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Mechanisms of Formation and Persistence of IgE Products and Potential Innovative Means of Therapy for Allergic Pathologies

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Abstract—This review is devoted to the analysis of the main mechanisms of the formation of IgE-producing cells in the body and a brief review of the main, most striking candidate agents for use in innovative methods of therapy for IgE-dependent pathologies. Data are presented according to which the role of IgE^+ plasma cells and various subpopulations of memory B-lymphocytes in the formation and persistence of the state of sensitization to a harmless allergen differs depending on the model system used or the clinical case under study. Therefore, drugs that target signaling pathways involved in the regulation of both plasma cells and memory B-lymphocytes are especially promising in the treatment of allergic diseases. The authors conclude that the components of the cellular response to oxidative stress and related genotoxic stress and ER stress are the most promising as such targets, since (a) all of them directly or indirectly affect the processes that regulate both of these subpopulations; (b) are involved in the process of formation and maintenance of local allergic inflammation. The review presents data pointing to the particular promise of using nanoparticles of noble metals and complexes of rare earth metals of lanthanides in this regard, due to their ability to induce long-term effects in small doses due to changes in the properties of innate immunity cells and long-term accumulation in the body.

Keywords: IgE, B-lymphocytes, asthma, cellular stress, oxidative stress, low molecular weight pharmacological inhibitors, inorganic nanoparticles

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Around the world, especially in developed countries, there is a significant increase in the number of patients with allergic diseases caused by the formation of IgE production against harmless antigens [1, 2]. These pathologies include allergic asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis [1–4]. Despite the fact that the mechanisms responsible for the formation and persistence of IgE production are studied by many research groups, both in Russia [5, 6] and abroad [1, 7], the mechanisms of these processes are not yet well understood. One of the most important unresolved problems is the question of the roles of various subpopulations of B-lymphocytes and plasma cells in the persistence of the state of IgE-mediated sensitization of the body to allergens and the mechanisms of formation of such subpopulations. Without an understanding these issues, it is impossible to develop new methods of allergen-specific immune therapy that would be aimed not only at inducing the synthesis of protective antibodies that block allergen binding to IgE on the surface of basophils and mast cells [8, 9], but also at eliminating existing producers and their immediate predecessors.

According to the classical point of view, the formation of B-lymphocytes producing isotypes other than IgM and IgD always occurs in germinal centers, structures formed in B-cell follicles in the cortical zone of the lymph nodes [10, 11]. In the process of the primary immune response, both plasma cells develop from these structures, terminally differentiated cells characterized by a developed secretory apparatus responsible for the production of antibodies, and memory B-lymphocytes that retain the expression of membrane isoforms of the corresponding Ig, do not produce soluble antibodies, but are capable of a new encounter with an antigen to proliferation and differentiation in the process of secondary immune response [12, 13]. Due to the scarcity of IgE^+ B-lymphocytes and the presence on the surface of most B-lymphocytes and plasma cells of a low-affinity receptor for IgE of the CD23 molecule, which is capable of binding IgE produced by other cells, the definition of "true" IgE^+ B-lymphocytes and plasma cells are strongly impeded [14, 15]. Despite the rather long period of time during which the issue has been studied by different research groups, the specific cell subpopulations responsible for the persistence of IgE-mediated sensitization and

their exact localization have not yet been unequivocally determined. The results of studies of allergic models using laboratory animals obtained by different groups are contradictory and not always consistent with data obtained in clinical practice. Due to significant differences in the mechanisms that ensure the persistence of memory B-cells and plasmatic B-cells, the range of agents aimed at their specific elimination from the body will be significantly different in both cases.

The purpose of this review is a brief summary of the most important data obtained in recent years regarding the identification of subpopulations responsible for the persistence of the state of IgE-dependent sensitization and the mechanisms of its formation and maintenance in the body. In addition, some data on potential targets for new etiotropic therapy of allergic diseases aimed at eliminating IgE-producers and their precursors will be presented and some potential innovative drugs for the treatment of allergic pathologies will be briefly described.

FORMATION OF IgE$^+$ B-LYMPHOCYTES

It is well known that the formation of B-lymphocytes producing antibodies of the IgG and IgA classes in response to a foreign antigen occurs with the participation of the germinal centers of the B-cell follicles of the core zone of the lymph nodes [5, 11]. At the same time, a number of clinical data have shown that the presence, at least in some cases, of increased IgE production compared to healthy donors in patients with various forms of allergy is not accompanied by increased IgG (IgA) production [16, 17], or at least by lack of correlation between IgE production and other subclasses [18, 19], may indicate the presence of a special pathway for the formation of IgE producers.

In the works of the early 2010s, it was shown that IgE$^+$ B-lymphocytes in germinal centers are very few in number and quickly disappear from these structures during their maturation, which is due to the tendency of such cells to apoptosis [20, 21]. The formation of germinal centers requires induction in both B- and T-lymphocytes of the expression of the transcriptional repressor Bcl6 (protein 6 of B-cell lymphoma) [10]. However, it was previously found that the transcriptional Bcl6 repressor prevents B-lymphocytes from switching to IgE synthesis, in particular, by direct switching from IgM to IgE [22]. These data are in conflict with clinical practice, which indicates the persistence of IgE production and switching to IgE in patients with type I allergies [2–4], which indirectly indicates the possible role of germinal centers as structures responsible for the formation of long-lived B-memory lymphocytes and plasma cells [10, 11], in the immune response to allergens [2–4]. In addition to germinal centers, B-lymphocytes upon activation form extrafollicular foci located in the medullary zone of lymph nodes and do not require Bcl6 expression in B-lymphocytes at mature stages [23]. It would be logical to assume that these structures are involved in the formation of IgE production. In fact, according to some earlier and more recent data, isotype switching can also occur outside the germinal centers [24, 25]. However, in extrafollicular foci, mainly short-lived plasmablasts are formed, which are not capable of forming long-term plasma cells and memory B cells [15].

In this regard, the dominant point of view today is that the switching of B-lymphocytes to the synthesis of IgE occurs in two main ways. First, by a direct route from the IgM isotype during the primary immune response in early germinal centers, with the emerging IgE$^+$ cells quickly leave the germinal centers and further develop extrafollicularly into short-lived plasmablasts [20, 21]. Second, sequentially through the IgG isotype$_1$, especially during a secondary encounter with an allergen [26]. A number of works indicate the predominance of sequential switching in the formation of IgE production. According to published data, during the primary immune response, several subpopulations of memory B cells are formed, the most important of which are PD-L2$^+$CD80$^-$CD73$^-$, PD$^-$L2$^+$CD80$^+$CD73$^-$, and PD-L2$^+$CD80$^+$CD73$^+$. During a re-encountered with an antigen, only the last subpopulation is prone to rapid switching to subsequent isotypes, including IgE (usually with IgG$_1$-isotype), and the first two form the germinal centers of the secondary immune response [26, 27]. Thus, the formation of IgE production and germinal centers in the secondary response may not be related to each other, although the formation of IgG$_1^+$ memory B-cells during the primary immune response, including those capable of sequential switching to IgE, occurs in germinal centers [26]. The results obtained in experimental models are confirmed by the data of new studies on the analysis of samples from the tonsils and nasal polyps of patients with allergic rhinitis and asthma, in whom the formation of IgE production occurred extrafollicularly, or at least was not associated with the induction of germinal centers [28, 29]. Data for single IgE$^+$ transcriptome sequencing plasma cells indicate that the latter have a gene signature closer to that of IgG1$^+$ plasmablasts than IgG$_1^+$ plasma cells and are characterized by "immaturity" and, therefore, most likely form extrafollicularly [30].

Such a mechanism for the formation of IgE production explains, in particular, the meaning of switching B cells both to IgG$_4$ (IgG$_1$ in mice), and on IgE when stimulated by the cytokine IL-4 in vitro [31, 32]. In allergy sufferers, STAT6, which is activated by IL-4, stimulates the switch to IgE. This can be explained not only by the participation of additional transcription factors, such as NFIL3 [33], which change the activity of STAT6, but also by the fact that more of the IgG$_1^+$ cells are not capable of further secondary formation of germinal centers, but instead switch from IgG$_1$ on IgE.

However, despite the presence in the literature data on increased production of IgG_4 for an allergen in patients compared with healthy donors [34, 35], we have previously shown the absence of a significant difference in the production of specific IgG in general and IgG_4 in particular, between sick and healthy donors [17], which is consistent with other literature data [18, 19].

Thus, the latest knowledge about the molecular mechanisms of switching suggests a model according to which the state of sensitization to the allergen is explained by the existence of IgG_1^+ (Human IgG_4-subclass) memory B-lymphocytes formed in germinal centers capable of rapid secondary (including extrafollicular foci) differentiation into short-lived IgE^+ plasma cells and plasmablasts during a second encounter with an allergen [15, 26]. In this case, it is memory B-lymphocytes that are responsible for maintaining the state of sensitization. Such information is obtained on models using laboratory animals [15, 26]; however, this contradicts the clinical data that indicate the absence of correlations between the production of IgE and IgG_4 in patients with various forms of IgE-dependent allergies [16–19]. In addition, despite the increase in the content of IgE in the blood upon a new encounter with the allergen, significant production of IgE persists in patients even with prolonged absence of contact with it [1, 4]. Therefore, it can be assumed that there is a different cellular mechanism associated with the preservation of the state of sensitization due to the existence of long-lived IgE^+ plasma cells. Below, we will consider the results of the work to identify such cells.

LONG-LIVING IGE$^+$ PLASMA CELLS: ARGUMENTS "PRO AND CON"

The above data on the low probability of the formation of IgE^+ B-lymphocytes within the germinal centers, apparently do not confirm the hypothesis of direct formation of IgE^+ plasma cells from naive B-lymphocytes after initial contact with the antigen. It is also important to emphasize that, according to the results obtained in the work of Yang et al., nascent IgE^+ plasma cells retain the surface expression of the membrane isoform of Ig, in contrast to differentiating plasma cells producing other classes of Ig [21]. In addition, the signaling pathway triggered by activation of the B-cell IgE type receptor by an antigen leads to a change in the intracellular localization of the anti-apoptotic myochondrial protein Hax1 and the induction of apoptosis [36]. The presented results collectively suggest that a leading role for IgE^+ long-lived plasma cells in maintaining the state of sensitization in patients with constant re-exposure to the allergen is unlikely. It has also been shown that one of the features of IgE^+ early plasma cells is a weak migration in the direction of the gradient of the chemokine CXCL12 (not associated with lower expression of its CXCR4 receptor), which prevents migration to the bone marrow and persistence there for a long time [37]; therefore, the formation of long-lived IgE^+ producing cells is very difficult, if possible. As well, IgE^+ plasma cells express less of the S1PR1 sphingosine-1-phosphate receptor required for cell exit from the germinal center and initial stages of migration from lymph nodes [36]. Recent data indicate that IgE^+ B-lymphocytes are characterized by increased expression on the surface of CD19, CD79a/b, BAFF-R, and IL4RA molecules, which induce a prolonged tonic release of calcium ions into the cytoplasm and a special variant of the calcium-dependent signaling cascade that ultimately activates calcineurin-B1–Bcl2L11 dependent apoptosis [38].

Nevertheless, the presence of relatively stable production of specific IgEs in patients with various types of IgE-dependent hypersensitivity should indicate the existence of long-lived IgE^+ plasma cells [1–4], which was also confirmed by studies on clinical material [30]. However, in this work, the analysis of the transcriptome of such cells indicated that they belonged to immature plasmablasts rather than to mature long-lived plasma cells [30]. Despite this, in some laboratory animal models of allergy, the existence of IgE^+ plasma cells was confirmed experimentally. In the food allergy model, not only the formation of IgE^+ Memory B-cells already during the primary immune response, but also their extremely long persistence in the body were found [39]. The results of a newer work indicate that with a relatively short-term (4 weeks) intake of the allergen through the mucous membranes of the body, despite the induction of a short-term IgE response, the formation of IgE-expressing plasma cells practically does not occur. With prolonged (15 week) allergen intake, their formation and migration to the bone marrow is observed, as in the case of plasma cells of other isotypes [40]. With explicit expression of the transcription factor Blimp1, which determines the development program of plasma cells, not all IgE^+ cells that migrated to the bone marrow expressed CD138, which could lead to an underestimation of their number in earlier studies [40].

It is most likely that long-lived memory B-lymphocytes, including those of other isotypes that differentiate into IgE, can participate in the generation and maintenance of specific IgE^+ production when the allergen enters the body again, and IgE^+ B memory cells. The role of these two different subpopulations in different systems may be different. Thus, it is obvious that as targets for the development of agents aimed at the elimination of IgE-producing cells and their precursors, it is necessary to choose signaling pathways that are important for the functioning of these two subpopulations.

IgE$^+$ PLASMA CELLS AND MEMORY B-LYMPHOCYTES: ASSOCIATION WITH SIGNALING PATHWAYS INVOLVED IN CELLULAR RESPONSE TO DIFFERENT TYPES OF STRESS

It is well known that signaling pathways responsible for the cellular response to different types of stress are among the universal signaling pathways that operating in many cell types. There are three main types of cellular stress: oxidative stress resulting from the damaging effect of reactive oxygen species (ROS) on various cellular structures [41], genotoxic stress arising in response to various types of DNA damage [42, 43], and ER stress (stress of the endoplasmic reticulum) caused by the accumulation of defolded proteins in the ER [44, 45]. Although they are associated with AFK activation of many signaling pathways, including antiapoptotic and MAP-kinase, which is important for immune cell proliferation [46, 47], the main specific signaling mechanism responsible for protecting cells from ROS and being activated by them is the Keap1-Nrf2-signaling pathway [48, 49]. Briefly, its essence lies in the fact that the expressed transcription factor Nrf2 in the cell cytoplasm binds to the Keap1 protein, which catalyzes its ubiquitination and degradation. ROS oxidize the free thiol groups of Keap1 cysteine residues, which leads to a decrease in its affinity for Nrf2 and dissociation from the latter, as a result of which Nrf2 accumulating in the nucleus and activates the expression of genes for antioxidant defense enzymes [48, 49]. The main "players" in the cellular response to DNA damage are ATM and ATR serine/threonine kinases, as well as DNA protein kinases, whose target phosphorylation stops the cell cycle and triggers the expression of components of the DNA repair system [50]. Finally, "classic" ER stress activates three different independently activated signaling pathways: RE1a-dependent, PERK-dependent, and ATF6a-dependent [51, 52]. At the same time, IRE1a, having endonuclease activity, not only reduces the total mRNA pool in cells and reduces protein synthesis, but is also responsible for specific splicing of the XBP-1 transcription factor mRNA, enhancing its expression and accumulation. One of the targets of XBP-1 is the DNA sequences encoding the GRP78 molecular chaperone, as well as the CHOP protein, which has pro-apoptotic activity. The accumulation of defolded proteins induces the dissociation of GFP78 from its complexes with the lumenal domains of the IRE1a and PERK proteins in the ER. This leads to a change in the conformation of the latter, oligomerization, and autophosphorylation, which triggers the corresponding signaling pathways. PERK is a kinase that phosphorylates the factor eIF2a, which stops the synthesis of most proteins, with the exception of some proteins that perform a pro-apoptotic role [51, 52]. ATF6a is a transmembrane protein of the Golgi apparatus, which, when the ER is stressed, undergoes limited proteolysis, as a result of which its part facing the cytoplasm dissociates and is transported to the nucleus, where it acts as a transcription factor. Signaling pathways involving IRE1a and ATF6a mainly perform an antiapoptotic function and are responsible for enhancing the synthesis of chaperones and ER lipids. If ER stress persists, then CHOP initiates apoptosis in the cell.

It is known that the above signaling pathways play a very important role in regulating the function of adaptive B and T lymphocytes. For example, oxidative stress of moderate intensity is required to induce the differentiation of antibody-producing cells [53]. Oxidative stress in T-lymphocytes stimulates the production of IL-4 [54]. Low-intensity genotoxic stress in B-lymphocytes stimulates the differentiation of germinal centers, and in the case of higher intensity, it can inhibit this process (by phosphorylation of the Bcl6 factor by ATM kinase and its subsequent degradation) [55, 56]. The induction of homeostatic ER stress is part of the normal developmental program for plasma B cells. In the classical version, differentiation of plasma cells is associated only with the activation of IRE1-dependent and ATF6-dependent signaling pathways that promote survival [57]. A positive correlation between IgE secretion and CHOP and GRP78 expression was recently found in nasal samples from patients with allergic rhinitis, suggesting an additional PERK-dependent pathway in IgE production [58]. Taking into account the unique structure of IgE molecules and the features of the processes of maturation of their affinity it remains to be seen which of the stress EPR branches dominates IgE$^+$-producing in cells.

It is very important that the processes in tissue cells exposed to agents that induce cellular stress can also have a stimulating effect on the synthesis of pro-allergic antibodies. Reactive oxygen species can damage cells of the epithelial barrier [59], which leads to the release of alarmins (ATP [60], uric acid [61] and others) and production of tissue cytokines (IL-33 and thymic stromal lymphopoietin) [62], activating various parts of innate and adaptive immunity towards the development of type 2 inflammation [62]. In fact, in laboratory animal models of allergy, the association of allergic inflammation with not only tissue oxidative stress [59, 63], but also with genotoxic [59, 64] and ER stress [65] has been confirmed.

According to one of the leading hypotheses developed in the literature since the early 2000s, the increase in the number and prevalence of allergic diseases in developed countries is due to the adverse effects of air pollutants, especially particles that are products of incomplete combustion of diesel fuel and their components, polycyclic aromatic hydrocarbons (PAH), on the immune system [3, 67, 68]. In recent studies, it was found that PAHs adsorbed on particles have adjuvant activity that enhanced the formation of IgE production and the development of asthma in mice [69]. In addition, the prototype PAH

benzo(a)pyrene is capable of inducing allergic inflammation similar to arising under the influence of whole particles [70–73], which was confirmed by us in recent experiments (the results are being prepared for publication). We also revealed the adjuvant properties of diesel fuel particles on the induction of allergen-specific antibodies [74]. It is also known that excess body weight and associated processes in adipose tissue are the cause of increased symptoms of allergic diseases [75, 76]. It is believed that both in the case of induction of inflammation under the action of aeropollutants [77] and in the case of obesity [78], it is the cellular response to oxidative stress and, consequently, to the associated genotoxic stress [65] that can play the leading role in the initial stages and ER stress [66]. Thus, the signaling pathways responsible for the cellular response to these types of stress are the first candidates in the search for molecular targets for the etiotropic therapy of IgE-dependent pathologies.

It is known that AMP-dependent protein kinase (AMPK) regulates both the formation of memory B-lymphocytes after the reaction of the primary immune response and plasma cells. In the case of plasma cells, it suppresses their production of immunoglobulins and, by inhibiting mitophagy, leads to the accumulation of reactive oxygen species in cells, which causes their death. In the case of memory B cells, in contrast, it is necessary for their differentiation [79]. Thus, the effect of AMPK on the secondary immune response may differ depending on which cells it is predominantly active in. Despite this, the AMPK-dependent signaling cascade is also quite universal in memory B-lymphocytes and plasma cells. In T-lymphocytes, this enzyme also plays an important role, stimulating Bcl6 expression and subsequent differentiation into T-follicular helpers [80]. If we take this into account and assume that extrafollicular activation, but not the activation of germinal centers, plays a predominant role in the production of IgE (which has been shown by others [28, 29] and by us [81]), it can be assumed that AMPK activation should inhibit the production of IgE pro-allergic IgE antibodies because: (1) AMPK-dependent differentiation of T-follicular helpers [80], which are important components of the germinal center reaction [10, 11], can potentially shift the activation of B-lymphocytes towards the formation of germinal centers due to an increase in the probability of formation of contacts between B-lymphocytes with an increased number of T-follicular helpers and (2) AMPK inhibits the production of immunoglobulins by terminally differentiated plasma cells [79]. According to the initially obtained data, knockout of AMPK kinase in B-lymphocytes does not significantly affect the primary immune response to the T-dependent antigen [82]. However, more recent work suggests that this selective knockout results in a small but significant enhancement of the primary immune response to NP-KLH [83]. Thus, systemic administration of the AMPK AICAR activator dominates the effect associated with the function of T-lymphocytes [80], and T-lymphocytes are activated [80] dependent immune response, which is explained indirectly through the activation of T-follicular helpers [80]. However, if the dominant role in the secondary immune response to the allergen belongs to IgG_1^+ memory B cells that differentiate into IgE producers, as in the work of J.S. He [26], in this case, AMPK activation may be necessary for IgE production. This also follows from the results of the work of the RMBoothby group, according to which the activity of AMPK kinase in memory B-lymphocytes is important for their survival [83]. Perhaps, there is another way in which AMPK activation can indirectly influence IgE production and allergic inflammation in general. It is known that activation of this kinase in B-lymphocytes is important for the induction of expression of the IgD isoform of the B-cell receptor [82]. Recent work has shown that the secretory isoform of IgD binds to basophils (but not mast cells) and, in the presence of an antigen, induces the secretion of BAFF by basophils (triggers the isotype switch itself in general) and IL-4 (determines the direction of the switch to the IgE isotype), and stimulates 2-th type of immune response to an allergen [84, 85].

The AMPK-dependent cascade is a kind of "hub," the activity of which regulates the formation of reactive oxygen species (oxidative stress) and the cellular response to ER stress, on the one hand, and, on the other hand, is itself regulated by cellular stress signaling pathways. Thus, depending on the circumstances, it can be activated or inhibited by reactive oxygen species [86, 87], activate the expression of chaperones that protect the cell from ER stress [88], and be activated by genotoxic stress [89]. It is important that Lkb1 kinase, which plays the leading role in the regulation of AMPK kinase, in B lymphocytes is itself regulated by genotoxic stress (it is activated in turn by ATM kinase) [55, 90]. The most important role in its regulation is played by the intensity of metabolism, which is determined by an increase in the AMP/ATP ratio [91].

Another signaling pathway, PI3K-Akt-mTOR signaling, is associated with AMPK kinase. Activation of PI3K (phosphatidylinositol-3-kinase) induces the activation of Akt-kinase in cells. This kinase phosphorylates AMPK and thus inhibits its activity. [92]. On the other hand, AMPK suppresses the activity of the mTORC1 protein complex [92]. As shown in recent work, the signaling pathway from PI3K and the processes associated with a long-term increase in the concentration of calcium ions in the cytoplasm of the cell are very important both for the formation of IgE^+ B-lymphocytes, and IgE producing plasma cells [38]. The effect of the PI3Kδ isoform on the regulation of local allergic inflammation in asthma was studied [94], which suggests that PI3Kδ may play a leading role in the synthesis of IgE during the primary and secondary immune response to an allergen.

Thus, the signaling pathways responsible for the cellular response to various types of stress, PI3K- and AMPK, can be considered promising in the search for molecular targets for the etiotropic therapy of IgE-dependent pathologies. Interestingly, although the effect of pharmacological modulators of these signaling pathways on the content of IgE producers and their precursors has not been studied in sufficient detail, a number of such pharmacological modulators have already shown their therapeutic effect in various models of allergic inflammation and clinical studies. Thus, various studies have shown the therapeutic effects of various low-molecular-weight antioxidants, for example, in [95–98]. Administration of the pharmacological inhibitor of DNA protein kinases NU7441 to BALB/c mice inhibited the development of asthma symptoms in the ovalbumin induction model [99]. In a model of asthma induced by house dust mite allergens, a therapeutic effect was shown by the so-called "chemical chaperones," that is, taurodeoxycholic acid (TUDCA) and structurally related molecules that prevent the defolding of ER proteins and inhibit the ATF6a signaling pathway [100, 101]. The results of [102] show the potential use of selective inhibitors of IRE1a and PERK signaling in the treatment and prevention of contact dermatitis. Finally, the selective PI3Kδ inhibitor IC87114 has also been shown to be effective in a model of LPS-ovalbumin-induced asthma [103].

Further research is needed to determine how these components affect IgE^+ cells and their precursors, IgE production, not only in the primary, but also in the secondary response to the allergen, which is important for further evaluation of the prospects for their use in clinical practice.

NANOPARTICLES BASED ON INORGANIC COMPONENTS AS PERSPECTIVE MEANS OF NON-SPECIFIC THERAPY FOR IgE-DEPENDENT PATHOLOGIES

When discussing potential promising innovative therapies for IgE-dependent pathologies, one cannot fail to mention nanoscale objects, that is, objects of bionanotechnology. Among numerous nanostructures, nanoparticles based on inorganic components, metals and their oxides, as well as nonmetals, are relatively inexpensive, easy to obtain, and easy to standardize. Particles based on noble metals, such as gold [104], silver [105], and platinum [106], are most often used in biomedicine, but particles based on metal oxides, such as titanium [107], iron [108], etc., are also used. Among nonmetallic inorganic nanoobjects, selenium-based nanoparticles [105, 106], carbon nanotubes [111], and fullerenes [112, 113] are most often mentioned. It is important that one of the main mechanisms of action of most known nano- and microparticles on the body is the induction of oxidative stress, which is usually associated with the nonenzymatic formation of ROS on the surface of nanoparticles [114]. It is in this context that it is very appropriate to mention nanoparticles in the framework of this review. Thus, a similar effect has been shown for nanoparticles of gold [115], silver [116], copper oxide [117], iron oxides [118], titanium oxide [119], carbon nanotubes [120, 121], and graphene-based nanostructures [122]. Obviously, the effects of such ROS depends on the intensity of their formation (dose of particles) and, in principle, can be identical to the effect of ROS generated enzymatically during the immune response. At the same time, it is known that a significant antioxidant effect of a number of nanoparticles was obtained in a number of experiments. This primarily applies to nanoparticles based on selenium [123] and cerium (IV) oxide [124, 125] (selenium compounds are generally known as antioxidants, while cerium in the composition of cerium(IV) oxide nanoparticles can change the oxidation state from "+4" to "+3"). According to most studies, fullerene-based nanostructures also have antioxidant properties [126–128]. The presence of antioxidant properties in platinum nanoparticles has been claimed [129]. As is known, oxidative stress is strongly associated with genotoxic stress and ER stress.

Based on what was said in the previous section, it would be most logical to assume that nanoparticles with antioxidant properties can be considered as a means of nonspecific therapy for IgE-dependent pathologies. In fact, the effect of suppressing the symptom complex of allergic asthma in a mouse model has been shown in the case of fullerene nanostructures [127, 128, 130]. In the case of selenium nanoparticles, studies on models of asthma and allergy have not been carried out, but their inhibitory activity against other inflammatory pathologies, in particular, rheumatoid arthritis, has been shown [131].

There is also information about the therapeutic effect of gold nanoparticles, which are most often used in biomedical work and have a prooxidant effect. This follows from the results of a recent study published in 2022, according to which gold nanoparticles, when inhaled to BALB/c mice 1 hour before sensitization, inhibited the development of ovalbumin-induced glucocorticoid-resistant inflammation in an asthma development model [132]. The effect was associated with the induction of the Nrf2 signaling pathway, which restores redox homeostasis. This effect, taking into account the prooxidant properties of gold nanoparticles as such, seems quite unexpected. Nevertheless, these data are consistent with the results of [133], in which long-term administration of small doses of particles, products of combustion of diesel fuel, induced in the lungs of mice the expression of components of the antioxidant defense enzyme system (regulated by the Nrf2 factor) and proteasome components responsible for the degradation of defolded proteins, which provides protection against large doses of such particles. Here, the so-called "pre-adaptation"

effect, or the hormesis effect, previously described by Lucky [134–136] for cases with ionizing radiation, can be observed. In this case, hormesis should be considered as a stimulating effect. Moderate doses of stressors (insufficient doses, which is extremely important for the development of a pathological effect) is expressed in "pre-adaptation" of the acquisition by the body of resistance to large doses of a stressor. In the case of the effect of gold nanoparticles, small doses of such particles contributed to hormesis with the acquisition of body adaptation to oxidative stress caused by antigen provocation in an asthma model [134]. It is quite possible that a similar effect was observed earlier by another group in the case of silver nanoparticles injected a few days before antigen challenge, although the authors believed that this was due to the direct antioxidant effect of the latter [137].

It should be noted that the attractiveness of nanoparticles based on inorganic materials as nonspecific therapy for IgE-dependent pathologies lies in their relatively slow clearance when administered through the respiratory system or even systemically. Thus, according to recent results, with the systemic administration of gold nanoparticles with different coatings, their concentration in internal organs (liver, spleen, and kidneys), which reached a maximum in the first 30–60 minutes after administration, did not decrease significantly within 4 weeks, and after administration intranasally their half-life from the lungs reached 180 days in some cases [138–141]. The accumulation of such particles occurs mainly in cells that perform a phagocytic function [138, 139].

At the same time, the effect of such nanoparticles on the body can actually last even longer. Recently, the concept of "trained" innate immunity (trained immunity) has become very widespread in the scientific community, which consists in the fact that cells (mainly macrophages and monocytes were studied) treated with TLR or NLR receptor agonists change their epigenetic program so that they respond more strongly or weakly to the action of the same (or similar) stimulus [142–145]. The change in the epigenetic program is associated with a change in cell metabolism, that is, a change in the balance between aerobic and anaerobic glycolysis in them, and is quite stable [144]. Such a phenomenon, if the doses of the stimulus in the case of the first contact are small, can also be considered as a variant of hormesis within the immune system. It is important that not only PRR receptor ligands, but also gold nanoparticles (and most likely other noble metals) can act as the primary stimulus, which has been shown in [146, 147]. In this case, induction of tolerance takes place to a greater extent, with a decrease in the ability to synthesize pro-inflammatory cytokines and secondary stimulation [146]. Although all this work has been done in vitro and ex vivo, and the results need to be confirmed in the system in vivo, they nevertheless seem quite promising. Such an approach can be easily used not only for therapy, but more importantly, for the prevention of IgE-dependent pathologies in individuals predisposed to them. Based on the foregoing, the effect of noble metal nanoparticles in these cases on the formation of IgE production, allergic inflammation, can include two components: (1) the general effect of hormesis, that is, "pre-adaptation," expressed in an increase in the body's resistance to oxidative stress that accompanies local inflammation and (2) the effect of "trained" innate immunity, which is a special case of hormesis in relation to the cells of the immune system.

The main cells with phagocytic activity against such nanoparticles are the cells of the phagocytic system, that is, macrophages and dendritic cells [104, 148]. B-lymphocytes are not specialized phagocytes, but have the ability to absorb large particles [149]. The results of a recent work published in 2022 indicate the ability of polyethylene glycol-modified gold nanoparticles to bind and then endocytose a specific subpopulation of aging-associated B-lymphocytes with the $CD19^+$ phenotype, $CD3^-CD11b^-CD11c^+$, and to a lesser extent with the $CD19^+$ subpopulation, $CD138^+$ plasmablasts, and immature plasma cells [150]. Importantly, there are reasonable assumptions regarding the first subpopulation that they are in fact memory B lymphocytes [151]. According to recent data, the bulk of IgE precursors$^+$ B-lymphocytes formed extrafollicularly in nasal polyps also express the CD11c marker [29]. This means that IgE^+ precursors and early IgE^+ B-lymphocytes may be among the few B-lymphocytes that can effectively absorb inorganic nanoparticles, and thus the latter can have a direct effect on them.

Recently, compounds and complexes of the rare earth metals lanthanides have become of particular interest for biomedical research. In 2008, Japanese scientists were among the first to obtain and characterize self-organizing nanostructures based on lanthanide cations and guanine dinucleotides [152]. In 2022, similar complexes were obtained by Chinese researchers, while monomeric AMP, GMP, and a mixture of them were used as ligands of lanthanide complexing agents [153]. Such complexes are formed due to covalent and donor–acceptor bonds of lanthanide cations with oxygen atoms of phosphorus residues of mono- or oligonucleotides, and nitrogen atoms N7 of purine residues [153]. Complexes of lanthanides (in particular, europium and other elements of this family) with a mixture of AMP and GMP (containing three trivalent lanthanide cations and two molecules of AMP and GMP each) formed nanosized structures capable of encapsulating the antigen (ovalbumin) in their composition. Such nanostructures, when administered subcutaneously to C57BL/6 mice, accumulated to a greater extent in regional lymph nodes, but not in the liver, and induced the production of protective antibodies of the IgG_1, IgG_{2a}, and IgG_{2c} classes, as well as the production of interferons, especially IFNγ, which

is responsible for the formation of a stable type I immune response [153].

In this study, a complex that mimics the molecule of cyclic guanosine adenosine monophosphate, the STING activator, was chosen as an immunostimulatory ligand [153]. Data on the effect of STING activation on the formation of allergic inflammation indicate its important stimulatory, but not inhibitory, role in the development of the latter [154, 155]. In this regard, as a means of therapy and prevention of allergic pathologies, the best solution would be to use complexes of lanthanides with other oligonucleotide ligands, in particular with CpG oligonucleotides, which have a pronounced suppressive effect on IgE production and allergic inflammation, stimulating the development of the first type of immune response, and in a number of cases, the production of immunosuppressive IL-10 [156–158]. However, such complexes, their stability, and properties have not yet been characterized in biomedical studies.

It is important that the introduction of small doses (1–1.5 orders of magnitude lower than those that induce pathological processes) of lanthanides can also induce hormesis. In a study by another group of Chinese scientists, it was found that small doses of Ln^{3+} cations administered for 30 days prior to the administration of a large dose of ethanol caused the induction of the Nrf2 factor and protected animals from oxidative stress [159]. In this regard, it can be assumed that in the case of a complex of a lanthanide and a ligand that suppresses allergic inflammation (CpG oligonucleotides or others), a double effect can be achieved, causing the prevention of allergic inflammation, that is, that due to the properties of the ligand itself, and the hormesis effect caused by the lanthanide.

These data do not exhaust the full potential of using nanomaterials as a means for the prevention and treatment of allergic pathologies; these are just some of the most striking examples of potential candidates.

At the same time, it should be taken into account that when using such drugs, it is necessary to strictly adhere to a certain "window" of therapeutic doses, since such nanomaterials, in particular, nanoparticles of noble metals and lanthanides, exhibit toxicity at high concentrations [114, 160]. In addition, there is a certain range of nanomaterials that are generally poorly suited for the treatment of IgE-dependent pathologies, since they are more likely to exacerbate allergic inflammation or are themselves its triggers. Such structures include nanoparticles based on metal oxides, aluminum, titanium, and nickel [161], cerium oxide [162], and some carbon nanotubes [120, 121].

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The data presented in this review indicate the possibility of the formation of IgE production during the extrafollicular response. In maintaining the state of IgE-dependent sensitization of the body, both IgE^+ memory cells, and B-lymphocytes expressing other isotypes, but quickly switching on the synthesis of IgE during the secondary immune response to the allergen. As therapeutic targets for the deletion of the above subpopulations, it is convenient to use target modulators, components of signaling pathways that regulate both the physiology of memory B-lymphocytes and plasma cells. Such targets include components of signaling pathways responsible for the cellular response to oxidative and related genotoxic stress and ER stress, which affect B-lymphocytes and plasma cells, including through the regulation of AMP-kinase. Pharmacological modulators of these signaling pathways are promising candidates for the treatment of IgE-dependent pathologies. Various nanoparticles, in particular, based on noble metals, or nanocomplexes based on lanthanides, can be used as such agents, due to their potential effect on the Nrf2 signaling pathway responsible for the induction of the expression of antioxidant enzymes. Due to a long half-life from the body and the ability to induce the phenomenon of "trained" innate immunity, nanoparticles can have a rather long-term effect, and therefore they are promising for use as a means of preventing allergic pathologies. Their use, however, requires strict application within the "therapeutic" window to avoid toxic effects. Numerous independent studies of their effect are required in vivo to confirm their safety and effectiveness.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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