The natural immunity to evolutionary atavistic endotoxin in carcinogenesis induced by chemical agents (a hypothesis)

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A hypothesis of the possibility of natural immunity to evolutionary atavistic endotoxin in chemical carcinogenesis is proposed. Age-dependent stimulation of IgM class natural specific antibodies to the endotoxin of gram-negative bacteria Alcaligenes faecalis 415 (IgMNAE) was confirmed in the blood of normal adult rats. This phenomenon was also revealed in human population. Simultaneously, the suppression and subsequent stimulation of natural immunity to endotoxin under the effect of carcinogenic substances such as benzo(a)pyrene (BP) and methylcholanthrene (MCh) were determined in rats.

At first, the primary age-related and the secondary carcinogen-induced enhancement of IgMNAE was explained as the compensatory reactions of the organism’s immune system. Later on, within the evolutionary resistance theory of the origin of cancer, based on the general biological laws (resistance to damage and atavism), which was formulated by the author in 2002–2005, another immunological IgMNAE enhancement mechanism was elucidated and explained by the possible activation of the dormant lipopolysaccharide molecules (atavistic endotoxin) alongside evolutionary resistance-related genes and oncogenes according to the inherited programme. All these mechanisms are transmitted from bacteria to mammal cells and possibly have an immense power to drive and control the process of carcinogenesis. It is the activation of these genes and their functions that helps the newly formed tumorous cells to revive the parasitic features in their unlimited division, invasiveness and metastatic growth. Its essence is a specific evolutionary response intended for the survival of damaged cells. Therefore, at present, there is a new oncological strategy problem – production of endotoxin-based vaccines and their application in cancer prophylaxis. IgMNAE can be undoubtedly helpful in elaborating new immunotherapeutic and diagnostic methods.

Key words: BP and MCh, evolutionary atavistic and bacterial endotoxin, endotoxin-based vaccines, IgMNAE, resistance to damage, atavism and endogenous parasitism of cancer cells
INTRODUCTION

Natural endotoxin (lipopolysaccharide molecules from outer membranes of gram-negative bacteria) immunity is supposed to have been acquired by the organisms in the process of evolution. Its phylogenetic origin and ontogenetic development are presumed. Natural antibodies, together with natural resistance functions of immunocompetent cells (monocytes, macrophages, natural killers, neutrophils), are evolutionarily earlier than the acquired immunity systems. To keep up normal homeostasis, all of them respond to environmental changes of the organism (1–4). So, they help maintain the balance of homeostatic reactions and functions that favours the organisms by an inherited programme to survive under the effect of harmful factors (5).

Therewithal, natural endotoxin immunity also involves immune compensatory functions. In the presence of immunosuppression, the compensatory reactions spontaneously arise, which represent an immunostimulatory variant and also contribute to strengthening the immune safeguarding agent in the formation of endogenous risk factors of cancer and other diseases (3, 5). The immune system without compensatory functions is unable to manifest the whole totality of immunoregulatory reactions important for the organisms’ survival.

We have shown that with ageing, when cellular immunity functions deteriorate, the content of IgM class natural specific antibodies to the endotoxin of *Alcaligenes faecalis* 415 (IgMNAE) in the blood serum of normal rats and practically healthy persons increases (6–8).

It was also found that specific IgMNAE synthesis was strongly (10 times) activated in 2-month-old rats after immunisation with an extract of transfected rat tumours. This phenomenon was explained by hypothesizing a potential role of atavistic endotoxin in tumour growth (9).

A UNIFYING HYPOTHESIS

The hypothesis, first, relates the activation of spontaneous or natural immunity to endotoxin with the age of the individual and, second, with a possible formation of IgMNAE to evolutionary atavistic endotoxin under chronic immune imbalance – immunosuppression caused by chemical carcinogenic substances and, based on the summarized data, to propose an integrated approach with the aim of employing the natural endotoxin immunity reactions for prognosticating the outcome of preventive and diagnostic oncology, and immunotherapeutic treatment. To contribute to the solution of these problems, the hypothesis of the potential role of immunity to the possible evolutionary atavistic endotoxin in the carcinogenesis caused by chemical agents – benzo(a)pyrene (BP) and methylcholanthrene (MCh) – is proposed.
substances (BP and MCh) as an inherited programme for damaged cells to survive (5, 14–16).

Studies on natural endotoxin immunity have shown that the natural immune functions of both immunostimulated and immunosuppressed organisms are closely related with IgM class natural specific antibodies (IgMNA) to the enterobacterial common antigen (ECA) from outer membranes of the intestinal microorganism *Alcaligenes faecalis* 415, i.e. endogenous or spontaneous antibodies to endotoxin (IgMNAE). IgMNAE was determined by precipitation reaction in agar gel (PA) according to O. Ouchterlony (1948) and by immunomembranoradiography (IR) according to D. A. Elgort and G. I. Abelev (1951) (16).

**Investigations with benzo(a)pyrene (BP)**

In experiments with Wistar rats, specific IgMNAE synthesis was strongly suppressed by BP. Rat blood serum was investigated upon a single subcutaneous injection of 5 mg of BP dissolved in 0.5 ml of peach oil; control rats received subcutaneously 0.5 ml of peach oil only. The control group comprised 54 rats and the test group consisted of 108 rats. The animals were desanguinated every two weeks: 6 animals in the control and 12 in the test groups. Their blood serum was examined in two replications (12–24 examples in each variant). IgMNAE determination was started six weeks following the carcinogen injection (at week 14 of age) and lasted up to 22 weeks of the test (or to the 30th week of the animals’ age) (16). The experiment was by four weeks shorter than the experiment with MCh.

During the first two months, both in control and in test animals the percentage of IgMNAE-positive serum was not high (17–33%). Immunostimulation was fixed to begin on week 10 of the trial: 100% of serum in control and 83% in test animals were positive. In the control group, the stimulatory effect of age was observed up to the end of the trial (83–100%), whereas in the test group, from week 18 up to the end of the trial (22 weeks) immunosuppression was found: only 8–25% of serum was positive (Table 1) (16).

At the end of the trial, IR reaction data confirmed the intensification of immunosuppression, which had started after 18 weeks: of the 92% negative samples found by the method of PA reaction, in IR reaction 59% were positive. After 20 weeks, of 75% of PA-negative samples, in IR reactions

<table>
<thead>
<tr>
<th>Age, weeks</th>
<th>Time after BP injection, weeks</th>
<th>Number of serum samples</th>
<th>PA% ± m%</th>
<th>IR% ± m%</th>
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<td><strong>Control groups</strong></td>
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<td>14</td>
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<td>33 ± 19.2</td>
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<td>17 ± 15.2</td>
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<td>6</td>
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<td>30</td>
<td>22</td>
<td>6</td>
<td>83 ± 15.2</td>
<td>17 ± 15.2</td>
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<td><strong>Test groups</strong></td>
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<td>6</td>
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<td>17 ± 11.2*</td>
<td>83 ± 11.2</td>
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</table>

* p value ≤ 0.05.
only 17% were positive. Thus, the effect of BP was found to result in immunosuppression only (Table 1) (16).

**Experiments with methylcholanthrene (MCh)**

In variant 1, in experiments with control groups of young (6–7 weeks of age) Wistar rats, which received subcutaneously 0.5 ml of peach oil, no IgMNAE was found in their blood serum by PA reaction. IgMNAE appeared only in the blood of animals aged 8–16 weeks – only 9% of animals had NA. Adult rats had it in 82% of cases (Table 2) (16).

All young rats had no NA during 2–6 weeks after MCh injection. On weeks 8–15 of the trial, immunostimulation was revealed: 62% of rats, i.e. by 53% more than in the same control group, showed antibodies. On weeks 16–20 when tumours began growing, NA were found only in 34% of rats, i.e. in this group the number of positive serum samples was by 28% less than in the previous group. After 22–26 weeks, NA suppression turned into secondary stimulation: NA were found in a considerably larger (by 42%) number of animals as compared with animals aged 16–20 weeks (p < 0.001), and this index did not differ from that of rats in the control group (Table 2) (16).

In variant 2, MCh was injected into adult Wistar rats three times. Their blood was taken from the caudal vein. Before injection, PA reaction had revealed NA in the serum of all 12 rats. The aim of the trial was an attempt to reveal the immunosuppressive effect of MCh at the initial stages of carcinogenesis. Following the first injection on days 20–24, initial chemical immunostimulation was revealed in nearly all animals.

Following the second and third injections on days 20–35 from the beginning of the trial, a statistically reliable immunosuppression was revealed (on days 28–50): 72% of serum samples were positive only in IR (p < 0.001). Later, on days 60–84 of the trial, the synthesis was restored and turned into stimulation. On day 60 of the trial one rat and on day 75 six rats died. On day 84, the last day of the trial, out of six samples five were positive in PA, and only one sample was positive in IR (Figure) (16).

Data obtained in 1985 on IgMNAE synthesis suppression and stimulation depending on animals’ age and on the effect of BP and MCh carcinogens on cells for a long time had only general immunological explanations (3, 6). The collected material had become of archival interest.

Only upon creating a new theory of the origin of cancer as a manifestation of evolutionary malignant resistance of cells to the damaging factors, these data acquired a new value and interpretation on the basis of this theory (5, 13, 14) to which also the hypothesis of a possible synthesis of the evolutionary atavistic endotoxin by tumorous cells (9) and the response of the immune system to the alien antigen – endotoxin – by stimulating IgMNAE synthesis is related.

Data of experimental studies with rats had revealed an age-stimulated IgMNAE synthesis in them and a secondary enhancement of this synthesis after induced immunosuppression. No secondary enhancement was found in the BP group, possibly because the duration of the experiment was by four weeks shorter than that of the experiment with MCh.

<table>
<thead>
<tr>
<th>Time after MCh injection, weeks</th>
<th>Number of serum samples</th>
<th>PA positive</th>
<th>n</th>
<th>% ± m%</th>
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<tr>
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<td>0</td>
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<td>0</td>
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<td>8–16</td>
<td>33</td>
<td>3</td>
<td>9</td>
<td>5.0*</td>
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<td>17–32</td>
<td>40</td>
<td>33</td>
<td>82</td>
<td>6.0*</td>
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<td>Test groups</td>
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<tr>
<td>2–6</td>
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<td>22–26</td>
<td>42</td>
<td>32</td>
<td>76</td>
<td>6.6*</td>
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* p value ≤ 0.05.

**Table 2. Specific IgMNAE in Wister rats treated with MCh (5 mg) (16)**
Therefore, there appeared a new possible interpretation of these data: at this stage of carcinogenesis, two mechanisms are possible: (1) the congenital age-related immunostimulation (3, 6, 7) and (2) the possible presence of a foreign antigen – atavistic endotoxin (lipopolysaccharide molecules) (9) in tumour cells induced by carcinogens. Atavistic endotoxin also propagates within the proliferating cancer cells resistant to chemical damage, which have adapted to survive in unfavourable conditions in the long period of their latency (9).

However, a question arises: how do these two mechanisms, one of them being protective and the other pathogenic, interact with one another? Do they possess a common mechanism of action, or is their mode of action essentially different? What are the possibilities of IgMNAE to join the possibly atavistic endotoxin and to eliminate it from tumour cells or from the organism?

DISCUSSION

These investigations allow distinguishing three phenomena: (1) an age-dependent IgMNAE synthesis stimulation, (2) suppression of the synthesis of these antibodies by carcinogens, and (3) a secondary stimulation of IgMNAE synthesis, induced by the evolutionary atavistic endotoxin possibly synthesized by the arising tumorous cells resistant to the carcinogens.

The age-related increase of IgMNAE synthesis in rats implies that the natural mechanism of immunity to endotoxin is intended for destroying damaged, atypical, degenerated and damage-proof (tumorous) cells in order to preserve the genetic stability of the organism throughout the whole life of an individual in conditions of a constant contact with the environmental and all other factors that are harmful to cells.

Meanwhile, under the effect of carcinogenic substances, an initial short-term IgMNAE synthesis stimulation was stated, followed by its suppression. Suppression, in its turn, was followed by a second stimulated NA synthesis in the MCh group. All these mechanisms of IgMNAE synthesis changes in carcinogenesis could be explained employing the evolutionary resistance theory of the origin of cancer, based on the general biological laws: (1) evolutionary malignant resistance of cells to damaging factors and (2) their regression to a more primitive
mode of existence (atavism) for adaptation in order to survive (13–15).

Now the initial interpretation (when all data published in 1985–1991 (6, 8, 16) were considered to be a non-specific response of the immune system to the harmful internal and environmental factors and its recovery from the effects of damaged and degenerated cells in the conditions when other components of the same – humoral – immunity chain and/or of the other – cellular – immunity chain are suppressed (6)) has acquired a new interpretation as a secondary synthesis of specific IgMNAE, corresponding to the resistance of tumorous cells to damage and their parasitism in order to survive (4, 5, 9, 13–15), which is possibly related to the activity of revived lipopolysaccharide molecules, together with an enhanced expression of evolutionary resistance-related genes and oncogenes suppressed in the course of evolution (9).

The appearance of cell resistance to damage is a general biological evolutionary law of nature: it is a feature of bacteria, somatic and tumorous cells. It shows that the protective mechanism is not a specific but an integrated response of all cells to the damaging factors, unrelated in respect of their structure and functions, although in its essence it is a specific evolutionary response intended for cell survival (14).

With the initiation of the tumorigenic process, alongside resistance-related genes and oncogenes (14), in the course of evolution the dormant stimulation of atavistic endotoxin synthesis also begins. It is exactly this atavistic endotoxic mechanism that allows the cells resistant to carcinogens to acquire parasitic features in their unlimited division and metastatic growth to ensure survival in a medium uncontrolled by the organism. The relation between the enhanced activity of these genes and their proteins and accelerated cell growth can be proven without much argument. Metastases are the visible biological expression and essence of the atavistic development of a tumour. Thus, natural immunity to endotoxin as a non-specific, evolutionary reaction that preserves cell homeostasis in the whole organism during carcinogenesis becomes a specific reaction in regard to tumorous cells, which helps them to survive. Most probably, simultaneously with the beginning of the synthesis of the alien antigen – endotoxin – initiated by tumorous cells, the immune system of the organism, although suppressed by carcinogens, is able to stimulate IgMNAE synthesis because the antigen is alien to the host.

We have established an identity between the possibly atavistic endotoxin and the endotoxin of gram-negative bacteria by PA reaction (9). Nevertheless, during the long latent period, there may appear functional differences from the bacterial endotoxin, caused by antigen-antibody interaction. Therefore, the present hypothesis-dilemma may certainly have its presumptions:

1. during immunosuppression, carcinogens may damage the mechanism of production of specific proteins, which is present in plasma cell ribosomes, and for this reason IgMNAE may fail to bind in due time to the endotoxin still present in tumorous cells;

2. the endotoxin, not bound to IgMNAE on a tumorous cell, is released into the organism’s medium. As a result, tumorous cells preserve their vitality; moreover, normal cells are damaged by the endotoxin freely circulating in the organism. The endotoxin may cause chronic cachexia in cancer patients (9), whereas tumorous cells preserve their parasitic properties as the evolutionary rivals of normal cells and continue proliferating and producing new portions of the endotoxin;

3. the atavistic endotoxin of tumorous cells, transported through the cell membrane, may join IgMNAE only in the blood, and the endotoxin producers may again remain undisturbed;

4. damaged plasma cell ribosomes in the immune system suppressed by carcinogens are unable to synthesize IgMNAE in significant amounts, while under the accelerated proliferation of tumorous cells more endotoxin is produced. The disturbed intensity of IgMNAE synthesis and the low level of these antibodies fail to neutralize the endotoxin, whereas chronic cachexia continues its exhaustive effects on the vital functions of the organism.

The above presumptions remain unconfirmed so far. Only the last presumption of the hypothesis-dilemma can be supported by our earlier (1975) work (17) in which the blood serum of 59 ± 3.6% of rats treated with BP and MCh and 21 ± 4.8% of untreated rats positively reacted (p < 0.01) with the ECA of different strains of *E. coli* and *Alcaligenes faecalis* 415. However, this showed no significant effect of IgMNAE on the development of induced tumours in the same animals during six months.
This conclusion was also confirmed by data obtained from the oncological patients that had IgMNAE in their blood serum. Among patients with tumours, this and other immunity chains were most frequently suppressed (2, 6).

However, IgMNAE synthesis activation before injecting carcinogenic substances to rats with ECA of *Alcaligenes faecalis* 415 extract during initial stages of carcinogenesis markedly inhibited the process, and the growth of induced tumours was slower (17). These data confirm the possible value of preventive investigations in cancer prevention programmes. "At present, the main problem in oncology is cancer prophylaxis"… (14). This statement, expressed in our theory of the origin of cancer, may be repeated here because the immune system exhausted by immunosuppression cannot eliminate tumorous cells from the organism.

It seems possible that it is only preventive vaccination with bacterial or atavistic endotoxin that could raise the IgMNAE level in the blood so as to destroy the cells damaged by carcinogens in the pre-cancer stage when the immune system is not yet damaged by carcinogenic factors. Therefore, at present, the main problem in oncology is cancer prophylaxis by reducing the polluting factors in nature and elaborating new immunological methods to maintain a high level of natural immunity to the possibly atavistic endotoxin in humans, first of all, in cancer prevention programmes (in high-risk groups of people) and then in the general population.

CONCLUSIONS

The author proposes a new hypothesis on the possibility of natural immunity to evolutionary atavistic endotoxin in carcinogenesis induced by chemical agents. Our studies on rats revealed an age-dependent stimulation of the synthesis of natural specific IgM class antibodies to endotoxin of gram-negative *Alcaligenes faecalis* 415 bacteria (IgMNAE).

Also, there had been elucidated the phenomena of suppression of natural immunity to this endotoxin and of a secondary (possibly atavistic endotoxic) immunostimulation under the effect of carcinogenic substances in rats. The compensatory age-related IgMNAE stimulation was also revealed in human population (6–8). Any inefficiency of the immune system may become an obstacle for the immune-specific antibodies to join the atavistic endotoxin, thus leaving a tumorous cell vital, capable of proliferation and further endotoxin synthesis.

Therefore, the hypothesis is an attempt to reveal the peculiarities of the problem. The mechanisms of the possible appearance of atavistic endotoxin (foreign lipopolysaccharide molecules) in tumour cells, induced by carcinogenic substances, are related to the fundamentals of the theory of the origin of cancer, proposed by the author; e. g., they are consistent with two evolutionary biological laws: (1) malignant resistance of cells to damaging factors and (2) atavistic regression into a more primitive mode of existence (14). The results of this work are in full agreement with the last argument of the theory – the potential role of the evolutionary atavistic endotoxin in carcinogenesis (9). The other 23 arguments have been published elsewhere (4, 13, 14).

Thus, as long as the mechanisms of IgMNAE synthesis and joining the possible atavistic endotoxin are not yet clear, the prospects of immunotherapy are limited. Preventive vaccine studies seem to be the most promising initial perspective. In order to prevent the ecological risks of tumorous diseases in the programmes of selective health checking intended for detecting pre-tumorous changes, it seems necessary to start developing methods of preventive vaccination with bacterial, or maybe also atavistic, endotoxin. Our experience in regard to safety while elaborating a control immune IgMNAE serum in rabbits is as follows: the animals survived rather well the intravenous vaccination and by their appearance and behaviour did not differ from non-vaccinated ones. IgMNAE in the immune serum was present six months and more.

The basis of our hypothesis is supported by certain causal assumptions. They permit to suppose that the lower risk of cancer among people working in environments polluted with bacterial endotoxin versus the general population (18, 19), different levels of malignancies in humans working in the same carcinogenic conditions (20) and cases of spontaneous regression of cancer (21, 22) are dependent on the level of IgMNAE in a person's blood. The low IgMNAE level in the blood may be an endogenous indicator of a high risk of cancer. This supposition can be useful in the early diagnosis of oncological diseases.
The possible developments of the hypothesis are as follows:

(1) elaboration of immunological methods to preserve a high level of natural immunity to gram-negative bacteria (endotoxin) and to possible evolutionary atavistic endotoxin in individuals at a high risk of cancer and in general population;
(2) production of endotoxin-based vaccines and their application in cancer prophylaxis;
(3) extrapolation of data obtained in our onco logical experiments to human cancer prophylaxis, elucidating individuals with high and low IgMNAE levels for high and low cancer risk programmes.

References

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Natural immunity to evolutionary atavistic endotoxin in carcinogenesis


Elena Moncevičiūtė-Eringienė

NATŪRALUS IMUNITETAS EVOLIUCINIAM ATAVISTINIAM ENDOTOKSINU CHEMINIAIS AGENTAI IndUKUOTOS KANCEROGenezės ATVEJU (HIPOTEZĖ)

Santrauka
Autorė siūlo hipotezę apie natūralaus imuniteto evoliuciniam atavistinių endotoksinių susiformavimo galimybę veikiant žiurkių organizmą cheminėmis kancerogēninėmis medžiagomis – benza(o)pyrenu (BP) ir metylcholantrenu (MCh). Nustatyta IgM klasės natūralių specifinių antikūnų prieš gram-neigiamų Alcaligenes faecalis 415 bakterijų endotoksnį (IgMNAE) stimuliacija normalių suaugusių žiurkių kraujyje, susijusi su amžiumi. Šis fenomenas buvo atskleistas ir žmonių populiacijoje. Eksperimento metu buvo išaiškinti natūralaus imuniteto šiam endotoksnui du fenomenai: imunostimuliacija ir imunosupresija.

Pradžioje pirminis dėl amžiaus ir antrinis kancerogeininis IgMNAE sintezės suaktyvėjimas buvo aiškinamas kaip imuninės sistemos asigynimo ir jos funkcijų atkūrimo kompensacinių reakcijos esant tos pačios humoralinio imuniteto grandinės kitų komponentų ir / ar įstelėjimo imuniteto grandies komponenčių imunosupresijos mehanizmams. 2002–2005 m. autorei sukūrus naują vėžio kilmės teoriją, pagrįstą bendrais biologiniais dėsningu- mais (rezistentiškumas žalojimui ir atavizmas), IgMNAE sintezę skatinantis mechanizmas, susiformavęs kancerogenės atveju po imuninės sistemos funkcijų supresinį pažeidimą, buvo aiškinamas šios teorijos dėsniais: evoliucijos procese galimai suaktyvėjusios paslėptų (snaudžiančių) liposacharido molekulių (atavistinės endotokinės) funkciomis kartu su suaktyvėjusia evoliucinio rezistentiškumo genų ir onkogenų veikla.

Visi šie mechanizmai iš bakterijų buvo perduoti žinduolių ląstelėms, o jų pajėgumas veikti ir kontroliuoti kancerogenės procesą gali būti labai didelis. Šių genų ir jų baltymų funkcijų aktyvacija ir paderė naujai be-siformuojančioms vėžinėms ląstėms įgyti parazitinių savybių, leminčių jų neribotą dalijimąsi, invaziškumą ir metastazinį plitimą. Metastazės yra akivaizdžių navikų atavistinio vystymosi biologinė apraška, kurios esmė yra specifinis evoliucinis atsakas, paderėtasis išgyventi pažeistomis ląstėmis. Taigi turėtų būti formuojama nauja onkologijos strategija, kurios pagrindas – bakterinio ar atavistinio endotoksnio pagrindu sukurtų priesvėžinių vakcinų gamyba ir jų panaudojimas vėžio profilaktikai. IgMNAE neabejotina gali būti naudingas tobulinant vėžio diagnostikos ir imunoterapijos metodus.

Raktas: BP ir MCh, bakterinis ir atavistinis endotoxinės, endotoksino pagrindu profiltukas, IgMNAE, rezistentiškumas žalojimui, vėžinių ląstelių endogeninis parazitizmas ir atavizmas