971; Moolten et al., 1981; Faiderbe et al., 1995).

On the basis of all these data authors offered the strategy of vaccination against Cg to induce the mucosal Abs for the cancer immunoprevention (Silbart et al., 1997; Schellenberger et al., 2011; Černohorská et al., 2012). Unfortunately the effects of immunization with PE on the S functions were not studied, while Abs against PE used widely for their detection (Qu et al., 2016).

2.2. Antibodies against steroids in experiments

Cholesterol. Immunization of rabbits with cholesterol-rich liposome induced anti-cholesterol Abs. The serum cholesterol level in form of very-low-density lipoprotein raised (60-fold) in nonimmunized rabbits fed a diet containing 0.5–1.0% cholesterol, but elevation was significantly less (35% lower) in the immunized ones. Immunization also resulted in a marked decrease of atherosclerosis plague formation in most areas of the aorta (Alving et al., 1996; Ordovas, 1996). Monoclonal anti-cholesterol Abs bound to cholesterol-rich lipid rafts and caveola at the cell surface of human or murine lymphocytes (Biró et al., 2007).

Corticosteroids. In rabbits immunized with hemisuccinate-albumin complexes of cortisol, corticosterone and deoxycorticosterone plasma concentration of cortisol and corticosterone rose above 100 μg/ml (control below 3.5 μg/100 ml). Some of the animals showed symptoms of hypercorticism (Gless et al., 1974). Polyclonal anti-cortisol Abs was capable of reducing bioactivity of corticosteroids that strongly suppressed lymphocyte proliferation (Rozell et al., 1992). After immunization with triamcinolone-protein conjugate it was possible to generate an auto-anti-idiotypic Abs2 that bound to glucocorticoid receptor (Cayanis et al., 1986). The similar Abs bound to membrane glucocorticoid receptor in cell from human leukemic patients and lymphoma cells lines (Gametchu and Watson, 2002).

Mineralocorticoids. In rabbits immunized with aldosterone the percentage of bound steroid in serum was drastically increased. The aldosterone-immunized animals showed a significant increase of the nuclear volume in the adrenocortical zona glomeruloza (Nieschlag et al., 1974). The colonic electrical potential produced by intravenous infusion of aldosterone decreased in aldosterone-immunized rabbits (Lennane et al., 1976). After immunization of mice with aldosterone-protein conjugate the monoclonal auto-anti-idiotypic Abs2 were generated. Abs2 inhibited aldosterone binding to aldosterone receptors but had no effect on glucocorticoid receptors (Lombes et al., 1989). Another monoclonal Abs against the hormone-binding domain of human mineralocorticoid receptor inhibited the binding of aldosterone and progesterone to this receptor (Jalaguier et al., 1997).

Sex steroids. There is a large literature on the immunization of animals with sex steroids (Nieschlag et al., 1974; Hillier et al., 1975; Chang et al., 1987; Croker et al., 1987; Wrobel et al., 1990; Bourtourault et al., 1991; Scaramuzzi et al., 1993). It was shown: increasing the plasma levels of corresponding hormones; changes in feedback control; changes in target tissues and biological function (fertility and pregnancy). Immunization with anti-idiotypic Abs2 had the same effects (Khole and Hegde, 1993). Also immunization against estradiol (Es) induced the regression of estrogen-

sensitive tumors in mice (Caldwell et al., 1971). Abs specific to Es and progesterone (Pg) receptors (ER and PR) were able to modulate the rapid non-genomic effects of these hormones as agonists or antagonists on the various cells in vitro (Sömjen et al., 1997; Norfleet et al., 2000; Luconi et al., 2004; Modi et al., 2007; Chaudhri et al., 2012, 2014). Anti-idiotypic monoclonal Abs2 to Es acted as agonist of Es in the some in vitro systems while F(ab) 2 dimer acted as agonist (Sömjen et al., 1996) presumably through membrane ER.

2.3. Antibodies against chemical carcinogens and steroids in humans

Chemical carcinogens. The most of articles were focused on studies of Abs against carcinogen-DNA adducts in human serum (Verdina, 2006). There were light positive associations of Abs to Bp-diolepoxide –DNA adducts with PAH-air pollution in the general population (Petruzzelli et al., 1998; Galati et al., 2001); in the industrial workers (Newman et al., 1988; Santella et al., 1995; Galati et al., 2001; Borska et al., 2014); in the smokers (Newman et al., 1988; Pulerà et al., 1997; Petruzzelli et al., 1998; Pauk et al., 2013), in family with lung cancer (LC) history (Petruzzelli et al., 1998). In LC and chronic obstructive pulmonary diseases patients there was found a major decrease in the level of Abs against Bp-diolepoxide –DNA adducts and serum anti-Bp of IgA class in comparison with healthy subjects (Pauk et al., 2013). The levels of serum IgA against PAH conjugated with proteins were increased in breast and ovarian cancer patients versus healthy donors (Chagnaud et al., 1992; Pouns et al., 2009).

Cholesterol. Anti-cholesterol Abs levels were found to be considerably lower in patients with peripheral occlusive atherosclerosis and cerebrovascular diseases compared with the levels in healthy individuals. By contrast these levels were considerably higher in patients with severe coronary heart disease (Horváth et al., 2001; Horváth and Biró, 2003). Low-density lipoprotein dose-dependently inhibited the binding of human anti-cholesterol Abs to solid phase cholesterol (Horváth et al., 2001). Strong negative correlation was found between Abs and low-density lipoprotein-cholesterol levels (Biró et al., 2005). Cardiovascular incident stroke developed significantly less frequently in patients with high anti-cholesterol Abs (Veres et al., 2002). There was proposed that naturally occurring Abs to cholesterol in normal human plasma contribute to low-density lipoprotein-cholesterol turnover by opsoning lipoproteins for removal by complement receptors (Alving and Wassef, 1999). The serum levels of anti-cholesterol Abs were higher in patients with viral infections, systemic lupus erythematosus and chronic Chagas' disease (Avila et al., 1996; Nagy et al., 2001; Biró et al., 2003; Horváth and Biró, 2003) and LC (Egri and Orosz, 2006; Sarkar et al., 2008). A humanized monoclonal Abs targeting proprotein convertase subtilisin-kexin type 9 (bococizumab) reduced the levels of low-density lipoprotein-cholesterol and cardiovascular disease as well (Ridker et al., 2017; Schmidt et al., 2017).

Sex steroids. The high level of serum anti-estrogen Abs was determined as a risk factor for vascular thrombosis in women on oral hormone contraceptives (Beaumont et al., 1992) and for systemic lupus erythematosus (Counihan et al., 1991; Moinuddin, 1998). Hypersensitivity to Es and Pg after intradermal hormone injections was revealed in women with recurrent miscarriage but not in healthy ones (Itsekson et al., 2011). High levels of Abs to Pg and Es were associated in women with menstrual cycles symptoms including asthma and dermatitis (Roby et al., 2006). High frequency of anti-Pg Abs occurrence in women with habitual loss of pregnancy was revealed (Menzhinskaya et al., 2008). Anti-ER Abs were found in the serum of healthy donors (Mudarris and Peck, 1987; Borkowski et al., 1991) and were associated with autoimmune disorders (Feldman, 1987; Colasanti et al., 2012; Giovannetti et al., 2013; Ortona et al., 2014). The natural human Abs to ER were able to induce an estrogenic effects in mammary carcinoma cells, producing an ER down-regulation and an increase in the PR level (Tassignon et al., 1997) and to decrease the available ER sites in these cells (Borkowski et al., 1991). Anti-ER Abs purified from breast cancer patients (BCP) sera were able to recognize ER expressed at the cell surface, to trigger rapid extracellular signal regulated kinase phosphorylation and to induce cell proliferation (Maselli et al., 2015). Circulating Abs to human androgen receptor were found at high titers in blood sera of some patient with prostate diseases. These Abs were not interacted with nuclear and cytosolic receptors for Es, progestin, or dexamethasone (Liao and Witte, 1985). There were described the single cases of Pg-autoimmune dermatitis (Garcia-Ortega and Scorza, 2011) and testosterone-autoimmune hypergonadotropic hypogonadism (Kuwahara et al., 1998).

3. Cooperative effects of antibodies to chemical carcinogens and endogenous steroids on human diseases

Experimental investigations had shown that Abs to Cg and S influenced on the serum concentration of these compounds and changed their biological functions. The revealed association of these Abs with the various diseases had confirmed their participation in pathways. However all the studies described the separate effects of Abs. Meanwhile both Cg and S act simultaneously and combinely. Therefore it's need to research the cooperative effects of Abs to various Cg and S on human health. We began to study Abs to Bp in cooperative with Abs to Es and Pg in the LC patients (LCP), BCP and women with malformation (MW).

Shortly there were revealed:

- the levels of serum IgA-Bp positively correlated with the levels of IgG-Bp in healthy donors and LCP (Glushkov et al., 2014b). It means, indirectly, that induction of mucosal IgA-Abs against Cg could lead to formation of corresponding serum Abs;
- the levels of serum Abs-Bp positively correlated with the levels of Abs-Es and Abs-Pg in healthy donors, LCP, BCP and MW (Glushkov et al., 2014b, 2015a, 2016b). It means that formation of Abs to Cg (PAH) and Abs to S (at least to sex S) are interdependence;
- the absence or low levels of all three Abs were associated with the low cancer risk (Glushkov et al., 2016c), meanwhile the immunization of animals against Bp or Es was associated with high levels of corresponding Abs and inhibition of carcinogenesis [see above];
- the LC and BC risks significantly increased when serum levels of IgA-Bp and IgA- Es were elevated together, but did not separately. However, the cancer risks dramatically decreased when the levels of IgA-Pg elevated together with IgA-Bp and IgA-Es. So IgA-Bp and IgA-Es acted as co-initiator and co-promoter in developing cancer scenario, but IgA-Pg acted alone or with IgA-Bp and IgA-Es as inhibitor of human carcinogenesis (Glushkov et al., 2016c). This phenomenon was revealed only in ER+, but not in ER– BCP (Glushkov et al., 2016b). It means that immunomodulation of Cg- and S-dependent diseases (stimulation or inhibition) realize in cooperative action of Abs to Cg and S. This action realize through cell receptors for these compounds;
- the high levels of Abs to Bp, Es and Pg were associated with high Es concentration but low Pg concentration in the blood serum of healthy pregnant women (Glushkov et al., 2014a). The maintenance of Es and Pg positively correlated with levels of corresponding Abs in the serum of postmenopause women. Relationship between Es and Abs-Es separately were significant,

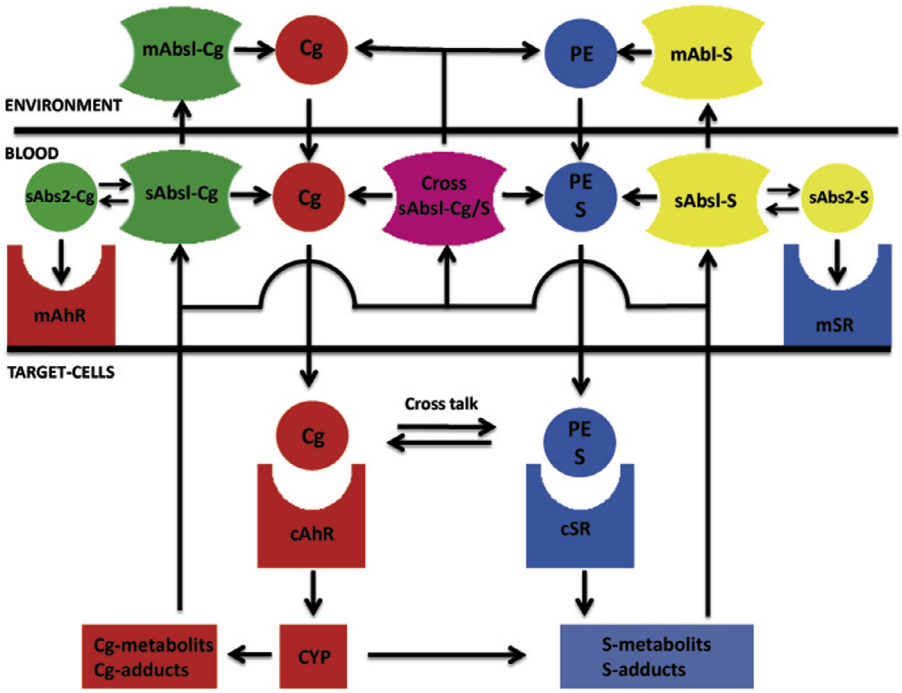

Fig. 1. Formation and effects of antibodies against environmental carcinogens, phytoestrogens and endogenous steroids (Cg – environmental carcinogens; PE – phytoestogens; S – endogenous steroids; cAhR – cytoplasmic aril hydrocarbon receptor; mAhR – supposed membrane AhR; cSR – cytoplasmic steroids receptor; mSR – membrane steroids receptor; sAbs1 – serum antibodies; mAb1 – mucosal antibodies; sAb2 – antiidiotypic antibodies).

but between Pg and Abs-Pg separately were absent in BCP (Glushkov et al., 2015b). High Es and Pg concentration were revealed when both Abs-Es and Abs-Pg levels were elevated instead of these levels were low in the serum of healthy women (HW). High Pg concentration but not Es concentration was found when Abs-Pg levels were elevated in ER+PR+ BCP (Glushkov et al., 2017). It means that Abs to S influence really on S concentration in the human blood serum as well as in experimental animals after immunization;

– the simultaneously high levels of Abs-Es and anti-idiotypic Abs-Es (IgG-Es1 and IgG-Es2) were reveled in ER+PR+ BCP and ER +PR- BCP, but not in ER-PR- BCP and HW. High ratio IgG-Es1/IgG-Es2, but not IgG-Es1 and LgG-Es2 separately were associated with high Es concentration in serum in ER+ but not in ER- BCP (Glushkov et al., 2016a). It means that anti-idiotypic Abs2 to S take part in interaction of S with their cell receptors and with corresponding Abs1.

Thus every person has a unique composition of Abs1 and Abs2 according to the specificity and class to the different Cg and S. And this personal Abs-composition determines the pathway of Cg- and S-dependent diseases.

4. Formation and effects of antibodies against environmental carcinogens and endogenous steroids: proposal mechanism

The conception of immunomodulation of Cg- and S-dependent diseases is proposed based on the known experimental and clinical studies of Abs to these compounds (Fig. 1). Cg (PAH) penetrate through the surface epithelium into the blood and into the target cells. After the binding with cytoplasmic aril hydrocarbon receptors (cAhR) Cg activate cytochrome P-450 (CYP), turn into metabolites and form the adducts with DNA and proteins. Being the haptens Cg induce the specific Abs formation. Circulating serum Abs (sAbs1-Cg) stimulate the penetration of Cg through surface epithelium and transport to the target cells including retransport into the surface epithelium. Mucosal Abs (mAbs1-Cg) bind Cg on the border with environment and inhibit Cg penetration through surface epithelium. In turn sAbs1-Cg induce the formation of corresponding anti-idiotypic Abs (Abs2-Cg) which modify the sAbs1-Cg synthesis and functions.

Environmental PE penetrate into the blood and with the S reach the target-cell. They turn into metabolites and form the adducts under the action of Cg-activated CYP. Being the haptens PE and S induce the specific serum and mucosal Abs1 (sAbs1-S and mAbs1-S) and corresponding anti-idiotypic Abs2-S. One more couse for induction of Abs2-S is a mutation of S receptors (SR) which was found in BC cells. Serum Abs1-S and mAbs1-S stimulate or inhibit the genome effects of S and PE by influence on the PE penetration, PE and S serum concentration and metabolism as well as Abs1-Cg do. Abs2-S modify the action of Abs1-S as well as Abs2-Cg do. In addition Abs2-S act as agonist or antagonists of S in realization of epigenomic effects through the membrane S receptors (mSR). Abs2-Cg could be able to act through the membrane AhR (mAhR) but their existence is not evidence yet. Evidently some Abs1 are able to bind both Cg and S (cross Abs1-Cg/S) by the similarity of structure (PAH and heterocyclic amines are like S).

So the reciprocal action of Cg and S on some human diseases can be explained not only by well-known mutual influence on their cellular receptors (cross talk) and by Cg-activated *CYP* with the following formation of S-adducts but through the cooperative synthesis of Abs to them. The specificity of Abs1 and Abs2 to Cg and S depends on individual peculiarity of adducts formation and immune reactions on them. The personal composition of specific Abs determines their participation in pathway of either disease. For example, Abs1-Bp together with Abs-Es stimulate Es-dependent cancers.

5. The new approaches for prediction and prevention

Some authors offer to use immunization against Cg as a new strategy for cancer prevention (see above). This strategy may be useful for prevention of other S-dependent diseases as Cg take part in their pathway. The principal question is – active or passive immunization? Active induction of anti-Cg Abs may be accompanied by anti-S Abs formation. In this case the combined action of anti-Cg and anti-S Abs may lead to stimulation of carcinogenesis and evidently other S-dependent diseases. The necessary condition of immune defense from Cg is absence or low levels serum Abs-Cg and Abs-S. So the passive immune protection from Cg is more safer.

For this purpose we suggest to use the known probiotics or natural automicroflora (Glushkov et al., 2013), gene-modified by early generated human recombinant Abs against PAH (Ustinov et al., 2015). For example Saccharomyces boulardii would be especially well suited for this purpose due to its ability to perform eukaryotic post translation modification (Hudson et al., 2014; Palma et al., 2015). Adsorption of environmental PAH on the surface of transformed probiotics would be able by expression of membrane-bound Abs1 against PAH. Alternative way is the gene-modification of probiotics by anti-idiotypic Abs2 against Cg. Probably Saccharomyces boulardii transformed by early generated human recombinant Abs2 to PAH (Studennikov et al., 2017) would be able to generate mucosal Abs1 against PAH. It's need to study the effectiveness both of these approaches as the new ways for immunoprotection from Cg.

If mucosal immune defense from environmental Cg will be effective and the levels of serum Abs to Cg and S will be low, the risks of other S-dependent diseases evidently will be low too.

Another way for decision of these problems consists in immunological prediction and nonimmunological prevention of Cg- and S-dependent diseases. For example, simultaneously formation both Abs-Bp and Abs-Es is endogenous risk factor for ER+BC in healthy women (see above). In these cases the well-known selective inhibitors of ER (tamoxifen and others) will be more effective for BC prevention, because they act only on ER+BC (LaCroix et al., 2010; Cuzick et al., 2013). It is important that elevated ER expression is a significant risk factor for LC in both men and women (Fucic et al., 2010). Women who received anti-estrogens as BC treatment have a significantly decreased risk of dying from LC (Bouchardy et al., 2011). The high levels of both Abs-Bp and Abs-Es associated with LC in men (see above) will be the informative criterium for ER+LC prediction with the following prevention by selective inhibitors of ER.

6. Conclusion

This view on immunomodulation is the attempt to imagine the participation of Abs in the interactions between Cg, S and their cellular receptors. The future investigations will allow to understand the nature of immunological phenomenons, revealed in cancer patients:

- *immunological silence:* the absence of specific immune reaction on both Cg and S is associated with the low risks of Cg- and S-dependent diseases;
- *immunological intervention:* the specific immune reactions on Cg or/and S modulate the pathways of corresponding diseases;
- *single immunological weakness:* the separate specific immune reaction on single Cg or S is associated with the week increased of diseases risk;
- *cooperative immunological amplification:* the simultaneous specific immune reaction on the Cg and some S stimulates the pathway of corresponding diseases;
- *cooperative immunological neutralization:* the specific immune reaction on the Cg and some S (or corresponding Abs2-formation) decreased the stimulating effect of cooperative immunological amplification.

The study of these phenomenons will be useful to find new methods of prediction and prevention of Cg- and S-dependent diseases.

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