REVIEW

Long-Lived plasma cells: mysterious sentinels and persistent IgE producers?
Biology of long-lived plasma cells and their potential connection to IgE persistence

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Summary

Long-lived plasma cells (LLPCs) constitute a specialized and durable arm of humoral memory. While their role in maintaining long-term IgG and IgA immunity is firmly established, their contribution to IgE-mediated allergic disease remains clinically unproven. Nevertheless, recent advances in LLPC biology—accelerated substantially since 2021—have shown that IgE^+ LLPC-like cells do exist in human bone marrow and chronically inflamed tissues, providing an immunological basis for exploring their potential involvement in persistent sensitization.

LLPCs arise through tightly orchestrated developmental programs and rely on survival niches shaped by stromal cells, cytokines and metabolic adaptations. These features allow continuous antibody secretion for years or decades, independently of antigen re-exposure. Their metabolic resilience and resistance to apoptosis make them among the most durable effector cells in adaptive immunity.

In parallel, several mechanisms already known to support IgE persistence—early-life programming of type-2 responses, Treg/Tfr disequilibrium, sequential class switching from IgG1 memory, and rapid recall from non-IgE memory B cells—form a robust framework capable of sustaining long-term allergic sensitization irrespective of LLPC involvement. Within this architecture, the confirmed presence of IgE^+ long-lived plasma cells offers a biologically plausible, though not yet clinically validated, explanation for the remarkable stability of IgE profiles observed in many allergic conditions. Considering LLPCs within the broader context of IgE persistence highlights an area of growing immunological relevance while underscoring that their precise contribution to allergic disease remains to be determined**.**

Key words

Long-lived plasma cells; stromal survival niches; IgE persistence; immune memory trajectories; Treg regulation.

IMPACT STATEMENT

LLPCs are long-lived, niche-supported antibody producers whose sustained secretion and resilience might interface with IgE-associated circuits, offering a mechanism that could contribute to the long-term stability and persistence of allergic sensitization**.**

INTRODUCTION

Plasma cells were identified between the late nineteenth and mid-twentieth centuries through seminal histological and functional studies, which ultimately established their role as antibody-secreting descendants of B lymphocytes (1). For decades, plasma cells were therefore regarded as short-lived terminal effectors, dedicated to transient antibody production during acute immune responses. Beginning in 1997, this view was challenged by the identification of a distinct subset of long-lived plasma cells (LLPCs), capable of persisting for years within specialized tissue niches and sustaining antibody secretion independently of antigen re-exposure (2). The same persistence mechanisms that ensure durable protective immunity may, in specific contexts, also contribute to the maintenance of unwanted or pathological antibody responses (3).

Allergic disease became conceptually defined as a reproducible immunological condition in the twentieth century with the identification of immunoglobulin E (IgE) as the molecular mediator of immediate hypersensitivity (4–6). Despite the short serum half-life of IgE, allergic sensitization frequently persists for years or decades, indicating that IgE-associated immune responses can remain remarkably stable over time (7). This clinical persistence raises the question of whether long-lived antibody-secreting compartments may also sustain IgE responses. Among these, long-lived plasma cells may represent a cellular substrate of durable antibody production.

The introduction of component-resolved diagnostics (CRD) refined the molecular characterization of IgE sensitization and enabled allergen-specific IgE responses to be followed longitudinally (8,9). Beyond their diagnostic value, these approaches have consistently revealed the long-term stability of individual IgE repertoires, even in the absence of continuous allergen exposure, reinforcing the concept that IgE persistence reflects durable immunological memory rather than ongoing stimulation alone.

Allergen immunotherapy (AIT) further illustrates this persistence. While AIT can modify disease expression through induction of regulatory pathways and competing antibody responses, complete extinction of IgE memory is uncommon, and IgE production often rebounds after treatment discontinuation (10,11). Together, these observations suggest that mechanisms capable of maintaining long-lived antibody production may also operate within IgE-mediated immunity.

Within this framework, allergic disease provides a clinically accessible model in which long-term humoral immune persistence can be interrogated. The question is therefore not whether IgE-mediated responses persist, but to what extent long-lived plasma cells may contribute to the stabilization of IgE sensitization over time.

This review aims to integrate recent advances in long-lived plasma-cell biology with established mechanisms of IgE persistence in allergic disease. In doing so, it addresses the current knowledge gap between the emerging evidence for IgE^+ long-lived plasma cell–like populations in humans and the still unresolved extent of their quantitative and clinical contribution to long-term allergic sensitization.

INSIDE THE LIFE OF LONG-LIVED PLASMA CELLS

Long-lived plasma cells (LLPCs) represent one of the most durable outcomes of adaptive immunity, capable of sustaining antibody production long after antigen clearance. Early radiocarbon “bomb-pulse” studies provided the first compelling evidence that a subset of human antibody-secreting cells can persist for decades, long before their cellular identity and regulatory mechanisms were formally defined (2,8).

Despite this early evidence of longevity, LLPCs have long remained experimentally elusive. In humans, they account for only 20–25% of bone-marrow plasma cells and less than 1% of total marrow cellularity, and even after robust immune stimulation only a few antigen-specific LLPCs can typically be detected (9). Several factors have historically limited their investigation, including:

- their extreme numerical rarity within lymphoid tissues;
- their anatomical sequestration within specialized survival niches, particularly in the bone marrow and mucosal sites;
- the lack of unique and definitive surface markers allowing prospective identification;
- their phenotypic overlap with shorter-lived plasma cells, complicating functional discrimination.

These constraints have only recently been overcome through advances in single-cell profiling, lineage tracing, and niche-aware experimental approaches. In particular, high-resolution studies such as those by Liu et al. have demonstrated that LLPCs do not represent a homogeneous endpoint, but instead comprise

phenotypically and ontogenetically distinct subsets defined by isotype, developmental origin, and tissue context (9).

The authors identified IgG$^+$ or IgM$^+$ LLPCs as EpCAM$^+$CXCR3$^-$, whereas IgA$^+$ LLPCs exhibited a Ly6A$^+$Tigit$^-$ profile (9). High-resolution single-cell work provided the first systematic definition of LLPC heterogeneity across immunization, autoantigen exposure, and microbial stimulation.These analyses established that LLPCs are not a uniform entity but a constellation of phenotypically and ontogenetically distinct subsets. IgG and IgM LLPCs adopt an EpCAM^{hi}CXCR3^{lo} phenotype, whereas IgA LLPCs display a Ly6A^{hi}Tigit^{lo} signature. Germinal center (GC)–derived, somatically hypermutated clones predominantly feed the IgG/IgA LLPC pool, while IgM LLPCs include abundant "public," innate-like, T-independent clones reactive to microbial and self antigens (9).

These phenotypic and developmental features allow a practical distinction between short-lived and long-lived plasma cells, summarized in Table I.

Phenotyping and developmental heterogeneity of LLPCs

Although essential, LLPCs represent a quantitatively small population: in humans they account for only 20–25% of bone marrow plasma cells and <1% of total marrow cellularity. After immunization, fewer than ten antigen-specific LLPCs per milliliter of bone marrow are typically detected (9), and in mice even robust viral infection generates only ~20,000–30,000 antigen-specific LLPCs in the entire organism. A key limitation—beyond their rarity—has been the inability to prospectively separate LLPCs from their much more abundant shorter-lived counterparts. In humans, LLPCs are thought to reside in a CD19$^-$CD38$^+$CD138$^+$ bone marrow fraction enriched for IgG- and IgA-secreting cells, although the extent of heterogeneity within this population remains unclear (2). A major practical challenge has been the development of prospective flow cytometry–based strategies to isolate LLPCs. Mining transcriptomic datasets, Liu et al. identified IgG$^+$ or IgM$^+$ LLPCs as EpCAM$^+$CXCR3$^-$, whereas IgA$^+$ LLPCs exhibited a Ly6A$^+$Tigit$^-$ profile (9). High-resolution single-cell work provided the first systematic definition of LLPC heterogeneity across immunization, autoantigen exposure, and microbial stimulation. These analyses established that LLPCs are not a uniform entity but a constellation of phenotypically and ontogenetically distinct subsets. IgG and IgM LLPCs adopt an EpCAM^{hi}CXCR3^{lo} phenotype, whereas IgA LLPCs display a Ly6A^{hi}Tigit^{lo} signature. Germinal center (GC)–derived, somatically hypermutated clones predominantly feed the IgG/IgA LLPC pool, while IgM LLPCs include abundant "public," innate-like, T-independent clones reactive to microbial and self antigens (9).

Tissue survival niches and stromal conditioning

LLPCs remain difficult to study because of their rarity, anatomical sequestration, and the lack of unambiguous surface markers. Foundational work on human and murine plasma-cell origins highlighted the profound diversity of the plasma-cell compartment (10), while analyses of human bone marrow plasma cells revealed maturation gradients and transcriptional heterogeneity within LLPC-enriched fractions (11). GC imaging clarified the distinct routes by which early plasmablasts diverge toward short-lived or long-lived fates (12). Refinements in phenotypic classification outlined molecular signatures that differentiate resident from recirculating antibody-secreting cells (13), and recent commentary underscored the implications of these findings for the overlooked population of long-lived IgE-secreting cells (14). A central principle of LLPC biology is the requirement for specialized stromal survival niches. Mapping of bone marrow architecture identified CXCL12$^+$ reticular cells, sinusoidal endothelial networks, and regulatory myeloid populations as key determinants of LLPC anchoring and trophic support (15). Work in chronic inflammatory settings further showed that LLPCs can adopt distinctive phenotypes shaped by local tissue environments (16), demonstrating that LLPC identity is not fixed but niche-conditioned.

Ontogeny, lineage dynamics, and persistence

Maintenance of the memory–plasma cell compartment relies on extrinsic and intrinsic mechanisms that prevent apoptosis and stabilize secretory output (17). Developmental studies clarified how survival dynamics diverge between short-lived plasmablasts and durable LLPCs (18), while trajectory analyses confirmed that LLPC identity is imprinted progressively rather than instantaneously (19). Newly generated antibody-secreting cells undergo metabolic and transcriptional maturation as they transition from blood to bone marrow, acquiring increased mitochondrial dependence, enhanced secretory capacity, and stress-response competence (20). The long-term persistence of discrete plasma-cell clones has been demonstrated through high-fidelity fate-mapping and timestamping approaches (21), showing that antigen-specific, non-dividing LLPCs remain in situ for extended periods. Reconstructions of plasma-cell ontogeny

highlight parallel contributions of GC-derived and extrafollicular lineages to the LLPC pool (22). Imaging and computational analyses distinguish genuine LLPCs from transient antibody-secreting cells (23), while extended lineage models reveal unexpected plasticity under chronic immune stimulation (24). Earlier conceptual work framed plasma-cell differentiation as a balance between proliferation arrest, commitment to antibody secretion, and dependence on niche-derived cues (25), while more recent syntheses integrate LLPC longevity within coordinated metabolic, stromal, and epigenetic programs (26). A major advance concerns IgE LLPCs. Miranda-Waldetario et al. demonstrated the existence of bona fide long-lived IgE plasma cells with stable transcriptional profiles and protected tissue residence (27). Glaros and Kreslavsky (13) showed that IgE LLPCs persist predominantly in splenic niches, displaying survival signatures distinct from IgG LLPCs. Advanced 2D and 3D epithelial–stromal coculture systems have demonstrated that mucosal tissues possess the intrinsic capacity to sustain LLPC-like plasma cells outside canonical bone-marrow niches. These ex vivo models—based on layered epithelial sheets, stromal support cells, and matrix-based 3D architectures—recreate key features of mucosal microenvironments, including cytokine gradients, cell–matrix interactions, and survival factors such as IL-4, IL-6, APRIL, and TSLP. Together, they provide functional evidence that inflamed airway and intestinal tissues can maintain long-lived IgA- or IgE-secreting plasma cells independently of marrow-derived stromal networks (28).

Metabolic programming and survival fitness

The longevity of LLPCs relies on a profoundly remodeled metabolic program centered on mitochondrial fitness, oxidative phosphorylation (OXPHOS), and sustained endoplasmic reticulum (ER) homeostasis. During the transition from blood to bone marrow, nascent antibody-secreting cells acquire increased mitochondrial mass, elevated spare respiratory capacity, controlled glycolytic flux, and a lipid-handling program compatible with continuous membrane biosynthesis (19). A defining feature is the preferential use of pyruvate as a mitochondrial substrate. LLPCs depend on an efficient mitochondrial pyruvate carrier (MPC1/2) to transport pyruvate into the mitochondrial matrix, fueling the Tricarboxylic Acid (TCA) Cycle and sustaining high-level OXPHOS. Adequate pyruvate availability is essential to maintain ATP generation, mitochondrial membrane potential, and long-term survival. These metabolic adaptations support the continuous secretory load while preventing apoptosis through enhanced UPR activity within the ER (25). LLPCs counterbalance chronic ER stress through stabilized secretory architecture, coordinated lipid remodeling, and robust proteostasis mechanisms (22). Their metabolic resilience is niche-dependent: IL-6, APRIL/BAFF, and stromal-derived metabolites from $CXCL12^{+}$ perivascular cells supply essential substrates that reinforce both mitochondrial and ER homeostasis (14). Key metabolic adaptations are summarized in Table II.

Microbiota-driven imprinting

The microbiota integrates naturally into this metabolic architecture. As shown by Liu et al. (8), a substantial fraction of IgM LLPCs derive from T-independent, microbiota-reactive public clones, indicating that commensal signals can seed durable LLPC reservoirs. Human data from Ding et al. (9) show that mucosal antigenic tone shapes early plasma-cell trajectories, influencing the metabolic imprinting associated with LLPC persistence. These observations collectively position the microbiota not merely as a generator of short-lived plasmablasts but as a driver of long-term LLPC programming. Taken together, these elements outline the internal logic of LLPC persistence—an interplay between niche signals, metabolic fitness, and microbial imprinting—providing the conceptual framework illustrated in Figure 1.

THE IMMUNOLOGICAL FOOTPRINT OF LONG-LIVED PLASMA CELLS

Long-lived plasma cells (LLPCs) are not static repositories of immunological memory but active regulators of long-term humoral immunity. By residing in specialized stromal niches of the bone marrow and mucosal tissues, LLPCs sustain durable IgG and IgA production long after antigen clearance, preserving serological protection for years or decades and reflecting plasma-cell differentiation pathways shaped by germinal center responses, particularly in viral infections.

During the COVID-19 pandemic, it became clear that only a fraction of SARS-CoV-2–specific plasmablasts successfully entered the long-lived marrow niche, and this selective engraftment critically determined the durability of antiviral antibody titers (29). Complementary evidence showed that vaccine-induced plasma cells inefficiently establish residency in bone-marrow LLPC compartments, explaining the limited longevity of antibody responses after some mRNA vaccinations (30).The surge of research on LLPCs during this period

reflected an increased interest in understanding why some antibody responses consolidate into long-term humoral memory while others do not.

The persistence of LLPCs profoundly shapes secondary immune responses. The concept of original antigenic sin (OAS)—coined by Thomas Francis Jr. in 1960—captures the immune system's tendency to preferentially recall memory responses generated during the first antigenic encounter. Beyond antibodies, OAS also operates through $CD4^+$ T-cell imprinting, whereby rapid activation of cross-reactive memory T cells limits naïve-cell recruitment upon exposure to antigenically drifted variants**.** Mechanistic work in SARS-CoV-2 infection shows that early T-cell imprinting narrows epitope targeting during variant exposure, reinforcing dominance of pre-existing responses (31). Broader immunological reviews confirm that both influenza and coronavirus immunity are strongly shaped by early exposures, influencing vaccine responsiveness and serological breadth (32,33).

In this landscape, LLPC-derived antibodies actively contribute to immunological imprinting. Persistent titers directed against conserved epitopes modulate antigen availability, influence B-cell competition, and shape the distribution of T-cell help—mechanisms that can reinforce immune trajectories established during the initial encounter. Importantly, imprinting is not inherently restrictive: LLPC-mediated cross-reactive antibodies can mitigate disease severity upon re-exposure to related pathogens providing an early stabilizing layer of protection**.** Some theoretical frameworks propose that stable antibody landscapes may even limit diversification of autoreactive clones, suggesting a possible protective dimension of imprinting.

Interferons add another regulatory dimension. Type I IFNs—elevated in viral infection and chronically activated in autoimmune diseases—enhance early plasmablast differentiation and can potentiate emerging LLPC programs by amplifying IRF4- and BLIMP-1–dependent transcriptional networks (34). Chronic IFN-I exposure also remodels stromal environments in bone marrow and inflamed tissues, altering the production of APRIL, BAFF, and CXCL12 and favoring survival of autoreactive LLPCs. IFN-γ similarly supports extrafollicular antibody responses and contributes to LLPC retention in chronically inflamed tissues, linking inflammatory tone to persistent autoantibody production (34).

In autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis, autoreactive LLPCs reside in bone marrow and inflamed tissues and receive survival signals analogous to those sustaining protective LLPCs (35). Their lack of CD20 expression renders them resistant to B-cell–depleting therapies, and their deep integration into metabolic and stromal networks makes them particularly difficult to eliminate. Although autoimmunity is not the focus of this review, it is immunologically relevant that emerging therapeutic approaches—such as anti-CD38, anti-BCMA, and modulators of APRIL/BAFF signaling—aim to selectively reduce autoreactive LLPCs while attempting to preserve protective humoral memory (34). These strategies highlight the delicate balance between maintaining durable immunity and mitigating pathogenic chronic antibody production.

LLPCs thus exert a lasting immunological footprint. They safeguard antiviral and antibacterial memory essential for survival, yet their stability can constrain adaptive flexibility or perpetuate chronic autoantibody responses. Evolution appears to have favored long-lived humoral memory because its protective advantages outweigh the trade-off in adaptability. In an era shaped by emerging pathogens, mucosal infections, and therapeutic pressures, recalibrating LLPC survival with precision represents a central immunological challenge—one that seeks to retain the evolutionary strengths of durable immunity while limiting its potentially harmful echoes (36).

IgE LLPCs and long-term allergic memory

Immunoglobulin E (IgE) occupies a uniquely specialized evolutionary niche, having emerged in mammals following divergence from the ancestral IgY approximately 220–300 million years ago (37). Retaining the four constant domains of its precursor, IgE evolved as a rigid, high-affinity effector molecule optimized for mammalian type-2 immunity—an architecture that explains both its potency and its biological constraints.

Classically, IgE has been considered incompatible with long-lived humoral memory because of its low serum concentration, rapid turnover, and the risks associated with maintaining a potent effector antibody systemically. Yet several IgE-mediated disorders—including venom allergy, persistent food allergy, and perennial aeroallergen sensitization—can persist for decades, implying the existence of a durable IgE-imprinted state that outlives the antibody itself. Early evidence supporting this possibility emerged from

chronic rhinosinusitis with nasal polyps, where local IgE class switching and IgE-secreting plasma cells were demonstrated within structured inflammatory niches, consistent with long-lived plasma-cell behaviour (38). Subsequent studies strengthened this concept. Immunopathological analyses showed that CRSwNP tissues contain broad IgE repertoires and organized IgE-driven inflammatory networks, suggesting an integrated and persistent IgE–plasma cell axis (39). Together, these observations provided early mechanistic clues that chronic type-2 mucosal inflammation can sustain IgE-producing cells long term.

More recent mechanistic studies directly demonstrate that IgE-secreting plasma cells can acquire long-lived characteristics under specific microenvironmental conditions (40,41). In chronically inflamed mucosae, tertiary lymphoid–like structures, epithelial-derived cytokines, and sustained type-2 signals (IL-4, IL-13, TSLP) enable differentiation and persistence of IgE plasma cells outside the bone marrow, establishing a noncanonical, tissue-resident LLPC niche (42). These cells display minimal proliferation, resistance to apoptosis, and stable antibody secretion—features aligned with LLPC biology even when expressed in peripheral tissues (43).

These tissue-resident IgE LLPCs help explain the stability of allergic IgE imprinting, accounting for long-term allergen specificity and the difficulty in extinguishing chronic IgE responses.

This inflammation-driven LLPC architecture also clarifies why anti-IgE therapy—such as omalizumab, which neutralizes circulating IgE but does not eliminate IgE-secreting plasma cells—rarely induces durable immunological reprogramming, allowing rapid IgE rebound after treatment discontinuation (37). Conversely, therapies targeting plasma-cell survival pathways may influence IgE LLPCs, although selectivity and safety remain open challenges (44). Allergen immunotherapy (AIT) appears instead to reshape the microenvironment sustaining IgE LLPCs by modifying T-cell help, attenuating epithelial alarm signalling, and promoting IgG4 competition (37,42).

Altogether, current evidence indicates that IgE can support long-term memory through noncanonical, inflammation-driven, tissue-resident LLPC niches rather than classical bone-marrow sanctuaries. This framework resolves the long-standing paradox of a potent effector antibody capable of imprinting decades-long allergic susceptibility and identifies IgE LLPCs as a central determinant of persistent and treatment-resistant allergic disease.

TRANSLATIONAL ENTRY POINTS INTO IgE PERSISTENCE

Persistent IgE-mediated diseases often show long-term stability even when allergen exposure is minimized. This observation suggests that IgE production reflects an underlying and durable immunological organization rather than being maintained solely by recurrent allergen contact, consistent with long-standing patterns of sensitization observed across different allergic conditions.

Component-resolved diagnostics (CRD) offer increasingly refined tools to characterize IgE sensitization. The Italian nsLTP consensus highlights the clinical utility of CRD in stratifying risk and guiding management (45), while recent work on *Parthenium hysterophorus* maps immunodominant epitopes and supports the development of more precise molecular approaches (46).

Severe asthma, characterized by recurrent or relapsing disease activity, provides a complementary illustration. Longitudinal biomarker trajectories from the Italian Registry on Severe Asthma (IRSA) show reproducible patterns of IgE, eosinophils and FeNO over time, even across heterogeneous treatments (47). Mechanistic studies emphasize the role of epithelial–immune crosstalk—via IL-33, IL-25 and TSLP—in maintaining type-2 readiness at mucosal barriers (48).

Some patients remain allergic even under strict avoidance, indicating that IgE persistence reflects a pre-established immunological trajectory rather than continuous allergen exposure, pointing toward deeper immunological mechanisms.

Early-life interactions between the immune system and the microbiota provide an explanatory framework for how such trajectories become fixed. Prenatal, perinatal and early postnatal life represent windows in which immune maturation is highly sensitive to environmental signals. Microbial colonization, microbial metabolites such as short-chain fatty acids, and early cytokine cues influence whether immune pathways acquire stable regulatory properties or diverge toward type-2–prone profiles (49).

A large population-based study further confirms these long-term trajectories: although most children outgrow cow's-milk allergy by school age, a substantial minority remain allergic into adulthood (50), illustrating how a subset of patients follows a lifelong IgE-stabilizing pathway.

In parallel, the biology of oral tolerance provides an additional explanatory layer. Oral tolerance is now understood as an active mucosal programme involving antigen sampling, induction of FoxP3$^+$ regulatory T cells, generation of IgA responses, and continuous low-dose antigen exposure supported by microbiota-derived cues**.** Failure to consolidate this programme during early life leaves mucosal tissues insufficiently regulated and predisposed to type-2 reactivity, helping to explain why allergic sensitization may persist even in the absence of significant allergen contact (51).

Beyond early-life imprinting and tolerance, IgE itself functions as a potent amplifier of adaptive immunity, enhancing secondary immune activation through FcεRI- and CD23-mediated pathways, modulating antigen presentation, and shaping helper T-cell polarization—processes that reinforce IgE-centric circuits (52,53).

Koenig proposes that the persistence of allergen-specific IgE arises from the convergence of several complementary processes. These include the absence of a true IgE memory compartment; recall responses generated from non-IgE memory B cells capable of IL-4-dependent secondary switching; the indispensable role of IL-4-producing helper T cells; and the possibility of minimal or cross-reactive exposures sustaining recall machinery.

Within this conceptual framework, IgE persistence could reflect the contribution of recall-supporting circuits, alongside additional mechanisms that may include the long-term survival of IgE-secreting cells (54).

Within this broader landscape, long-lived plasma cells (LLPCs) provide an additional explanatory dimension. IgE-expressing LLPCs have been identified in human bone marrow (55), suggesting that in some contexts a fraction of IgE production may become partially independent of ongoing exposure. Additional support comes from LLPC-like behaviour in extramedullary tissues such as the spleen (27). Although their quantitative impact remains uncertain, LLPCs could provide one stabilizing component of IgE persistence.

Tissue environments help stabilize these circuits. At mucosal sites, epithelial-derived cytokines such as TSLP, IL-33 and IL-25 can license dendritic cells and lower the threshold for re-engaging type-2 immunity (48). In contrast, bone-marrow niches enriched in CXCL12, APRIL and BAFF support plasma-cell survival, offering a permissive environment for persistent antibody production**.** These complementary niches—mucosal for reactivation, marrow for persistence—illustrate how long-term IgE stability can emerge from distributed but interacting immunological sites.

This framework also clarifies why certain interventions can modify long-term IgE trajectories. Allergen immunotherapy (AIT) promotes allergen-specific Treg responses, enhances IL-10 and TGF-β, and redirects class switching toward IgG4. Long-term studies indicate that these changes can persist after treatment discontinuation**.** Biologic therapies targeting IL-4Rα or TSLP attenuate key cytokine nodes in type-2 inflammation and may synergize with AIT. Combined strategies have shown encouraging results in severe asthma (56–58).

Within this framework, Figure 2 provides a visual synthesis of how LLPC persistence emerges from the interplay between niche-derived cues, immune signaling, and antigenic imprinting, highlighting key convergence points for therapeutic intervention.

CONCLUDING REMARKS

Long-lived plasma cells (LLPCs) have moved from being viewed as terminal survivors to active, adaptive participants in immune memory. Rather than static remnants, they integrate transcriptional programs, metabolic demands, and niche-derived cues to maintain antibody production across years or decades. Their persistence is not a fixed attribute but a continuous exchange with their environment.

This duality lies at the centre of their paradox.

The same biology that preserves life-long protection against pathogens may also sustain persistent IgE responses in allergic disease. In this sense, persistence is neither inherently beneficial nor harmful; it reflects the accumulated history of signals that shape LLPC fate over time—some adaptive, others maladaptive in contemporary settings.

Emerging methods, from single-cell transcriptomics to spatial imaging and metabolic tracing, reveal that LLPCs form not a uniform category but a spectrum of states, each defined by its niche and its past. Long-term immunity therefore appears less as a static endpoint and more as a dynamic equilibrium between survival cues, regulatory forces, and antigenic experience.

Future therapies could succeed not by erasing persistence, but by redirecting it—preserving the durable

memory that protects us while attenuating the circuits that sustain IgE-mediated disease. Guiding this equilibrium, rather than dismantling it, may represent the next step toward restoring tolerance.

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Table I. Comparison between short-lived plasma cells (SLPCs) and long-lived plasma cells (LLPCs).

Feature	Short-lived plasma cells (SLPCs)	Long-lived plasma cells (LLPCs)
Origin	Mainly extrafollicular B2-derived plasmablasts, early primary responses	Mainly germinal centers; also extrafollicular (especially IgM and mucosal IgA) and B1-derived
Antibody affinity	Low–moderate; limited SHM	High; extensive SHM
Lifespan	Days to weeks	Months to decades
Survival niche	Minimal or unstable	Specialized, cytokine-rich niches (BM, gut, spleen)
Microenvironmental dependence	Modest	Strong (IL-6, APRIL, BAFF, CXCL12)
Metabolic profile	Predominantly glycolytic	OXPHOS-driven; pyruvate-dependent; robust UPR
Markers	CD138 variable; BCMA low	CD138^{++}, BCMA^{+}, TACI^{+}, CXCR4^{+}
Localization	Inflammatory sites, spleen	Bone marrow; intestinal lamina propria (IgA LLPCs); spleen (including IgE LLPCs)
Therapeutic sensitivity	Sensitive to B-cell depletion (CD20 dependence)	Resistant to anti-CD20; niche-protected
Main function	Rapid but transient antibody production	Stable, long-term antibody secretion

SLPCs mediate early, transient antibody responses, whereas LLPCs provide durable humoral immunity supported by specialized survival niches and metabolic adaptations.

Abbreviations: SLPCs, short-lived plasma cells; LLPCs, long-lived plasma cells; SHM, somatic hypermutation; BM, bone marrow; IL-6, interleukin-6; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; CXCL12, C-X-C motif chemokine ligand 12; OXPHOS, oxidative phosphorylation; UPR, unfolded protein response; BCMA, B-cell maturation antigen; TACI, transmembrane activator and CAML interactor; CXCR4, C-X-C motif chemokine receptor 4; IgE, immunoglobulin E.

Table II. Differentiation, maturation, and maintenance of long-lived plasma cells (LLPCs).

Phase / Component	Principal processes	Key molecules / cells
Commitment to plasmacytic fate	B-cell activation → CSR → IRF4/Blimp-1 induction	CD40–CD40L, IL-4, IL-21, Tfh cells
Plasmablast stage	Migration, early secretion, partial metabolic rewiring	CXCR4↑, IRF4↑, XBP1↑
Niche entry	Competitive access to limited survival spaces	CXCL12, VLA-4/VCAM1, CD44
Maturation into LLPCs	Full metabolic specialization (OXPHOS, pyruvate use, UPR)	Mitochondrial fitness, GLUT1/ASCT2, ATF4/XBP1
Long-term maintenance	Anti-apoptotic signaling + nutrient support	APRIL, BAFF, IL-6; BCMA, TACI; stromal cells, eosinophils, Treg
Tissue localization	BM (primary), gut mucosa, spleen	CXCL12^{+} stromal niches, mesenchymal support
Isotype-specific features	Predominantly IgG/IgA; presence of IgM	IgE LLPCs recently identified in spleen

Phase / Component	Principal processes	Key molecules / cells
	LLPCs	
Fine regulation	Continuous competition; nutrient/oxygen modulation	Survival cytokines, metabolic circuits

Major cellular and molecular processes governing LLPC differentiation, maturation, and long-term survival.

Abbreviations: LLPCs, long-lived plasma cells; CSR, class-switch recombination; IRF4, interferon regulatory factor 4; Blimp-1, B lymphocyte–induced maturation protein 1; IL-4, interleukin-4; IL-21, interleukin-21; Tfh, T follicular helper cells; CXCR4, C-X-C motif chemokine receptor 4; XBP1, X-box binding protein 1; CXCL12, C-X-C motif chemokine ligand 12; VLA-4, very late antigen-4; VCAM1, vascular cell adhesion molecule 1; OXPHOS, oxidative phosphorylation; UPR, unfolded protein response; GLUT1, glucose transporter 1; ASCT2, alanine–serine–cysteine transporter 2; ATF4, activating transcription factor 4; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; TACI, transmembrane activator and CAML interactor; Treg, regulatory T cells; BM, bone marrow; IgG, immunoglobulin G; IgA, immunoglobulin A; IgE, immunoglobulin E.

FIGURE 1

Figure 1. Immunobiology and persistence of long-lived plasma cells (LLPCs). Long-lived plasma cells (LLPCs) arise predominantly from germinal center (GC)–derived B2 cells, with additional contributions from extrafollicular and B1 pathways. T follicular helper (Tfh) cells and interleukin-21 (IL-21) support plasma-cell differentiation. LLPC persistence depends on metabolic adaptations including mitochondrial fitness, oxidative phosphorylation (OXPHOS), pyruvate import via the mitochondrial pyruvate carriers (MPC1/2), and activation of the unfolded protein response (UPR). Bone marrow niches primarily support IgG- and IgA-secreting LLPCs, whereas mucosal niches sustain IgA and rare IgE plasma cells under epithelial–stromal cues such as thymic stromal lymphopoietin (TSLP), interleukin-4 (IL-4), and interleukin-6 (IL-6). Stable long-term antibody production underlies durable serological protection and, in specific contexts, may contribute to allergic persistence through rare IgE^{+} LLPCs.

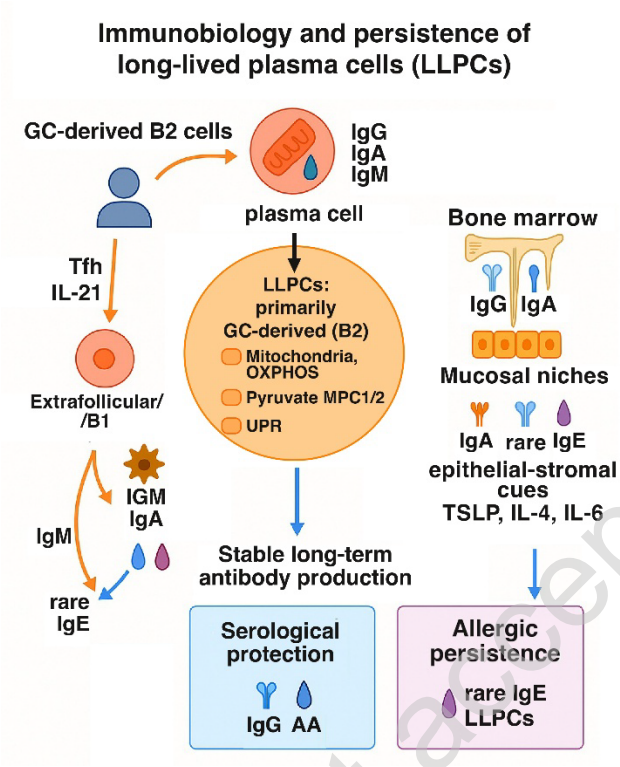

FIGURE 2

Long-term IgE persistence emerges from the convergence of early-life immune trajectories, core IgE maintenance mechanisms, and therapeutic modulation. Early-life conditioning includes microbial and immunological imprinting and the development of oral tolerance mediated by regulatory T cells (Treg), immunoglobulin A (IgA), and mucosal dendritic cells (DCs). Core IgE maintenance involves recall from non-IgE memory B cells in interleukin-4 (IL-4)–rich environments, dependence on IL-4–producing helper T cells, and amplification loops mediated by the low-affinity IgE receptor CD23 and the high-affinity receptor FcεRI. Therapeutic interventions such as biologics reduce type-2 cytokine pressure but do not delete IgE memory, whereas allergen immunotherapy (AIT) promotes allergen-specific regulatory T cells (Treg) and T follicular regulatory cells (Tfr). Within this framework, IgE^{+} long-lived plasma cells (LLPCs) represent a rare, niche-supported population that may contribute to stabilization of IgE responses.