

Human antibody levels against cancer-causing agents such as oestrogen, progestin, and benzopyrene.

Alena N. Estinov

Federal State Scientific Institution, Federal Research Centre Coal and Coal Chemistry, Russia

***Corresponding Author :** Alena N. Estinov,
Federal State Scientific Institution, Federal Research Centre Coal and Coal Chemistry, Siberian Branch of the Russian Academy of Sciences, Institute of Human Ecology, Kemerovo, Russia

Received : October 21, 2023

Accepted: October 22, 2023

Published : November 24, 2023

Abstract

Serum immunoglobulin A antibodies against benzo[a]pyrene and estradiol were thought to rise in tandem but not individually, hence increasing the risk of lung and breast cancer. However, when the levels of immunoglobulins A against progesterone increased either alone or in combination with immunoglobulins A against benzo[a]pyrene and estradiol, the risks of cancer significantly decreased. Therefore, in a developing cancer scenario, immunoglobulins A against benzo[a]pyrene and immunoglobulins A against estradiol acted as co-initiators and co-promoters; however, immunoglobulins A against progesterone acted in concert with or alongside immunoglobulins A against benzo[a]pyrene and estradiol as a potent inhibitor in the development of human carcinogenesis. Additionally, the precise mechanism of modulating carcinogenesis by the use of anti-idiotypic antibodies against progesterone and estradiol through their membrane steroid receptors was proposed.

Keywords : *Benzo[a]pyrene, Estradiol, Progesterone, Antibody, Anti-Idiotypic Antibody, Immunoglobulins A, Polycyclic Aromatic Hydrocarbons, Immunology, Lung Cancer, Breast Cancer, Cancer Risks*

Introduction

The protection of mucosal immunity from chemical carcinogens

is largely dependent on immunoglobulin A (IgA). As stated in our earlier work [1], it was thought that serum IgA could influence the development of cancer by binding endogenous hormones and chemical carcinogens and transferring them to the epithelial cells via membrane Fc receptors. These antibodies against estradiol (IgA-Es) and benzo[a]pyrene (IgA-BP) may accelerate the initiation and progression of cancer. On the other hand, progesterone-specific antibodies (IgA-Pg) may impede the promotion process in cells that rely on steroids. Depending on the ratio of stimulating to inhibitory antibodies, there was a potential increase or decrease in the probability of tumour transformation. Here are the newest findings on antibodies against Bp, Es, and Pg in patients with breast and lung cancer that support these hypotheses.

IgA Antibodies' Effects on Lung and Breast Cancer Risk Against Environmental Carcinogens and Sex Steroids

Numerous experimental studies have been conducted both in vivo and in vitro regarding the immunomodulation of carcinogenesis and tumour growth by antibodies directed against chemical carcinogens and sex steroid hormones [2]–[16]. Antibodies against carcinogen-DNA adduct and carcinogen-protein conjugates were found to rise in humans following exposure to carcinogens and in cancer patients [17]–[22]. It is yet unclear, nevertheless, what these anti-diets' functional importance is for humans. Antibodies were thought to either promote or prevent carcinogenesis under specific circumstances.

Serum IgA against Bp, Es, and Pg in LCP and BCP was examined in order to support the theory regarding immunomodulation of chemical carcinogenesis in humans. It was discovered that compared to healthy individuals, LCP and BCP had higher levels of IgA against Bp and Es more frequently (Table 1). Conversely, there were no variations in IgA-Pg across the examined populations. Cancer patients had higher ratios of IgA-Bp/IgA-Pg and IgA-Es/IgA-Pg than did healthy donors. Both the BC and LC risks rose sharply. These findings indicate that IgA-Bp and

IgA-Es dominance over IgA-Pg promotes lung and mammary gland carcinogenesis. Eight subgroups were created from the combination of high and low antibody levels against Bp, Es, and Pg, taking into account the genders of the participants. It was discovered that LCP had minimal or no IgA levels for all three substances.

The odds ratio (OR) did not rise when high levels of IgA-Bp along or IgA-Es along (groups 2 and 3, respectively) were discovered in BCP and healthy women at the same frequency. This indicates that there was no significant impact of IgA-Bp and IgA-Es on the development of lung and mammary gland cancers. Compared to healthy males, LCP showed higher levels of IgA-Bp alone or IgA-Es more frequently, and their OR increased to 4.1 - 2.5, respectively. In the instance of IgA-Pg along (group 4), there were no appreciable variations across comparable groups. It was noteworthy that cancer patients exhibited significantly higher levels of IgA-Bp in combination with IgA-Es (group 5) than did healthy donors. The risks for LC and BC went up to 16.2 and 6.2, respectively.

Therefore, carcinogenesis in the lung and mammary gland was accelerated by simultaneous IgA-formation to Bp and Es without Pg much more than when they functioned separately. According to the traditional chemical-induced carcinogenesis concept, IgA-Bp and IgA-Es antibodies operate as co-initiators and co-promoters because of their reciprocal amplification of their effects. There was no discernible increase in the risks of LC and BC when IgA-Pg combined with either IgA-Bp or IgA-Es (groups 6 and 7). Furthermore, compared to IgA-Bp and IgA-Es without IgA-Pg (group 5), the cancer risks were decreased when IgA-Pg was generated along with IgA-Bp and with IgA-ES (group 8; LC OR = 2.7; BC OR = 2.5). That indicates a co-inhibitory role for IgA-Pg.

The actions of IgA against chemical carcinogens and sex steroids that have been revealed can be explained by three mechanisms: 1) binding of these substances in blood serum; 2) immune complex transport into epithelial cells via membrane Fc-receptor; and 3) interaction between the substances and intracellular receptors with known biological effects.

According to the cancer immune-prevention strategy, stimulating IgA synthesis against environmental carcinogens may not be acceptable as these antibodies were primarily detected in conjunction with Es-antibodies, and in these circumstances, the risk of cancer rose [15]. For this reason, it was essential to

investigate the potential roles that IgA-Es inhibition and IgA-Pg synthesis stimulation could have in the immune-prevention of cancer.

Antiidiotypic Antibodies against Chemical Carcinogens and Endogenous Steroids Immunomodulate Human Carcinogenesis

In the past, serum from BCP and LCP was found to have antibodies against the polycyclic aromatic hydrocarbons (Ab1) and the matching antiidiotypic anti-bodies (Ab2) [27] [28]. Ab2 levels were demonstrated to be higher than Ab1. We assumed that Ab2 obstructed Ab1's protective mechanisms. The production of Ab2 against endogenous hormones was hypothesised to function similarly to Ab2's anti-protective effects against chemical carcinogens [1]. Simultaneously, there could be further effects of Ab2 on the onset and promotion of carcinogenesis. A few studies looked into the possibility of monoclonal Ab2 interacting with the oestrogen receptor (ER) by targeting the binding site of a monoclonal anti-Es Ab1. Ab2 1D5 was demonstrated to have Es-like effects (an increase in kinase activity) in vitro in female human and rat osteoblasts [32] and in vivo in epiphyseal cartilage, diaphyseal bone, uterus, prostate, and thymus of immature female animals [29]–[31]. Rat pituitary cells released more prolactin when exposed to rabbit polyclonal R4 antibodies that target the ER hinge region sequence. However, prolactin release was inhibited and the stimulatory effect of Es was stopped by monoclonal H 151 antibodies that were directed against a distinct hinge area epitope [33]. In human spermatozoa, two additional monoclonal antibodies that target the ligand binding domains of ER (H 222) and PR (C 262) inhibited the calcium response to Es and Pg [34].

When combined, these experimental findings provide evidence that antibodies directed against membrane steroid receptors can replicate the actions of homologous steroids. In the event that human Ab2-formation against Es and Pg occurs, these Ab2 may attach to target cell membrane receptors and either promote or prevent the development of cancer. Should the aryl hydrocarbon-like receptor be able to express itself in the cell surface membrane, Ab2-Bp may be able to replicate the effects of Bp on the start of carcinogenesis. In any case, the established processes of aryl hydrocarbon receptor-steroid receptor cross-talk would allow anti-bodies against steroid hormones to influence the Bp-initiation [35] [36].

Case Report

It was clear and previously mentioned how speculative those assumptions were. All of our data collectively demonstrate that LPS and CpG have the most potent inhibitory impact on the development of several allergen-specific Th2 responses in mice. Our findings encourage more clinical testing of TLR9 and TLR4 agonists, which have already been employed as adjuvants in clinical SIT trials [9, 23]. Curiously, a large reduction in the allergic reaction did not always correlate with a strong induction of allergen-specific Th1 responses, indicating that this indicator of an efficient SIT response could not always result in a reduction in the allergic response.

References

1. Glushkov, A. (2014) Immunological Disbalance in Carcinogenesis. *Medical Hypotheses*, 83, 166-171. <http://dx.doi.org/10.1016/j.mehy.2014.05.003>
2. Coldwell, B.V., Tillson, S.A., Esber, H. and Thorneycroft, I.H. (1971) Survival of Tumours after Immunization against Oestrogens. *Nature*, 231, 118-119. <http://dx.doi.org/10.1038/231118a0>
3. Cernohorska, H., Klimesova, S., Lepsa, L., Jinoch, P., Milcova, A., Schmuczerova, J., Topinca, J. and Labaj, J. (2012) Influence of Immunization with Non-Genotoxic PAH-KLH Conjugates on the Resistance of Organisms Exposed to Benzo[a]pyrene. *Mutation Research*, 742, 2-10. <http://dx.doi.org/10.1016/j.mrgentox.2011.10.016>
4. Chagnaud, J.L., Faiderbe, S. and Geffard, M. (1993) Effects of a Monoclonal Anti-Idiotypic Antibody, Internal Image of Benzo(a)pyrene, on Rat Sarcomas. *Academy of Sciences Paris, Science de la vie*, 316, 1266-1269.
5. Creech, H.J., Oginsky, E. and Tryon, M. (1947) Immunological Studies of Hydrocarbon-Protein Conjugate. *Cancer Research*, 7, 301-304.
6. Curtis, G.L., Ryan, W.Z. and Stenback, F. (1978) Antibody Stimulation of Benzo(a)pyrene Carcinogenesis. *Cancer Letters*, 4, 223-228. [http://dx.doi.org/10.1016/S0304-3835\(78\)94677-3](http://dx.doi.org/10.1016/S0304-3835(78)94677-3)
7. De Buck, S.S., Augustijns, P. and Muller, C.P. (2005) Specific Antibody Modulates Absorptive Transport and Metabolic Activation of Benzo[a]pyrene across Caco-2 Monolayers. *Journal of Pharmacology and Experimental Therapeutics*, 313, 640-646. <http://dx.doi.org/10.1124/jpet.104.081034>
8. Grova, N., Prodhomme, E.J., Schellenberger, M.T., Farnelle, S. and Muller, C.P. (2009) Modulation of Carcinogen Bioavailability by Immunization with Benzo[a]pyrene-Conjugate Vaccines. *Vaccine*, 27, 4142-4151. <http://dx.doi.org/10.1016/j.vaccine.2009.04.052>
9. Moolten, F.L., Capparel, N.L. and Boger, E. (1978) Induction of Antibodies against Carcinogenic Polycyclic Aromatic Hydrocarbons. *Nature*, 272, 614-616. <http://dx.doi.org/10.1038/272614a0>
10. Moolten, F.L., Capparel, N. and Boger, E. (1978) Reduction of Respiratory Tract Binding of Benzo(a)pyrene in Mice by Immunization. *Journal of the National Cancer Institute*, 61, 1347-1349.
11. Moolten, F.L., Schreiber, B. and Rizzone, A. (1981) Protection of Mice against 7,12-Dimethylbenz(a)anthracene-Induced Skin Tumors by Immunization with Fluorinated Analog of Carcinogen. *Cancer Research*, 41, 452-459.
12. Peck, R.M. and Peck, E.B. (1971) Inhibition of Chemically Induced Neoplasia by Immunization with an Antigenic Carcinogen-Protein Conjugate. *Cancer Research*, 31, 1550-1554.
13. Silbart, L.K. and Keren, D.F. (1989) Reduction of Intestinal Carcinogen Absorption by Carcinogen-Specific Immunity. *Science*, 243, 1462-1464. <http://dx.doi.org/10.1126/science.2928780>
14. Silbart, L.K., Mc Allen, F. and Rasmussen, H.V. (1996) Selective Induction of Mucosal Immune Responses to 2-Acetylaminofluorene. *Anticancer Research*, 16, 651-660.
15. Silbart, L.K., Rasmussen, H.V. and Oliver, A.R. (1997) Immunoprophylactic Intervention in Chemical Toxicity and Carcinogenicity. *Veterinary and Human Toxicology*, 39, 37-43.

Case Report

16. Verdina, A. (2006) Carcinogen-Modified DNA and Specific Humoral Immunity toward Carcinogen-DNA Adducts. *Annali dell'Istituto Superiore di Sanità*, 42, 189-194.
17. Chagnaud, J.L., Faiderbe, S. and Geffard, M. (1992) Identification and Immunochemical Characterization of IgA in Sera of Patients with Mammary Tumors. *International Journal of Cancer*, 50, 395-401. <http://dx.doi.org/10.1002/ijc.2910500312>
18. Galati, R., Zijno, A., Crebelli, R. and Falasca, G. (2001) Detection of Antibodies to the Benzo[a]pyrenediol Epoxide-DNA Adducts in Sera from Individuals Exposed to Low Doses of Polycyclic Aromatic Hydrocarbons. *Journal of Experimental & Clinical Cancer Research*, 20, 359-364.
19. Glushkov, A.N., Polenok, E.G., Verzhbitskaja, N.E., Titov, V.A., Vafin, I.A. and Ragozina, S.E. (2014) Antibodies to Chemical Carcinogen and Steroid Hormones in Lung Cancer Patients. *Russian Journal of Immunology*, 2, 219-227. (In Russian)
20. Harris, C.C., Vahakangas, K. and Newman, M.J. (1985) Detection of Benzo[a]pyrenediol Epoxide-DNA Adducts in Peripheral Blood Lymphocytes and Antibodies to These Adducts in Serum from Coke Oven Workers. *Proceedings of the National Academy of Sciences of the United States of America*, 82, 6672-6676. <http://dx.doi.org/10.1073/pnas.82.19.6672>
21. Pauk, N., Klimesova, S. and Kara, J. (2013) The Relevance of Monitoring of Antibodies against the Polycyclic Aromatic Hydrocarbon (PAH) Adducts in Serum in Relation to Lung Cancer and Obstructive Pulmonary Disease (COPD). *Neoplasma*, 60, 182-187. http://dx.doi.org/10.4149/neo_2013_024
22. Petruzzelli, S., Seli, A. and Pulera, N. (1998) Serum Antibodies to Benzo(a)pyrenediol Epoxide DNA Adducts in the General Population: Effects of Air Pollution, Tobacco Smoking and Family History of Lung Diseases. *Cancer Research*, 58, 4122-4126.
23. Glushkov, A.N. (1999) Mechanisms of Antibodies Formation and Functions at Carcinogenesis. *Experimental Oncology*, 21, 3-8. (In Russian)
24. Glushkov, A.N. (2002) Immunostimulation of the Chemical-Induced Carcinogenesis in the Phase of Initiation. *Medical Hypotheses*, 5, 501-503. [http://dx.doi.org/10.1016/S0306-9877\(02\)00224-4](http://dx.doi.org/10.1016/S0306-9877(02)00224-4)
25. Glushkov, A., Polenok, E., Kostyanko, M., Titov, V., Vafin, I. and Ragozina, S. (2015) Mutual Effects of Antibodies to Benzo[a]pyrene, Estradiol and Progesterone on the Lung Cancer Risk. *Russian Journal of Immunology*, 9, 343-349. (In Russian)
26. Glushkov, A., Polenok, E., Kostyanko, M., Antonov, A., Verzhbitskaja, N., Vafin, I. and Ragozina, S. (2016) Postmenopausal Breast Cancer Risk in Relation to Benzo[a]pyrene, Estradiol and Progesterone Specific Antibodies. *Iranian Journal of Cancer Prevention*, 9, e4212.
27. Glushkov, A.N., Polenok, E.G., Anosova, T.P., Savchenko, Y.A., Bakanova, M.L., Minina, V.I., Mun, S.A., Larin, S.A. and Kostyanko, M.V. (2011) Serum Antibodies to Benzo[a]pyrene and Chromosomal Aberrations in Lymphocytes Peripheral Blood at the Workers of Coal Processing Enterprise. *Russian Journal of Immunology*, 5, 39-44. (In Russian)
28. Ustinov, V.A., Matveeva, V.A., Kostyanko, M.V. and Glushkov, A.N. (2013) Antibodies against Benzo[a]pyrene in Immunized Mouse and Lung Cancer Patients. *Experimental Oncology*, 35, 207-210.
29. Mor, G., Amir-Zaltsman, Y., Barnard, G. and Kohen, F. (1992) Characterization of an Anti-idiotypic Antibody Mimicking the Actions of Estradiol and Its Interaction with Estrogen Receptors. *Endocrinology*, 130, 3633-3640.
30. Somjen, D., Amir-Zaltsman, Y., Gayer, B., Mor, G., Jacqord, N., Weisman, Y., Barnard, G. and Kohen, F. (1995) Anti-Idiotypic Antibody as Estrogen Mimetic: Removal of Fc Fragment Convert Agonist to Antagonist. *Journal of Endocrinology*, 145, 409-416. <http://dx.doi.org/10.1677/joe.0.1450409>
31. Somjen, D., Amir-Zaltsman, Y., Mor, G., Gayer, B., Lichter,

- S., Barnard, G. and Kohen, F. (1996) Anti-Idiotypic Antibody as an Estrogen Mimetic in Vivo: Stimulation of Creatine Kinase Specific Activity in Rat Animal Models. *Journal of Endocrinology*, 149, 305-312. <http://dx.doi.org/10.1677/joe.0.1490305>
32. Somjen, D., Kohen, F. and Lieberherr, M. (1997) Nongenomic Effects of an Anti-Idiotypic Antibody as an Estrogen Mimetic in Female Human and Rat Osteoblasts. *Journal of Cellular Biochemistry*, 65, 53-66. [http://dx.doi.org/10.1002/\(SICI\)1097-4644\(199704\)65:1<53::AID-JCB6>3.0.CO;2-Y](http://dx.doi.org/10.1002/(SICI)1097-4644(199704)65:1<53::AID-JCB6>3.0.CO;2-Y)
33. Norfleet, A., Clarke, C., Gametchu, B. and Watson, C. (2000) Antibodies to the Estrogen Receptor-Alpha Modulate Rapid Prolactin Release from Rat Pituitary Tumor Cells through Plasma Membrane Estrogen Receptors. *The FASEB Journal*, 14, 157-165.
34. Luconi, M., Francavilla, F., Porazzi, I., Macerola, B., Forti, G. and Baldi, F. (2004) Human Spermatozoa as a Model for Studying Membrane Receptors Mediating Rapid Non-Genomic Effects of Progesterone and Estrogens. *Steroids*, 69, 553-559. <http://dx.doi.org/10.1016/j.steroids.2004.05.013>
35. Kuil, C., Brouwer, A., van der Saag, P. and van der Burg, B. (1998) Interference between Progesterone and Dioxin Signal Transduction Pathways. *The Journal of Biological Chemistry*, 273, 8829-8834. <http://dx.doi.org/10.1074/jbc.273.15.8829>
36. Wihlen, B., Ahmed, S., Inzunza, J. and Matthew, J. (2009) Estrogen Receptor Subtype- and Promoter-Specific Modulation of Aryl Hydrocarbon Receptor-Dependent Transcription. *Molecular Cancer Research*, 7, 977-986. <http://dx.doi.org/10.1158/1541-7786.MCR-08-0396>