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Immunological disbalance in carcinogenesis

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ABSTRACT

It is postulated a conception of immunological disbalance between carcinogenesis inhibiting and stimulating antibodies (Ab). Inhibiting Ab prevent the carcinogens and estradiol but increase the progesterone penetration into the target cells. And vise versa do stimulating Ab. Inhibiting Ab could be blocked by corresponding antiidiotypic Ab. The processes of carcinogenesis initiation and promotion are intensified when stimulating Ab prevail over inhibiting ones.

Introduction

The strategy of cancer immunoprevention proposed by Creech and Franks [5,6] and developed by Moolten et al. [23–25], Silbart et al. [29–31], Chagnaud et al. [4], De Buck et al. [8], Cernohorska et al. [2] is based on the induction of antibodies against environmental chemical carcinogens (Ab-CG) with help of CG-protein conjugates or antiidiotypic Ab in experiments. However, Ab to CG-DNA adducts are found in humans in natural conditions and more often in cancer patients [9,20,26,28,35]. Cancer patients have raised Ab levels to native CG then healthy donors [3,12–15]. These data indicate that Ab-CG do not carry out the defense functions. Moreover, it was suggested that under certain conditions Ab-CG could stimulate processes of carcinogenesis [7,10,11].

It is well-known, that steroid hormones (SH) could stimulate (estradiol, Es) or inhibit (progesterone, Pg) the promotion of carcinogenesis in some tissues [32,33]. Immunization against SH modulated the growth of some experimental tumours [1].

Meanwhile, Ab-CG and Ab-SH in humans are poorly studied to understand the mechanisms of their formation and function. Nothing is known about the features of Ab formation to SH when exposed to CG, including cancer patients. Whether Ab are simple ≪witnesses≫ of the CG impact in the body or do they affect the process of carcinogenesis? If Ab to CG and SH perform physiological functions, i.e. prevent the appearance of tumours, why are these features not effective in cancer patients? If Ab to CG and SH perform pathogenetic functions, i.e. stimulate the formation of tumours, which are the mechanisms of such immunostimulation?

Protecting functions of antibodies to chemical carcinogens are blocked by corresponding antiidiotypic antibodies

Why antibodies to chemical carcinogens do not perform the defense functions? Previously, Kovalev et al. have proposed the concept of immunochemical homeostasis [21,22]. According to authors ideas an adaptation of an organism to low-weight organic compounds is as follows. Low-weight xenobiotics activate biotransformation enzymes (cytochromes P-450) and the synthesis of specific antibodies (Ab1). Ab1 bind the excess of xenobiotics and eliminate them from the body, therefore the biotransformation enzyme activity decreases. In response to the emergence of Ab1 the appropriate antiidiotypical Ab2 are formed, and the synthesis of Ab1 is inhibited.

To research the formation of Ab1 and of Ab2 the mice were immunized with the conjugate of benzo[a]pyrene (Bp)-protein [34]. The levels of Ab1 to Bp in blood serum were raised. The corresponding antiidiotypical Ab2 were defined in the same serum species. It became clear that intact mice had low Ab levels, but the quantity of Ab2 exceeded Ab1 and the ratio Ab1/Ab2 was 0.5. The levels of Ab1и Ab2 rised and the ratio of Ab1/Ab2 reached 1 after the first injection of the Bp-protein conjugate. The levels of Ab1 growed faster than Ab2, and Ab1/Ab2 ratio reached 2 after the second and the third injection. Earlier in similar experiments it was shown that after such immunization the appearance of CG-induced tumours was slowed down [6,23–25,27]. It is obvious that the twofold excess of Ab1 provided a protective effect of immunization.

Previously we detected the Ab1 and corresponding Ab2 to the polycyclic aromatic hydrocarbons in the serum of patients with mammary gland tumours [12]. In addition, the features of Ab formation to Bp in lung cancer (LC) patients were investigated [34]. It turned out that the Ab2 levels exceeded Ab1 levels

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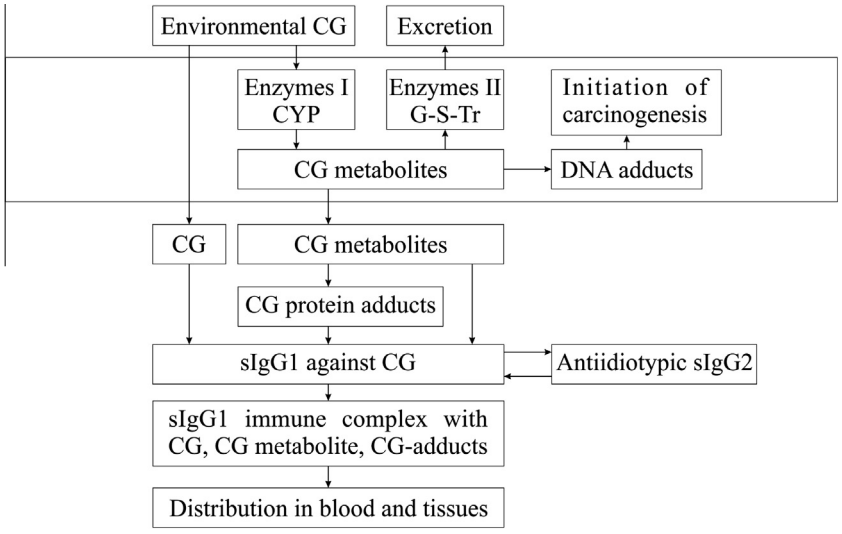

Fig. 1. IgG-Ab formation and functions against environmental carcinogens (CG).

(Ab1/Ab2 $\leqslant$ 0.5) in healthy donors. The Ab1 level was significantly higher in LC patients than in healthy donors, and that was confirmed by the previous results [17–19]. The level of Ab2 was also high, but the individual ratio of Ab1/Ab2 was no greater than 1, as in mice after the first injection of the Bp-protein conjugate. It was obvious that the excessive number of Bp metabolites and its adducts with macromolecules in LC patients induced the Ab1 synthesis, but an equivalent formation of Ab2 blocked the protective functions of Ab1. The hypothetical scheme of Ab1 formation against CG and corresponding Ab2 in carcinogenesis cites on Fig. 1.

How the antibodies to chemical carcinogens and steroid hormones could stimulate carcinogenesis?

In experiments in vivo [23,24,29] it was shown that mucosal antibodies (mAb) bind the environmental CG and prevent their penetration into the bronchial and gastrointestinal epithelium cells. In experiments in vitro [18,30] it was established that the model Ab, imitating the serum Ab (sAb), strengthened CG transport through the permeable membrane and monolayer of epithelial cells. Silbart et al. [29–31] considered that the mAb to CG but not sAb play the main role in protection against CG. So sAb could stimulate CG penetration into epithelium, hence the strategy of cancer immunoprevention should be aimed to achieve a high ratio mAb/sAb.

According to De Buck et al. [8] sAb reduced the number of genotoxic metabolites in the epithelial cells and contributed to the redistribution of CG on body tissues, less sensitive to CG. In this point of view sAb could inhibit carcinogenic transformation in bronchial and gastrointestinal epithelium.

However the model experiments in vitro overlook the fact that the sAb in the natural conditions are represented by the different classes of Ig. It is obvious that the increase of the sIgA-CG levels reflects the local immune response to CG-adducts in the bronchial and gastrointestinal tissues. The elevated sIgG-CG level is a sign of a systemic immune response to CG. Both sIgA-CG and sIgG-CG are able to bind the CG, entering the bloodstream through the surface epithelium, and redistribute CG in the body according to the model [8], thereby providing the outflow of CG from the basal membrane of epithelium and reducing the risk of cancer of the lung and gastrointestinal tract. The ability of sAb to change the CG distribution in various organs was proved by the experiments in vivo after the intraperitoneal immunization of animals by the CG-protein conjugate [2].

But sIgA are also a source of mIgA. Binding CG under the basal membrane, sIgA are able to penetrate back into the epithelium. The complex of IgA with CG dissociate inside the cells then CG could transform into genotoxic metabolites by enzymes. In other words sIgA-CG are potentially able to provide the return transport of CG into epithelium cells and thereby increase the probability of their malignant transformation. The hypothetical scheme of IgA-CG formation and functions in carcinogenesis cites on Fig. 2. It takes into account the possible modulating action of corresponding antiidiotypical Ab (sIgG2).

The role of Ab-SH is more unclear in the carcinogenesis. The receptors of Es and Pg were found in various organs including a lung [36]. There is a reason to believe that Es is a promoter and Pg is an antipromoter of the carcinogenesis [32,33]. In this case, it is appropriate to assume that sIgA-SH are able to bind circulating SH and transport them in the bronchial, gastrointestinal and mammary gland epithelial cells strengthening the biological action of SH in these tissues. On the contrary, the sIgG-SH hold the SH in circulation and limit their penetration in to the epithelial cells. Ab-Es and Ab-Pg have the opposite effects on the proliferation of epithelial cells. The hypothetical scheme of Ab-Es functions in carcinogenesis cites on Fig. 3. It takes into account the possible influence of food Es and modulating action of corresponding antiidiotypical Ab to Es (Ab2-Es).

An indirect confirmations of these assumptions are the results of studies of Ab-Bp, -Es, -Pg formation in LC patients [18]. Figs. 4–6 show the calculating equations of linear regression between levels of these Ab from healthy donors and LC patients. The medium or strong correlation ($r = 0.58–0.92$) were detected between the compared indicators. The coefficients "a" in the equations showed how the Ab(y) level raised at the increase of the Ab(x) level.

A weak correlation ($r = 0.28$) between IgA-Bp and IgG-Bp (Fig. 4) was found in healthy donors. Such a relationship was more expressed ($r = 0.6$) in LC patients. Each level of IgG-Bp in LC patients corresponds to the higher level of IgA-Bp compared with the normal ($a = 0.19$ and $a = 0.08$, respectively). It is expected that the probability of the reverse transport of Bp in the epithelial cells by IgA-Bp in LC patients was higher than in healthy subjects at the same quantity of IgG-Bp.

One more argument of the fact that the IgG-CG are able to inhibit and the IgA-CG to stimulate genotoxic effects of CG is the result of studies of the chromosomal aberrations (CA) in the blood lymphocytes of the coal power plant workers [16]. The workers with low levels of IgA-Bp and IgG-Bp had the CA frequency equaled