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Review

# Guardians and Conductors of Immunity: Natural Immune System in Health and Autoimmunity

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**Abstract:** Natural autoantibodies (nAAbs) recognize self-antigens and are an important component of the immune system have evolved from invertebrates to vertebrates and are viewed as stable byproducts of immune function to essential players in health and disease. Initially characterized by their conserved nature and multi-reactivity, primarily as IgM isotypes, nAAbs are now recognized for their adaptability in response to infections and vaccinations, bridging innate and adaptive immunity. The nAAbs and the cellular elements, such as  $\gamma\delta$ -T, *i*NKT, and MAIT cells of the natural immune system, perform a primary defense network with moderate antigen-specificity. This comprehensive literature review was conducted to analyze the role of natural autoantibodies (nAAbs) in health and disease. The review focused on research published over the past 40 years, emphasizing studies related to infectious diseases, vaccinations, and autoimmune disorders. Recent studies suggest that nAAbs engage in complex interactions in autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and type 1 diabetes. Their roles in immunological processes, such as maternal tolerance during pregnancy, further underscore their complexity. Emerging evidence indicates that nAAbs and the cellular elements of the natural immune system may contribute to both disease pathogenesis and protective mechanisms, highlighting their dual nature. Continued research on nAAbs is vital for improving our understanding of immune responses and developing therapeutic strategies for autoimmune disorders and infectious diseases.

**Keywords:** natural immune system; natural autoantibodies (nAAbs); immune function; autoimmunity; Systemic lupus erythematosus; Rheumatoid arthritis; Systemic sclerosis; Type 1 diabetes; innate immunity; adaptive immunity; immunological tolerance; infectious diseases; pathogenesis; compensatory mechanisms; IgM isotype; therapeutic strategies

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## 1. Introduction

When Irun Cohen proposed to revise the clonal selection theory and replace it with the cognitive paradigm, there was already a lot of data on natural autoimmunity [1]. It has long been known about the presence of autoantibodies in the blood serum of healthy individuals without clinical symptoms of autoimmune diseases.

The study of natural autoantibodies (nAAbs) has evolved significantly over the past few decades, prompting a deeper exploration of their multifaceted roles in health and disease. Historically viewed as static byproducts of immune function, nAAbs are now recognized for their dynamic contributions to immune regulation, autoimmunity, and vaccination responses. Recent studies focusing on the natural immune system have led to a better explanation of the biological role of the interaction between nAAbs and the cellular components of the immune system.

Specialized subsets of cellular immunity have been described over the last few decades. The evolutionary aspects of some T cell subpopulations with invariant T cell receptor chains were clear, but their role in immune regulation was not known. Similarly, the potential interactions of the gamma-delta ( $\gamma\delta$ ) T, invariant natural killer T-cells (iNKTs), and mucosa-associated invariant T-cells (MAIT) cells with the nAAb network and nAAb-producing B1 cells were studied only recently.  $\gamma\delta$  T cells, iNKTs, and MAITs are subgroups of (unconventional) innate-like T cells, collectively making up ~10–30% of the total T cell compartment [2] and performing many roles the innate immune system does, but also phenotypically resembling and having strong ties to cells of the adaptive immunity [2,3]. On the other hand, literature is scarce about the connections these innate-like T cells might have with the nAAb network and the innate-like B cell subgroup, the B1 cells.

The present paper aims to help better orientation in the vast and heterogeneous literature on cellular and humoral components (nAAb network) of the natural immune system, often characterized by contradictory findings, and in order to clarify their complex role in different immunological contexts. By mapping the scientific advances in nAAb research along a timeline, we aim to highlight gaps in knowledge, guide future investigations and emphasize the potential of nAAb network as biomarkers and therapeutic targets in autoimmune and infectious diseases.

## 2. Cellular and Humoral Components and Their Role in the Natural Immune System

### 2.1. Potentially Mutual Influence of $\gamma\delta$ -T-cells and nAAb Network

Gamma-delta ( $\gamma\delta$ ) T cells, which make up about 0.5–10% of circulating lymphocytes, act as a connection between innate and adaptive immunity due to their unique properties [4]. These cells play a significant role in supporting immune defense, tumor surveillance, and B-cell maturation, as well as being involved in autoimmune responses [4].  $\gamma\delta$  T cells recognize the antigen in natural form and do not require antigen presentation by the major histocompatibility complex (MHC) [5]. They aid in the maturation of autoreactive immature B cells in the spleen by providing key signals—such as IL-4 production and CD30L interaction—that encourage B cells to develop into antibody-producing cells capable of recognizing a broader range of antigens [4]. In  $\gamma\delta$  T cell-deficient models, immature B cells were found to stall in their development, which suggests  $\gamma\delta$  T cells are crucial in maintaining proper B-cell maturation, potentially impacting autoimmune processes when absent or dysfunctional [4].

In contrast to most unstimulated  $\alpha\beta$  T cells, which are antigenically naive and metabolically inactive, many peripheral  $\gamma\delta$  T cells in non-immunized mice are already in a state of moderate activation [6], and there are clues that  $\gamma\delta$  T cells continuously affect the nAAb repertoire in mice; thus there might be a connection to B-1 and marginal zone (MZ) B-cells [7]. However, this might be a dynamic bidirectional connection, as nAAb network help opsonize dead or damaged cells and pathogens, marking them for clearance by phagocytes. The  $\gamma\delta$  T cells may respond to this clearance process, recognizing the cellular stress signals produced during phagocytosis. This process can create a local environment rich in cytokines and chemokines, which may activate  $\gamma\delta$  T cells, prompting them to produce inflammatory cytokines (e.g., IL-17, IFN- $\gamma$ ) that further modulate the immune response [8,9]. The  $\gamma\delta$  T cells can also present antigens and release cytokines that modulate both innate and adaptive responses. If  $\gamma\delta$  T cells recognize stress or microbial signals in an environment where nAAb network have already marked pathogens or apoptotic cells, they may be further activated to recruit more immune cells or enhance the antibody production by B cells [9–11]. On the other hand,  $\gamma\delta$  T cells can help counterbalance potential autoimmune activation by nAAb network against self-antigens via regulatory cytokines (such as IL-10). This regulation could be particularly relevant in preventing excessive inflammation or autoimmunity when nAAb network bind to self-antigens, as seen in chronic inflammatory conditions or autoimmune diseases [12–15].

## 2.2. Connections of *i*NKT and B-1 Cells

*i*NKTs are capable of detecting glycolipids on non-polymorphic MHC class I-like molecule, CD1d, with a T-cell receptor composed of a moderately variable  $\alpha$  chain and a mostly germline-defined  $\beta$  chain [16]. Similarly to conventional T-cells, *i*NKTs also have many subgroups, each presenting different and specific functionality [17]. The general function of *i*NKTs involves mounting an early and rapid immune response to pathogens until the adaptive immune response is deployed [16–18], but they also have key regulatory roles in autoimmunity, cancer, infection, and tolerance [19], and bystander activation of both CD8+ and CD4+ memory T cells, contributing to immunological memory maintenance [20]. There might be a multi-level interaction between B-1 cells and *i*NKT, consisting of antigen presentation, cytokine signaling, and nAAb-mediated feedback.

Many cells present CD1d; however, antigen-presenting cells have upregulated expression, and among all, marginal zone (MZ) B cells (CD21<sup>hi</sup>CD23<sup>lo</sup> IgM<sup>hi</sup> IgD<sup>lo</sup>) and B-1 cells stand out in the level of expression in mice and humans [21–23], marking the potential of MZ or B-1 mediated antigen presentation to *i*NKT cells. CD1d cycle from the cell surface back into an endosomal network, where they are loaded for presentation within the same endosomal and lysosomal compartments that process foreign protein antigens [23]. In these compartments, CD1d replaces its glycolipid ligands with either endogenous or externally derived lipids before returning to the cell surface [23].

Considering cytokine interactions, *i*NKT has a regulatory-supportive role in many B cell subgroups, including autoreactive B cells [24]. In contact sensitivity, a study [25] found that antigens and IL-4 from *i*NKT activate B-1 cells via the STAT-6 signaling pathway as part of a cooperative interplay between *i*NKT and B-1 cells.

On the level of autoantibodies, an *in vitro* study showed that physiological doses of polyclonal IgM inhibit  $\alpha$ -gal-ceramide induced IFN- $\gamma$  production of *i*NKT [26,27]. Related studies suggest that activated *i*NKT plays a role in murine renal ischemia, which IgM nAAbs do not mediate directly, but IgM nAAbs protect against it through the regulation of *i*NKTs, although the exact mechanism is unknown, only suggested to involve receptor inhibition [27].

## 2.3. Conjecture of MAIT and B-1 Cell Interaction

Both B-1 lymphocytes and mucosal-associated invariant T (MAIT) cells are primarily present around the barriers: B-1 is predominantly in peritoneal and pleural cavities with a small portion in the lymph nodes, and spleen [28] and MAIT cells are present around the mucosal surface, lungs, liver, and blood with importance in host defense and tissue repair [29–32]. MAIT performs innate-like as well as Th1- or Th17-like functions depending on TCR-dependent or independent activation [30]. MAIT cells express a semi-invariant TCR $\alpha$  chain that recognizes small molecules, such as pterin analogs and riboflavin metabolites, presented by the non-polymorphic MHC class I-related molecule, MR1 [33].

MAIT cells can activate B-2 cells and influence antibody production, class-switch and memory B cell formation [34,35]. A subgroup of MAIT has TCRs crossreacting with self-structures and is proposed to have regulatory functions in immune homeostasis and involvement in pathological processes [36]. To date, potential B-1 and MAIT cell interplay is a blindspot of literature, but it remains an exciting conjecture that these cells, on the basis of self-recognition, might have interaction with nAAb-producing B-1 cells.



#### 2.4. B-1 Cells and Natural Autoantibodies (nAABs)

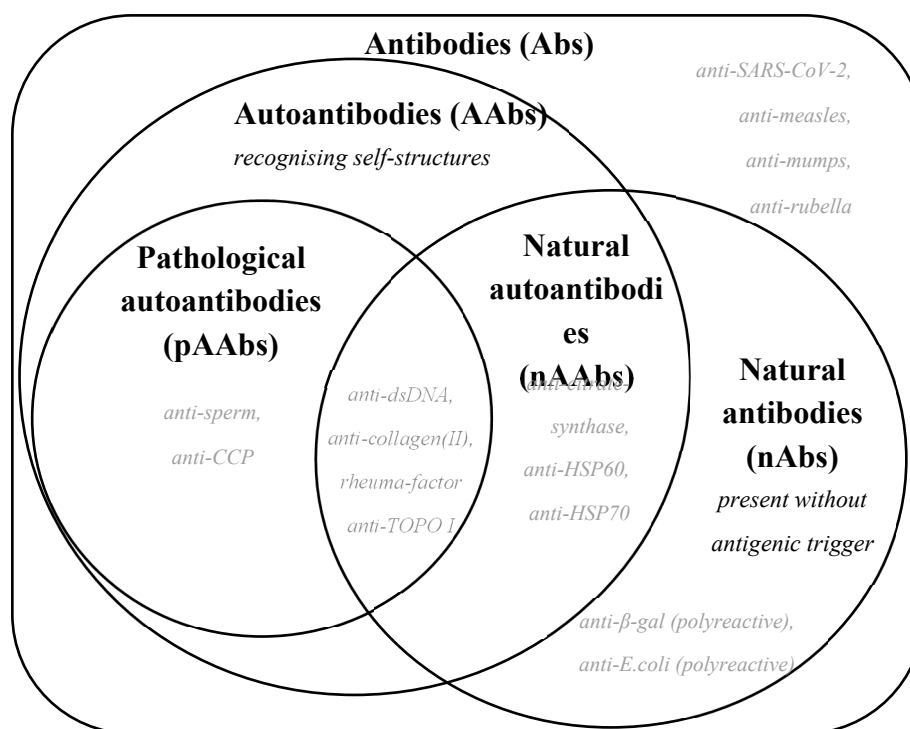
Human B-1 cells, originating mainly in the fetal liver, are found in the serous layer of body cavities and mucosal tissues, playing a pivotal role in early immune defense. Identified in both mice and humans, B-1 cells are marked by the CD20<sup>+</sup> CD27<sup>+</sup> CD43<sup>+</sup> CD70<sup>-</sup> profile in humans, contributing to immunity by remarkable phagocytic activity resulting in antigen presentation on both MHC class I and II [37–39] and production of broad-reactivity antibodies, influencing T-cell activity, and targeting conserved antigens [37–42]. B-1 cells can further be divided based on cell surface expression of CD5 (CD5<sup>+</sup> B-1a and CD5<sup>-</sup> B-1b cells) [43]. In comparison to B-1a, cells of the B-1b subset have higher IgM production but milder inducibility by LPS [44,45]. B-1b also has an enhanced CCR6-regulated migration to the spleen [45]. Vergani et al. (2022) [46] performed a time-stamping experiment on mice B-cells, resulting in new insights that challenge the mainstream idea that B-1 cells are naïve and Ig production is unbiased by antigens [40,47]; instead. They proposed that B-1 activation happens in a predominantly neonatal developmental window shared with other antigen-experienced memory B cell compartments prior to the activation of B-1 cells by self-antigens and foreign antigens. Specifically, B-1a cells shall be accounted for as predominantly neonatally induced IgM memory subsets with self-sustaining capabilities, but this scheme can be helpful to study B-1b, MZ B, iNKT, and MAIT cells as well [46].

Both B-1 cell subsets produce natural antibodies that recognize both protein and non-protein antigens, showing promise for T-independent responses and vaccine development, especially against resistant bacteria [48]. In infections such as *Borrelia* and SARS-CoV-2, B-1-derived antibodies rapidly target stable antigens, providing adaptive-like immunity and cross-reactivity with unrelated pathogens. This flexibility, unlike the specificity of B-2 antibodies, allows B-1 nAABs to adapt to evolving pathogens, potentially offering sustained immune coverage and relevance for immunotherapy [37–42,48–61].

#### 2.5. Role of Natural Autoantibodies (nAABs)

One way to look at physiological autoimmunity is the so-called immune computation model [62]. The immune system, consisting of innate and adaptive receptors and effectors, processes molecular signals reflecting the body's condition—such as infection, trauma, malignant transformation, or cellular aging. Based on predefined rules, it computes a molecular- and cellular-level response that leads to outcomes like cell death, proliferation, differentiation, migration, and blood vessel formation, ultimately promoting healing, tissue remodeling, or contributing to disease. This process also allows the immune system to adjust its rules for future responses.

Antibodies serve as essential molecular mediators between the organism, its immune system, and both symbiotic (microbiome) and pathogenic foreign entities, functioning at cellular and molecular levels. While the complete functional characterization of the entire antibody repertoire (the “antibodyome”) remains unfinished, immunoglobulins can be classified based on their origin and target (**Figure 1**). Serological assessments offer an indirect but valuable representation of numerous underlying immunological processes, many of which cannot be fully understood by clinical manifestations alone.



**Figure 1.** Venn-diagram showing definitions of antibody classification according to their origin and target. Bold text shows the terminology and abbreviation, and definitions are recited with italics. Each set shows a few potential examples with grey italics text; however, it is worth noting that literature has limited information on the exact mechanism of generation of these antibodies and the links to disease or health.

## 2.6. Natural IgM Autoantibodies

Natural antibodies are produced without (known) antigenic stimulation, unlike adaptive antibodies generated by B-2 lymphocytes with T-cell help. In humans, B-1-like cells, constituting a large portion of the umbilical cord, and adult circulating B cells resemble the self-reactive B-1 population in mice, suggesting an early immune role [41,63,64]. B-1 cell identity, linked to its B cell receptor (BCR), can be transferred to non-self-reactive B-2 cells through allelic replacement, further demonstrating BCR's role in B cell function and development [65].

Most natural antibodies are natural autoantibodies (nAAbs) that bind to self-structures like damage-associated molecular patterns (DAMPs), cytoskeletal proteins, and mitochondrial proteins, forming a broad, low-affinity immune network [65–67]. nAAbs predominantly belong to the IgM isotype and are polyspecific, recognize repetitive patterns efficiently (making them similar to receptors of the innate immune system, eg. TLRs), and derive from nearly unmutated germline genes [68–71].

IgM natural autoantibodies (nAAbs) are polyclonal and polyreactive, targeting conserved self-antigens and pathogen-associated patterns similar to innate immune receptors. Specific IgM nAAbs, like anti-phosphorylcholine, can recognize AB0 antigens, endotoxins, and apoptotic cell markers but not nuclear antigens or IgG, exemplifying that each IgM nAAb has a specific recognition pattern [66,72,73].

These IgM nAAbs play a dual role: they neutralize pathogens and toxins while aiding in the clearance of apoptotic cells, reducing inflammation, and preventing pathogenic IgG autoantibody induction [40,74].

Unlike adaptive antibodies, IgM nAAb levels do not necessarily rise with autoantigen levels, allowing for continuous production by B-1 cells independent of antigen exposure [66]. Some IgM nAAbs can bind to and neutralize self-reactive IgG, mitigating autoimmune risk, although certain conditions—like Hepatitis C infection—can lead to the formation of immune complexes that may cause kidney and skin complications [67,71,75–83].

## 2.7. The Dual Nature of Natural IgG Autoantibodies: Implications for Immune Tolerance and Autoimmune Disease Development

IgG natural autoantibodies (IgG nAAbs) exist in normal serum but are often masked by anti-idiotypic IgM nAAbs. Like IgM nAAbs, IgG nAAbs can bind conserved self-antigens, with around 15–20% of murine IgG showing polyreactivity, primarily in the IgG3 isotype produced by B-1 cells [71,81,84–86]. IgG nAAbs become active in mice after exposure to gut bacteria and in humans after around two years, with infections further increasing their levels [87–92].

Intravenous immunoglobulin (IVIG) therapy, rich in IgG nAAbs, has been effective in treating autoimmune diseases like Myasthenia gravis and Rheumatoid arthritis. IVIG's effects may involve various mechanisms, including idiotype-targeting and receptor modulation [93,94]. However, certain IgG nAAbs may signal a loss of immune tolerance, potentially leading to pathological class-switched autoantibodies if affinity maturation occurs [95].

More than a decade ago (2013), it was hypothesized that natural IgG autoantibodies (nAAbs) are abundant in human serum, with individual profiles that were stable over time but varied by age, gender, and disease, suggesting links to central tolerance and autoimmune risk [88]. This inspired further research to test the stability of nAAb profiles and their transition to pathological autoantibodies (pAAbs) in autoimmune conditions. Studies in NZB mice, a model for autoimmune hemolytic anemia, showed that nAAb levels against conserved antigens rise with age before disease onset, at which point pAAb levels increase, indicating plasticity in the nAAb pool [89,96–103].

Although under certain conditions (e.g., genetic predisposition [95,104,105] or repeated immunization [106]) B-1 cell-derived nAAbs can serve as templates for the development of higher-affinity, class-switched pathological autoantibodies (particularly those in the intersection of pathological autoantibodies and nAb sets on Figure 1) their exact physiological and pathogenic roles have yet to be fully elucidated [70].

## 3. Regulatory Role of the Natural Immune System in Pathological Conditions

### 3.1. From Clonal Selection to Self-Assessment: The Development of Autoreactivity in Immunology

Autoreactivity in healthy individuals has been recognized since the early 20th century, with foundational observations by Besredka in 1901 [107] and Landsteiner (1945) [108] noting the presence of self-reactive antibodies. Since the clonal selection theory from 1959 by Burnet [109] suggested a strong link between autoreactivity and disease, this concept has largely shaped immunological perspectives. However, in 1974, Jerne [110] demonstrated that autoreactivity can exist independently of autoimmune disease and is, in fact, a normal aspect of immune function. Building on this idea, Stewart (1992) [111] hypothesized that natural antibodies evolved primarily to recognize self, with non-self-recognition emerging later in evolution. Avrameas and colleagues further described the immune system as an “extraordinary tool for self-assessment,” emphasizing its role in physiological autoreactivity [112].

Irun Cohen [101] specified that the immune system is composed of networks of interacting cells and molecules, and therefore, we need to apply the thinking and tools of systems immunology to understand and regulate immune system behaviour. He defined the HSP60 and HSP70 molecules as examples of key hubs in physiological regulatory networks. HSP molecules, similar to other genetically highly conserved proteins and peptides, can be considered as natural system controllers, e.g. to modulate inflammatory responses. Irun Cohen termed this natural autoimmune structuring of the immune system the *immunological homunculus* - the immune system's representation of the body. It is a selective advantage of an immune system expressing patterns of built-in autoimmunity to particular sets of self-molecules, suggesting that the particular self-reactivities comprising the homunculus could serve as a set of biomarkers that help the immune system initiate and regulate the inflammatory processes that maintain the body [1,62].

### 3.2. *Shifting Balance Between Physiological and Pathological Autoimmunity*

Despite the scientific achievements detailed above, the boundary between physiological autoreactivity and pathological autoimmunity remains unclear [127–132]. Interpretation of the first observations suggested a tight regulation limits isotype switching and prevents somatic mutation in B-1 cells to avoid high-affinity IgG autoantibodies that could lead to autoimmunity [68–71]. Later studies on human samples, including responses to old (e.g. MMR vaccine) and new (SARS-CoV-2) antigens, showed that nAAb levels can change during immune activation, especially in the IgG type. Changes in nAAb levels in SLE also indicated flexible immune regulation. For instance, anti-dsDNA IgG-positive SLE patients exhibited elevated natural IgG antibodies to specific antigens, resembling an adaptive immune response, and fluctuations in nAAb levels in SLE also pointed to dynamic immune regulation [99,102,104,105].

Experiments in mouse models indicated the necessity to develop bioinformatic tools to study the human nAAb repertoire.

It has been found that human nAAb are organized in clusters that can distinguish healthy individuals from patients with, e.g. type 1 diabetes mellitus, type 2 diabetes mellitus or Behçet's disease [113].

### 3.3. *Challenging Conventional Views: Natural Autoantibodies and Their Dynamic Responses in Health and Disease*

For decades, the prevailing view of natural autoantibodies has centred on their stable and conserved nature, with minimal fluctuation or adaptive variation across time, sex and individuals. In seminal work 30 years ago, Coutinho (1995) [114] described natural autoantibodies of the IgM, IgG and IgA classes as universally present in normal individuals, with reactivity to various serum proteins, cell surfaces and intracellular structures. These antibodies are even found in human umbilical cord blood and in 'antigen-free' mice, with their variable region repertoire shaped by the body's antigenic landscape and conserved throughout life. Encoded by germline genes with few or no mutations, natural autoantibodies are inherently multireactive and typically lack affinity maturation in healthy individuals. This conserved nature allows natural autoantibodies to contribute broadly to physiological functions, including immune regulation, homeostasis, repertoire selection, resistance to infection, transport and modulation of biologically active molecules [114].

Challenged by the above ideas, Czömpöly and Nemeth in 2006 investigated whether anti-mitochondrial citrate synthase autoantibodies are components of the natural antibody network in humans. For IgM nAAb, they found that natural IgM autoantibodies to citrate synthase (CS) are present from infancy, remain stable in adults, may serve as a first line of defence against pathogens, and exhibit unique epitope recognition patterns in pathological conditions such as systemic lupus erythematosus (SLE), suggesting a potential link between innate immunity and autoimmune processes [115,116]. Due to the limited mutation and self-sustained constant presence of the source B cell population (B-1 cells), nAAb were considered constant. Another study in rodents in 2006 investigated the relationship between the natural antibody repertoire and the host biome. The results showed that habitat (wild vs. laboratory) had a greater effect on immunoglobulin levels than age, strain or sex. Wild rodents exhibited heightened immune responses similar to autoimmune (Th1-IgG) and allergic (Th2-IgE) responses with putative protective properties, challenging the notion of nAAb constancy, at least with respect to class-switched isotypes [117].

### 3.4. *Natural Autoantibodies in Health and Disease: Interplay Between Immunological Response and Pathogenesis*

In 2008, researchers "dissected" the cryoglobulins present in hepatitis C (HCV) infection and identified IgM nAAb targeting anti-HCV IgG1/K Fab (VH1-69) that expanded upon infection and contributed to cryoglobulinemia. This study demonstrated the potential characteristics of IgM nAAb: to expand upon immunological events and to cause indirect damage in non-physiological circumstances, with implications for HCV pathogenesis [118]. However, conflicting results



complicate the understanding of nAABs; a 2009 study [119], also using human samples, focused on IgM anti-Hsp60 levels as a known risk marker in atherosclerosis. Results showed that IgM anti-Hsp60 levels remained stable over a 5-year period, supporting the hypothesis that the immune system selectively preserves autoreactive B cells that target key self-antigens, including Hsp60. The study also showed that anti-HSP60 IgM nAAB levels did not correlate with maternal levels, indicating that nAAB patterns are independent of parental inheritance and specific to the fetus. Regarding IgG nAABs, a study [88] showed that IgG nAAB diversity in human serum increases with age and is generally higher in women than in men, while certain diseases such as Alzheimer's, Parkinson's and multiple sclerosis are associated with fewer detectable autoantibodies, from which some can potentially be specific to the disease and possibly reflect disease-related immune modulation, highlighting their potential in biomarker and therapy-target search [120–124].

### *3.5. From BCG and SARS-CoV-2 to Natural Autoantibodies: Investigating the Non-Specific Immune Enhancements and Their Mechanisms*

Human observations of non-specific effects (NSEs) of the Bacille Calmette-Guérin (BCG) vaccine suggest the involvement of both adaptive and innate immune mechanisms in trained immunity. This memory-like property of innate immune cells results from epigenetic reprogramming after exposure to a primary stimulus such as BCG, which subsequently affects cytokine production and cell metabolism [125]. Understanding the NSE of vaccination may help to improve the efficacy and safety of future vaccines. NSE may arise from trained innate immunity, emergency granulopoiesis and heterologous T-cell immunity [126]. Studies investigating the behaviour of nAABs in response to immunization have suggested, initially in rats, that immunization with different allergens enhances natural antibody networks (with a more pronounced effect on IgM than IgG) [96].

Investigation of a fatal COVID-19 case (2022) showed that de novo natural IgM  $\lambda$ -antibodies can emerge targeting the M antigen of the MNS blood group on RBCs without crossreacting with SARS-CoV-2 antigens. This first report of a natural bystander anti-RBC antibody highlights the extrafollicular humoral response in severe COVID-19 [127]. Böröcz et al. conducted human serological studies in 2023 to explore the role of nAABs in adaptive immunity and NSE [128], observing a statistically significant positive association between anti-HSP60, anti-HSP70 and anti-CS IgG titers and anti-SARS-CoV-2 IgG positive serum levels, especially in mRNA vaccine recipients. Elevated anti-CS IgM levels were also found in samples with a good response to vaccination (indicated by positivity for anti-SARS-CoV-2 IgG, IgA and IFN- $\gamma$ ). The continuation of this study showed that IgM nAAB levels are significantly related to anti-viral IgG autoantibody levels of "old" immunization (MMR vaccination/infection), and IgG nAAB levels are related to recently established anti-viral (anti-SARS-CoV-2) antibodies [129].

### *3.6. Natural Autoantibodies as Biomarkers and Modulators in Autoimmune Disorders: From Systemic Sclerosis through Type-1 Diabetes to Hashimoto Thyroiditis in Pregnancy*

Czömpöly et al reported the presence of both pathological and nAABs on the DNA topoisomerase I molecule in specific different epitopes at the same time [130]. The N-terminal domain specific pathological (IgG) autoantibodies are predominantly present in diffuse cutan form of systemic sclerosis, while the nAABs against the F4 fragment are also present in healthy individuals. Moreover, it was found that anti-CS IgG antibodies were significantly increased in anti-dsDNA IgG-positive compared to anti-dsDNA IgG-negative SLE patients [131]. The levels of anti-F4 and anti-CS IgM natural antibodies were significantly increased in anti-dsDNA IgM-positive compared to anti-dsDNA IgM-negative SLE patients. The study also considered the association of nAAB with virus-induced antibodies in SLE and found significantly higher levels of anti-CS IgG in anti-measles IgG-seropositive samples compared to seronegative samples in rheumatoid arthritis (RA), SLE and systemic sclerosis (SSc). A subsequent study [132] provided additional insight into the association of IgG anti-CS nAAB with active SSc, which may indicate compensatory immune responses that fail to counteract disease progression, highlighting their potential as complementary biomarkers alongside

double-negative 1 (DN1) B-cell ratios for the assessment of disease activity in SSc. Progress in exploring the role of B-1 B cells and nAAbs in type 1 diabetes (T1D) has shown that B-1 B cell-derived N-acetylglucosamine-specific IgM binds  $\beta$ -cell antigens, suppresses diabetogenic T cells, and delays T1D in recipients, suggesting a protective role in T1D [133].

Recent results from 2024 include a study showing a negative correlation between serum natural autoantibodies (CS IgM) and complement component C3 in diffuse cutaneous SSc, suggesting that natural autoantibodies may trigger C3 activation and hence consumption, potentially leading to tissue damage [134], and a serological follow-up study in pregnant women with Hashimoto's thyroiditis [134]; and a serological follow-up study of pregnancies in Hashimoto's patients and healthy individuals [135], which showed that pregnant women with Hashimoto's thyroiditis have elevated levels of anti-Hsp60 and anti-Hsp70 IgM nAAbs from the first trimester onwards, accompanied by lower levels of anti-Hsp70 and Hsp60 IgG nAAbs in the third trimester, suggesting a compensatory mechanism that may contribute to maternal immunological tolerance towards the fetus.

#### 4. Concluding Remarks

The historical timeline of research into natural autoantibodies (nAAbs) reveals a dynamic evolution in our understanding of their role in the immune system (**Appendix A**). Initially characterized by their conserved and stable nature, nAAbs were long regarded as mere byproducts of immune function, providing a baseline reactivity to self-antigens without significant variation over time or between individuals. Early studies demonstrated their presence in different immunoglobulin classes and highlighted their multireactive nature, suggesting a fundamental role in immune regulation and homeostasis.

As research progressed, the recognition of nAAbs as more than static entities began to take shape. Investigations revealed their ability to adapt in response to infectious agents and vaccination, suggesting a modifying role in bridging innate and adaptive immunity. Studies showed that nAAbs could expand in specific contexts, indicating that they could serve as first-line defenders against pathogens while also contributing to broader immune responses. This new understanding paved the way for exploring their implications in autoimmunity, where the line between protective and pathogenic roles has become increasingly blurred.

Recent research has highlighted the role of natural autoantibodies (nAAbs) as modulators or influencers in various autoimmune diseases, highlighting their importance in conditions such as systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis. In addition, their involvement in processes such as immunological tolerance during pregnancy further emphasizes their complexity and vital importance in both health and disease.

In conclusion, the path from the recognition of the conserved nature of natural autoantibodies to the understanding of their multiple roles shows a remarkable shift in immunological perspectives. This evolving narrative highlights the need for continued research to unravel the complex relationships between nAAbs, autoimmunity, infection and vaccination, ultimately improving our understanding of immune system dynamics and informing therapeutic strategies. The study of nAAbs not only enriches our knowledge of immune function but also opens new avenues for exploiting their potential in clinical applications. All this justifies once again treating natural immunity as a distinct compartment of the immune system, which carries the properties of both innate and acquired immunity in a functional network.

#### 5. Implications of the Study

The study of nAAbs provides important insights into their role in immunity and autoimmunity, but several biases and implications must be acknowledged. In particular, this review could not encompass the extensive and heterogeneous scientific literature of the last 40 years, which often presents conflicting results. Variability in experimental designs, methodologies and populations may

contribute to these discrepancies, potentially leading to biased interpretations of the functions of nAAbs.

In addition, the complexity of nAAbs, which can act as both protective and pathogenic factors, complicates their analysis, as their roles can vary significantly depending on the context, including specific autoimmune diseases and individual immune histories. Consequently, the conclusions drawn may not fully capture the diverse nature of nAAbs.

In conclusion, although this study advances our understanding of nAAbs, its results should be interpreted with caution. Future research should aim for a more integrated approach that reconciles the conflicting evidence, ultimately improving our understanding of the importance of nAAbs in health and disease and informing therapeutic strategies.

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Abbreviations

BCG vaccine	Bacille Calmette-Guérin vaccine
BCR	B-cell receptor
CCP	cyclic-citrullinated peptide
CCR	chemokine receptor
CD	cluster of differentiation
CS	citrate synthase
DAMP	damage-associated molecular pattern
dsDNA	double-stranded DNA
F4	fragment 4 of the human topoisomerase I
HCV	hepatitis C
HSP	heat-shock protein
IFN	interferon
Ig	immunoglobulin
IL	interleukin
iNKTs	invariant natural killer T-cells
IVIG	intravenous immunoglobulin
LPS	lipopolysaccharide
MAIT	mucosa-associated invariant T-cells

MHC	major histocompatibility complex
MMR	Mumps, Measles, Rubella
MZ	marginal zone
nAAb	natural autoantibody
nAb	natural antibody
NSE	non-specific effects
NZB mouse	New Zealand black mouse
pAAbs	pathological autoantibody
RA	rheumatoid arthritis
RBC	red blood cell
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLE	systemic lupus erythematosus
SSc	systemic sclerosis
STAT	signal transducer and activator of transcription 6
T1D	type 1 diabetes
TCR	T-cell receptor
TLR	Toll-like receptor
TOPO	topoisomerase
$\alpha\beta$ T-cell	alpha-beta T cell
$\gamma\delta$ T-cell	gamma-delta T cell

Appendix A

The table summarises the milestone literatures in historical order.

Year	Scientific question?	Immunoglobulin isotype-related conclusion (if applicable)	Reference
1991	How might the presence of natural autoantibodies affect the overall health and immune response of an unimmunized animal?	The immune system in unimmunized animals produces polyreactive and monoreactive IgM and IgG natural autoantibodies, encoded by unmutated germ-line genes, which interact with self-antigens to form a dynamic network supporting organismal homeostasis.	[71]
1995	In what ways do natural autoantibodies contribute to immune regulation and homeostasis?	Natural autoantibodies are conserved throughout life, maintaining stability without affinity maturation. Encoded by germline genes, these multireactive antibodies are found across individuals and species, supporting immune regulation, homeostasis, infection resistance, and modulation of biological molecules.	[136]
1995	How do natural antibodies influence pathogen spread and immune response in the body?	Natural antibodies, often dismissed as ‘background,’ are essential for immunity against infections. In antibody-free mice, viral and bacterial titers in vital organs were significantly higher, while titers in lymphoid organs were lower, compared to	[137]

		antibody-competent mice. This suggests that natural antibodies help prevent pathogen spread to vital organs and enhance immunogenicity by improving antigen trapping in secondary lymphoid organs.	
1998	What roles do natural autoantibodies (nAAbs) play in the immune system?	Natural antibodies, present in healthy individuals without prior immunization, often target self-antigens and are termed natural autoantibodies (nAAbs). Historically overlooked in immune regulation, nAAbs are now recognized as prevalent across vertebrate species, selected early in development, and essential for immune homeostasis. This study reviews the contemporary (and foundational) understanding of nAAb properties and their potential for therapeutic use.	[138]
2006	Are the anti-mitochondrial citrate synthase autoantibodies components of the natural antibody network?	Natural IgM autoantibodies to citrate synthase (CS) are present from infancy, are stable in adults, potentially functions as a first line of defence from pathogens and differ in epitope recognition under pathological conditions like SLE, indicating a possible link between innate immune responses and autoimmune disease processes.	[131]
2006	Could the presence of naturally occurring anti-hCS antibodies indicate a broader mechanism linking innate immunity to autoimmunity?	Human sera contain naturally occurring IgM antibodies recognizing human citrate synthase (hCS), with distinct epitope patterns in healthy and SLE conditions. Sera affinity-purified on hCS also cross-reacts with bacterial CS and nucleosome antigens, suggesting that these antibodies may both contribute to the innate defense and recognize autoantigens in systemic autoimmune disease.	[139]
2006	Is the natural antibody repertoire linked to the host biome?	Habitat (wild vs. laboratory) had a stronger impact on immunoglobulin levels than age, strain, or gender, with wild rodents showing heightened protective immune responses similar to both autoimmune (Th1-IgG) and allergic (Th2-IgE) reactions. Wild rats have significantly higher levels of autoreactive, polyreactive IgG, but not IgM, compared to laboratory rats, both quantitatively and qualitatively.	[140]
2008	What constituents can be found in cryoglobulins appearing during Hepatitis C virus infection?	IgM nAAbs against anti-HCV IgG1/K Fab (VH1-69) expands upon Hepatitis C virus infection, leading to mixed cryoglobulinemia.	[141]



2009	How do anti-human Hsp60 autoantibodies (known risk factor of atherosclerosis) change between mother and newborn's umbilical cord blood, and in adults? Is it a nAAb?	Levels of IgM anti-Hsp60 did not correlate to maternal concentrations. nAAb IgM anti-HSP60 level doesn't change in a 5-year-long period, supporting the idea that the immune system in a tightly regulated manner, selectively favors autoreactive B cells targeting a core set of immunodominant self-antigens, including Hsp60.		[142].
2013	Are there potential IgG autoantibody markers with clinical prevalence in non-immunological diseases?	IgG nAAb diversity in serum increases with age and is generally higher in females than males, while certain diseases like Alzheimer's, Parkinson's, and multiple sclerosis are associated with fewer detectable autoantibodies, possibly reflecting disease-related immune modulation.		[142]
2016	What role does natural IgM play in preventing autoimmune responses from autoreactive B and T cells that have bypassed tolerance mechanisms?	Polyreactive natural IgM autoantibodies (IgM-NAA) protect against pathogens and neo-antigens while inhibiting autoimmune inflammation through anti-idiotypic mechanisms, enhancing apoptotic cell clearance, masking neo-antigens, and modulating dendritic and effector cell function. Natural IgM also prevents autoimmune disorders driven by pathogenic IgG autoantibodies, autoreactive B and T cells, and genetic factors, such as in SLE.		[72]
2017	Can the immunization of rats with specific allergens enhance natural antibody networks?	nAAbs from immunized rat sera recognized more self-antigens across all organ extracts, with differences less pronounced in IgG than IgM.	Immunization of laboratory rats with different allergens was found to enhance networks of natural antibodies (with a more marked effect on IgM than IgG).	[143]
2018	Do vaccines (like BCG) provide broader health benefits beyond specific disease protection by enhancing innate immune memory through trained immunity?	The non-specific effects (NSEs) of the Bacille Calmette-Guérin (BCG) vaccine may involve both adaptive and innate immune mechanisms, with evidence suggesting a key role for trained immunity. This memory-like feature of innate immune cells results from epigenetic reprogramming after exposure to a primary stimulus like BCG, subsequently influencing cytokine production and cell metabolism.		[144]
2020	Is there an association between autoimmune disease-specific pathological autoantibodies and the natural autoantibody pool in different autoimmune diseases (SSc, SLE, RA)?	The levels of anti-F4 and anti-CS IgG antibodies were significantly increased in anti-dsDNA IgG-positive compared to anti-dsDNA IgG-negative SLE patients.	The levels of anti-F4 and anti-CS IgM natural antibodies were significantly elevated in anti-dsDNA IgM-positive compared to anti-dsDNA IgM-negative SLE patients.	[131]

2020	Is there an association between an external antigenic trigger (anti-measles vaccination or natural measles virus infection) and the consequently formed and still persisting antibodies and the nAAb pool in different autoimmune diseases (SSc, SLE,RA)?	Significantly higher levels of natural anti-CS IgG were detected in anti-measles IgG-seropositive compared to seronegative samples in RA, SLE and SSc.		[131]
2020	What functions can B-1a cells perform in anti-viral immunology?	B-1a cells are a unique B lymphocyte subpopulation essential for natural antibody production, innate immunity, and immunoregulation. They produce IgM, IL-10, and GM-CSF, which neutralize pathogens, modulate cytokine storms, and enhance IgM production, respectively. B-1a cells have shown protective effects against infections like influenza, sepsis, and pneumonia, highlighting their potential role in immune defense against SARS-CoV-2 and other infections.		[145]
2021	How do B-cell subgroups and anti-citrate synthase nAAbs reflect immunological dysregulation present in systemic sclerosis?	IgG anti-CS nAAb is associated with active systemic sclerosis (SSc) and may indicate compensatory immune responses that fail to counteract disease progression, highlighting their potential as supplementary biomarkers alongside DN1 B cell ratios for disease activity assessment in SSc.		[146]
2022	Case study - can the appearance of natural alloantibodies without mutation or class-switching suggest a unique immune activation pathway in severe COVID-19?	In a lethal COVID-19 case, a de novo natural IgM lambda alloantibody emerged, targeting the M antigen of the MNS blood group on RBCs, without cross-reacting with SARS-CoV-2 antigens. This first report of a bystander natural alloantibody against RBCs underscores the extra-follicular humoral response in severe COVID-19.		[146]
2023	How might understanding NSEs impact the development of future vaccine strategies and public health policies?	Live attenuated vaccines can lead to significant reductions in mortality and morbidity, while some non-live vaccines may increase these outcomes. Non-specific effects (NSE) might stem from trained innate immunity, emergency granulopoiesis, and heterologous T-cell immunity. These findings indicate that vaccine testing and regulation should account for NSEs.		[147]
2023	Is there an association between recent / aged antigenic triggers and the nAAb repertoire?	The study found statistically significant associations between SARS-CoV-2 vaccination (in terms of recent antigenic trigger) and	Significant associations were found between anti-CS IgM levels and the presence of IgG antibodies specific to measles, mumps, and rubella,	[148]

		increased levels of IgG natural autoantibodies (nAAbs)	suggesting an interaction between nAAbs and antibodies from an 'aged' (MMR vaccinations or infections) antigenic trigger	
2023	Is there an association between the immune response triggered by different COVID-19 vaccines and the natural autoantibodies?	A statistically significant positive connection was observed between anti-HSP60, anti-HSP70 as well as anti-CS IgG titers and anti-SARS-CoV-2 IgG positive serum levels, especially in mRNA vaccine recipients.	A positive correlation was found between anti-CS IgM nAAbs and the immune response, with elevated anti-CS IgM levels in cases of positive anti-SARS-CoV-2 IgG, IgA, and interferon- $\gamma$ results.	[149]
2023	What unknown factors could be influencing the preferential skewing of autoreactive VH4-34 antibodies toward the B1 cell population?	The study suggests that B cells with autoreactive B cell receptors may preferentially accumulate in the B1 cell pool or be excluded from the memory B cell pool. Alternatively, other factors might direct autoreactive VH4-34 antibodies toward the B1 population, with certain light chains reportedly suppressing inherent autoreactivity in these antibodies.		[150]
2023	Can the insights into B-1 B cells and natural antibodies influence future therapeutic strategies for preventing or treating T1D?	B-1 B cell-derived GlcNAc-specific IgM binds $\beta$ cell antigens, suppressing diabetogenic T cells, and delaying T1D in recipients, suggesting a protective role in T1D.		[151]
2024	Are there correlations between dcSSc-associated anti-Scl-70, anti-CS natural autoantibodies, and complement component C3 levels?	The negative correlation between serum natural autoantibodies (CS IgM) and complement component C3 in dcSSc suggests that natural autoantibodies may trigger C3 activation and, therefore consumption, potentially leading to tissue damage.		[152]
2024	How do nAAb levels change in healthy and Hashimoto Thyroiditis patients throughout the pregnancy?	Pregnant women with Hashimoto Thyroiditis have elevated anti-Hsp60 and anti-Hsp70 IgM nAAbs from the first trimester onward, accompanied by lower anti-Hsp70 and Hsp60 IgG nAAb levels in the third trimester, suggesting a compensatory mechanism that may contribute to maternal tolerance towards the fetus.		[153]

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