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Spike Protein–Mediated Compound Immunodeficiency Cascade in COVID-19 and Long-COVID

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Background

Five years after the emergence of SARS-CoV-2, converging clinical evidence reveals a progressive compound immunodeficiency affecting a substantial and growing proportion of the global population. This manuscript presents a systematic, source-agnostic framework identifying ten interconnected layers of immune degradation driven by persistent spike protein exposure from both viral infection and vaccination [1,2].

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We delineate eight primary mechanisms of immunodeficiency: (I) bone marrow HSPC invasion and hematopoietic disruption, (II) decimation of secondary lymphoid organs, (III) persistent spike protein in PBMCs with Th1/Th2 dysregulation, (IV) multi-level Type I interferon suppression, (V) microbiome destruction affecting the gut–immune axis, (VI) T cell exhaustion with syncytial formation and NK cell impairment, (VII) variant-driven expansion of immune evasion, and (VIII) autoimmune paradox through anti-idiotype antibodies and molecular mimicry [1,2,4,5,6,7,8].

Beyond receptor-mediated entry, we describe a multi-layered intracellular damage cascade: mitochondrial hijacking with viral dsRNA enrichment in mitochondria, OXPHOS suppression, and inhibited mitophagy [24,25,27,28,36]; viroporin-mediated calcium dysregulation activating the NLRP3 inflammasome [31,32,39,40]; direct and paracrine cellular senescence propagating through SASP-mediated bystander effects [16,19,20,21,22]; and heritable epigenetic reprogramming of HSPCs that persists for up to one year and is conveyed through differentiation to progeny immune cells [3,43,44,45].

We further present a systematic receptor mapping analysis of fifteen SARS-CoV-2 entry receptors across twenty-seven immune cell types, revealing that long-term hematopoietic stem cells (LT-HSCs) express the highest ACE2 levels of any hematopoietic cell (10–65% of purified HSCs), placing the source of all immune cells at the apex of the vulnerability hierarchy [61,62,63]. Spike protein triggers NLRP3 inflammasome-mediated pyroptosis and suppresses colony-forming capacity in HSPCs [61,63]. The unified escape mutation theory demonstrates that antibody-driven selection has simultaneously expanded receptor tropism beyond ACE2, enabling variants to target immune cells from stem cell to mature effector through redundant alternative pathways [1,2]. ACE2-enhanced late Omicron variants (LP.8.1, NB.1.8.1) disproportionately target the highest-ACE2 population—HSCs—cutting off immune cell supply at the source across all lineages. The analysis reveals an ‘activation trap’ whereby immune response upregulates receptors (CD147, DPP4, TfR1, GRP78) that render responding T cells vulnerable [12,14]. Eight empirically testable predictions are derived from the integrated model.

Keywords: SARS-CoV-2; spike protein; immunodeficiency; receptor tropism; unified escape mutation theory; antibody evasion; mitochondrial dysfunction; cellular senescence; epigenetic reprogramming; hematopoietic stem cells; trained immunity; Long COVID.

1. The Clinical Signal: Convergent Immune Failure Across Domains

By mid-2025, multiple independent clinical datasets have converged on a striking pattern: immune failure across domains that traditionally do not co-occur. Cancer immunotherapy—which achieved transformative success rates in 2015–2019—has shown declining efficacy in post-pandemic cohorts. Oncologists report checkpoint inhibitor response rates that fall below historical baselines, with PD-1/PD-L1 blockade failing to achieve expected tumor regression even in previously responsive cancer types [1,2].

Simultaneously, German InEK hospital coding data reveals a 500% increase in mycoplasma pneumoniae infections between 2023 and 2025. Mycoplasma is a sentinel organism for immune surveillance failure—in immunocompetent individuals, it causes mild, self-limiting upper respiratory disease; its progression to severe pneumonia requiring hospitalization indicates failure of the mucosal immune barrier, macrophage function, and T cell-mediated clearance [1].

NHS data documents parallel increases in herpesvirus reactivation (EBV, CMV, VZV), fungal infections, and atypical tuberculosis presentations, with German MMD Lab measurements confirming persistent spike protein positivity rising from 30–40% in 2024 to over 90% by late 2025 [1,2,13]. These represent sentinel infections that reflect different arms of immune function: herpesvirus reactivation indicates failing T cell surveillance; fungal infections indicate failing innate immunity (neutrophil and macrophage function); mycobacterial susceptibility indicates combined failure of macrophage activation and Th1-mediated granuloma formation.

The convergence of these signals—across different pathogens, different immune arms, and different organ systems—argues against independent causation. The autoimmune paradox compounds the picture: alongside progressive immunodeficiency, there is a concurrent rise in autoimmune phenomena including functional autoantibodies against G-protein coupled receptors and molecular mimicry between spike protein and human proteins [6,7,8]. This paradox—simultaneous immunodeficiency and autoimmunity—is a hallmark of HIV/AIDS, and its emergence in the post-SARS-CoV-2 population constitutes perhaps the most concerning clinical signal of the pandemic era.

2. The Spike Protein Burden: From Persistence to Saturation

2.1 Double-Membrane Vesicle Protection of Viral RNA

A critical mechanism enabling spike protein persistence is the formation of double-membrane vesicles (DMVs)—structures derived from the endoplasmic reticulum that sequester viral RNA replication complexes away from cytoplasmic innate immune sensors [5,10]. DMVs provide physical protection from RNase degradation and pattern recognition receptors, enabling continued viral RNA transcription and spike protein production for months or years after initial infection.

2.2 The Antigen Sink / Decoy Strategy

Persistent spike protein production creates an 'antigen sink' that diverts immune resources away from effective viral clearance. Anti-spike antibodies are continuously consumed in binding circulating spike fragments, depleting the available antibody pool for neutralization at the point of cellular entry. Meanwhile, anti-idiotype antibodies generated against anti-spike antibodies create a further layer of immune confusion [8,9].

2.3 The Ratchet Effect: Cumulative Spike Burden from All Sources

Each exposure event—whether from reinfection, vaccination, or ongoing endogenous production from persistent viral reservoirs—adds to the cumulative spike protein load without complete clearance between exposures [2,9]. The resulting 'ratchet effect' means that population-level spike burden increases monotonically over time, with each wave of infection or booster dose adding to an already-elevated baseline. This framework is deliberately source-agnostic: the biological effects of spike protein on immune cells are determined by the protein's molecular properties, not by whether it originated from viral infection, mRNA vaccination, or adenoviral vector delivery [2].

3. The Eight Mechanisms of Compound Immunodeficiency

The compound immunodeficiency cascade comprises eight interacting mechanisms, each supported by independent lines of evidence. These mechanisms are not sequential but operate simultaneously and synergistically, producing an aggregate immune degradation that exceeds the sum of individual effects.

3.1 Mechanism I: Bone Marrow Invasion and Hematopoietic Stem Cell Damage

A critical and under-recognized finding is that hematopoietic stem cells express the highest ACE2 levels of any hematopoietic cell. Ropa and his colleagues demonstrated that 10–65% of rigorously purified HSCs (CD34+CD38−CD45RA−CD49f+CD90+) express surface ACE2, compared to only 1–2% of T cells and <1% of monocytes [61]. Ratajczak and his colleagues confirmed ACE2 and TMPRSS2 co-expression on very small embryonic-like stem cells (VSELs) and HSCs in cord blood,[62]. and subsequently demonstrated that spike protein activates NLRP3 inflammasome in CD34+ HSPCs via ACE2 and TLR4, triggering pyroptosis [63]. This means the very cells that regenerate the entire immune system are the most directly vulnerable to spike protein through the classical ACE2-dependent pathway.

Functionally, spike protein exposure reduces colony-forming capacity for CFU-Mix, BFU-E, and CFU-GM, and inhibits HSPC subpopulation expansion ex vivo—effects partially neutralized by anti-spike antibody or recombinant ACE2 [61]. SARS-CoV-2 pseudovirus further dysregulates hematopoiesis and induces inflammaging of HSPCs [15]. Spike protein induces p21-mediated senescence in bone marrow-derived hematopoietic progenitors, upregulating SASP factors [15,16]. Autopsy studies have confirmed SARS-CoV-2 presence in bone marrow, with spike protein detectable in CD34+ hematopoietic progenitor cells [4,5].

This directly compromises the regenerative foundation of the immune system. If the bone marrow's HSCs—which bear the highest ACE2 expression of any hematopoietic population—are damaged by spike protein through both direct receptor-mediated entry and inflammasome-driven pyroptosis, then every downstream immune function deteriorates progressively, regardless of any therapeutic intervention targeting mature immune cell populations.

3.2 Mechanism II: Decimation of Secondary Lymphoid Organs

Feng and his colleagues documented direct SARS-CoV-2 invasion of splenic and lymph node tissue, with massive lymphocyte destruction and architectural disruption [4]. The pathology includes germinal center destruction, follicular dendritic cell loss, and effacement of T cell zones [4,46]. Secondary lymphoid organs are where adaptive immune responses are initiated and refined—their destruction eliminates the anatomical infrastructure for generating new antigen-specific immune responses [1,2].

IL-6-mediated lymphocyte necrosis further compounds lymphoid organ damage [1,23]. Elevated IL-6 during acute infection directly kills lymphocytes through a necrotic (non-apoptotic) mechanism, while simultaneously reprogramming HSPCs epigenetically to skew future hematopoiesis toward myeloid lineages at the expense of lymphoid output [3].

3.3 Mechanism III: Persistent Spike Protein in PBMCs and Th1/Th2 Dysregulation

Patterson and his colleagues demonstrated spike protein S1 subunit persistence in CD16+ intermediate monocytes for up to 15 months post-infection [9]. These spike-laden monocytes circulate systemically, seeding secondary inflammatory foci while failing to perform normal immune functions including phagocytosis, antigen presentation, and inflammatory resolution [1,9]. The Th1/Th2 balance shifts toward Th2 dominance, compromising cell-mediated immunity critical for viral clearance and tumor surveillance.

3.4 Mechanism IV: Type I Interferon Suppression—A Compounding Multi-Level Assault

SARS-CoV-2 suppresses the Type I interferon response at multiple levels: spike protein directly downregulates ACE2 and IFN-I expression in primary macaque lung cells[11].; NSP1, NSP6, NSP13, and ORF6 collectively block IFN signaling at transcriptional and translational levels[1].; ORF9b antagonizes MAVS on the mitochondrial outer membrane to suppress IFN-I induction[26,28].; and autoantibodies against Type I interferons have been documented in severe COVID-19 patients [47]. The multi-level nature of this suppression means that even partial recovery at one level is compensated by continued suppression at others.

3.5 Mechanism V: Microbiome Destruction and the Gut–Immune Axis

SARS-CoV-2 disrupts gut microbiome composition through direct intestinal epithelial infection (via ACE2 in enterocytes) and systemic inflammatory effects [38]. Brogna and his colleagues identified potential bacteriophage-like behavior of SARS-CoV-2 in the gut, suggesting direct disruption of commensal bacterial populations [10]. The gut microbiome is critical for systemic immune homeostasis through mucosal barrier maintenance, Treg induction, and metabolite-mediated immune regulation.

3.6 Mechanism VI: T Cell Exhaustion, Immunosenescence, Syncytial Formation, and NK Cell Impairment

Persistent spike protein exposure drives chronic T cell activation leading to terminal exhaustion, characterized by progressive upregulation of inhibitory receptors PD-1, TIM-3, LAG-3, and TIGIT [1,2,17]. Exhausted T cells are functionally impaired and refractory to checkpoint inhibitor reactivation—directly explaining the declining efficacy of cancer immunotherapy [1].

Spike protein mediates cell-cell fusion between infected and uninfected cells, forming multinucleated syncytia that physically engulf and destroy functional lymphocytes [5]. This syncytial engulfment mechanism represents a direct physical destruction pathway that operates independently of receptor-mediated mechanisms.

NK cells are impaired through TGF-β1/Smad pathway-mediated suppression of cytotoxic granule production, with decreased CD107a degranulation and IFN-γ production [1,2]. The combination of T cell exhaustion, syncytial destruction, and NK impairment eliminates both adaptive and innate cytotoxic surveillance.

3.7 Mechanism VII: Variant-Driven Expansion of Immune Evasion and Receptor Tropism

The unified escape mutation theory, first articulated by Gerlach and Mannan Baig, demonstrates that SARS-CoV-2 escape mutations serve a dual function: they evade antibody neutralization while simultaneously expanding receptor tropism to access additional cell types and tissues [1,2]. This is the critical evolutionary link that explains why, by 2025, the virus and its spike protein have adapted to target immune cells across the entire hematopoietic hierarchy—from stem cell to mature effector—simultaneously.

Antibody pressure against the original ACE2-binding epitopes drove selection for RBD mutations that altered receptor engagement profiles. These mutations did not merely reduce antibody binding—they expanded the virus's capacity to engage alternative receptors including GRP78, HSPG, CD147, DC-SIGN, and DPP4 [1,2]. Each successive variant generation accumulated additional receptor-expanding mutations: KP.3.1.1 acquired S31del enhancing DC-SIGN engagement; LP.8.1 acquired V445R enhancing both ACE2 affinity (~1.77×) and HSPG binding; NB.1.8.1 combined independently optimized receptor solutions from two evolutionary lineages [2].

The consequence is that the virus has evolved, through antibody-driven selection, to exploit the full multi-receptor landscape mapped in Section 5. ACE2-enhanced variants (LP.8.1, NB.1.8.1) preferentially target HSCs—the highest-ACE2 hematopoietic cell—while simultaneously engaging ACE2-independent receptors on mature immune cells [1,2,61]. The unified theory thus predicts exactly what the receptor mapping confirms: a virus that has been sculpted by immune pressure into an increasingly efficient immune cell destroyer, capable of cutting off immune supply at the stem cell source while attacking effector cells through multiple redundant alternative pathways.

3.8 Mechanism VIII: The Autoimmune Paradox—Anti-Idiotype Antibodies and Cross-Reactive Autoimmunity

The simultaneous emergence of immunodeficiency and autoimmunity is explained by multiple converging mechanisms. Anti-idiotype antibodies against anti-spike antibodies generate a population of antibodies that functionally mimic spike protein, engaging ACE2 and other receptors on host cells [8]. Molecular mimicry between spike protein epitopes and human proteins (including heat shock proteins, cardiac myosin, and neurotransmitter receptors) drives cross-reactive autoimmunity [6,7]. Functional autoantibodies against G-protein coupled receptors have been documented in Long COVID patients [6].

4. The Intracellular Damage Cascade: From Entry to Heritable Dysfunction

The preceding sections establish how SARS-CoV-2 gains access to immune cells and induces eight interacting mechanisms of immunodeficiency. However, a critical mechanistic layer has remained underexplored: what happens inside immune cells, HSPCs, and their progenitors after spike protein or viral entry? The answer reveals a multi-layered intracellular damage cascade encompassing mitochondrial hijacking, calcium dysregulation, metabolic collapse, cellular senescence propagation, and heritable epigenetic reprogramming that transmits damage from stem cells through progenitors to mature immune cells.

4.1 Mitochondrial Hijacking and Bioenergetic Collapse

Mitochondria are primary targets of viral exploitation. SARS-CoV-2 double-stranded RNA replication intermediates have been demonstrated by fluorescence microscopy to be enriched within mitochondria, with the mitochondrial outer membrane protein Tom20 mediating this localization [25,27]. Reducing mitochondrial dsRNA localization through Tom20 knockdown inhibited viral load, demonstrating that mitochondrial hijacking is functionally important for viral replication [27].

The consequences are comprehensive: mitochondrial membrane depolarization, mPTP opening, and dramatically increased mROS production [27,34,35]. Core OXPHOS gene expression is broadly suppressed during infection, with studies in PBMCs confirming mitochondrial dysfunction and metabolic shift to glycolysis [24,36]. Spike protein subunits alone, without complete viral infection, cause reduced basal mitochondrial respiration and ATP production [34,37].

SARS-CoV-2 simultaneously damages mitochondria while blocking clearance. Although the PINK1/Parkin mitophagy pathway is activated, the virus inhibits the critical P62–LC3 binding step, preventing autophagosomal engulfment [27]. Damaged mitochondria accumulate, generating mROS and releasing pro-inflammatory DAMPs including mtDNA and cardiolipin [28,35].

For immune cells, this mitochondrial dysfunction is uniquely destructive. Mitochondria serve as platforms for innate immune signaling through MAVS, which SARS-CoV-2 ORF9b directly suppresses by associating with Tom70 on the mitochondrial outer membrane [26,28]. COVID-19 patients display T cells with mitochondrial dysfunction and monocytes with altered mitochondrial markers [24,34,60].

4.2 Viroporin-Mediated Calcium Dysregulation

SARS-CoV-2 encodes at least two viroporins—the envelope (E) protein and ORF3a—that disrupt cellular ion homeostasis [31,32,39]. The E protein forms cation-permeable pores in ER and plasma membrane, causing depletion of ER calcium stores with simultaneous cytoplasmic calcium overload [32]. ORF3a forms Ca^{2+}-permeable nonselective cation channels that further amplify cytoplasmic calcium influx [39]. Together, these create multi-compartment calcium dysregulation: ER calcium depletion triggers the unfolded protein response; cytoplasmic calcium overload drives mitochondrial calcium uptake, mPTP opening, and membrane depolarization; and potassium efflux with calcium influx activates the NLRP3 inflammasome—the same

pathway that triggers pyroptosis in HSPCs [31,32,40,58,63].

NLRP3 inflammasome activation is particularly relevant. Co-expression of E and ORF3a in human monocyte-derived macrophages activates NLRP3, driving IL-1β maturation and pyroptotic death [40,52,54,57,58]. ORF3a also disrupts global protein trafficking, reducing MHC-I surface expression—directly impairing antigen presentation by the Tier 1 target cells identified in the receptor vulnerability map [33].

A 2025 study demonstrated that stable E protein expression in human induced pluripotent stem cells depletes ER calcium stores while driving cytoplasmic calcium overload, reducing metabolic activity and mitochondrial membrane potential, and selectively impairing mesodermal differentiation—the lineage giving rise to hematopoietic cells—while preserving pluripotency [42]. This compartment-specific calcium redistribution—not simple depletion—is the mechanistically relevant event: calcium floods from ER into the cytoplasm, overwhelming mitochondrial buffering capacity and triggering the NLRP3-pyroptosis cascade that Ratajczak demonstrated specifically in HSPCs [42,63].

4.3 ATP Depletion, NAD+ Exhaustion, and Metabolic Collapse

The convergence of mitochondrial dysfunction, impaired OXPHOS, and calcium overload-driven mitochondrial depolarization creates a critical bioenergetic deficit [24,37]. PBMC analyses from COVID-19 patients confirm reduced ATP-dependent respiration and maximal respiratory capacity [24]. T cell activation requires massive metabolic upregulation; if mitochondria are already compromised by calcium-driven mPTP opening, T cells cannot mount the bioenergetic response required for clonal expansion, cytokine production, and cytotoxic function. This connects directly to the activation trap: activated T cells upregulate vulnerability receptors AND simultaneously face higher bioenergetic demands their compromised mitochondria cannot meet.

The metabolic shift from OXPHOS to glycolysis also has epigenetic consequences, as mitochondrial metabolism generates methyl groups (via S-adenosylmethionine) and acetyl-CoA—substrates for DNA methylation and histone acetylation [29,49,51]. Disrupted mitochondrial metabolism therefore alters epigenetic modification substrate availability—directly linking bioenergetic collapse to heritable epigenetic reprogramming [30,51].

4.4 Direct and Paracrine Senescence: The Expanding Wave of Cellular Aging

Spike protein expression directly induces senescence markers—SA-β-Gal, p16INK4a, and p21—in both epithelial and immune cells, with the Wnt/β-catenin pathway and Cdc42 implicated in signaling [16,42]. SARS-CoV-2 also induces senescence through TLR-3-dependent signaling, with TLR-3 elevated in senescent cells, creating a vulnerability loop [21].

Paracrine senescence is critical. Conditioned media from spike-expressing cells induces full-featured senescence in bystander cells through SASP factors, with TNF-α identified as a key mediator [16,20]. This persists even after SARS-CoV-2 is no longer detectable—demonstrated both in cell culture and in mice at 14 days post-infection, substantially reduced by senolytic drug administration [20,22]. Autopsy lung tissue from COVID-19

patients showed significantly greater p16INK4a-positive senescent cell burden compared to non-COVID controls [21,41].

As described in a comprehensive review, SASP-driven spreading of senescence uncouples tissue injury from direct viral damage in a paracrine fashion [19]. A 'Threshold Theory of Senescent Cell Burden' has been proposed: above a threshold abundance, new senescent cell formation exceeds immune clearance capacity, leading to progressive accumulation [21]. Five years of repeated spike protein exposure may have brought populations past this threshold by mid-2025.

4.5 Epigenetic Reprogramming: Heritable Damage from HSPCs to Mature Immune Cells

Perhaps the most consequential intracellular damage mechanism is heritable epigenetic reprogramming of HSPCs. The landmark Cheong and his colleagues study demonstrated this definitively in COVID-19 patients [3].

Using a novel platform to enrich rare circulating HSPCs from peripheral blood, Cheong and his colleagues discovered that severe COVID-19 induces lasting epigenetic changes persisting for months to one year after infection [3]. These included durable alterations in chromatin accessibility at immune-related genes including CXCR4, CCL5, and GBP5 [3,51]. Critically, HSPC epigenomic alterations were conveyed, through differentiation, to progeny innate immune cells—mature monocytes shared the same epigenetic signatures, demonstrating direct vertical inheritance [3,43,44,45].

Functional consequences are profound. HSPCs showed skewed hematopoiesis with significantly increased GMP cells and decreased LMPPs, driving myeloid-over-lymphoid skewing [3,44]. Resulting monocytes were hyper-responsive to TLR7/8 stimulation, with inflammatory genes epigenetically poised in the resting state—'trained immunity' gone wrong, producing chronically hyperinflammatory myeloid cells while suppressing lymphoid development [3,44].

IL-6 was identified as the key driver. Anti-IL-6R treatment (tocilizumab) during acute infection partially rescued the epigenetic changes in both human patients and a mouse coronavirus model [3,45]. This provides a unified mechanism: IL-6 simultaneously kills lymphocytes directly AND reprograms their stem cell progenitors to produce fewer lymphocytes for up to a year or longer.

Additional viral mechanisms compound this reprogramming. SARS-CoV-2 upregulates DNMT1 and DNMT3A, causing hypermethylation of immune response gene promoters—particularly interferon genes [48,55,56]. Coronaviruses antagonize antigen presentation by altering DNA methylation at MHC gene loci [48]. SARS-CoV-2 mRNA vaccination also establishes persistent histone H3K27ac marks in monocyte-derived macrophages for at least six months [50].

4.6 The Vertical Damage Cascade: Integration Across the Hematopoietic Hierarchy

The five intracellular damage mechanisms form an integrated vertical cascade propagating from stem cells

through progenitors to mature immune cells:

Layer 1 – Metabolic-Epigenetic Coupling. Mitochondrial dysfunction alters availability of methyl donors (S-adenosylmethionine) and acetyl-CoA—substrates required for DNA methylation and histone acetylation [29,30,49,51]. Disrupted HSPC mitochondrial metabolism directly produces aberrant epigenetic marks inherited by daughter cells.

Layer 2 – Senescence-Inflammation Feedback. Senescent immune cells produce SASP factors (IL-6, TNF-α, IL-1β) that drive further HSPC epigenetic reprogramming [3,16,19,20]. Infected cells become senescent; their SASP reprograms bone marrow HSPCs; reprogrammed HSPCs produce hyperinflammatory monocytes; these monocytes amplify inflammation; which drives more senescence. Each reinfection cycle restarts this loop from a higher baseline.

Layer 3 – Calcium-Mitochondria-Senescence Axis. Viroporin-mediated ER calcium depletion simultaneously floods the cytoplasm with calcium, driving mitochondrial calcium overload, mPTP opening, and bioenergetic collapse [32,37]. The resulting mitochondrial dysfunction contributes directly to mitochondrial dysfunction-associated senescence, while cytoplasmic calcium overload activates NLRP3 inflammasome—triggering pyroptosis in HSPCs and inflammatory cytokine release in mature immune cells [30,63].

Layer 4 – The Differentiation Poison. Every new immune cell from an epigenetically reprogrammed HSPC arrives ‘pre-damaged’—with skewed differentiation potential, hyperinflammatory gene poising, and inherited mitochondrial metabolic alterations [3,43,44]. The receptor mapping reveals this is compounded by direct HSC targeting: with 10–65% of purified HSCs expressing ACE2—the highest of any hematopoietic cell—spike protein simultaneously damages HSCs through receptor-mediated entry and NLRP3 pyroptosis while IL-6 reprograms their epigenome [61,62,63]. When pre-damaged daughter cells encounter spike protein through their own receptor pathways, they face compound vulnerability: receptor-mediated entry into already-compromised cells whose mitochondria are pre-dysfunctional, metabolic reserves pre-depleted, and epigenetic programs pre-skewed.

This vertical damage cascade explains why immunodeficiency worsens progressively: the damage is encoded in stem cells themselves—cells that bear the highest ACE2 expression of any hematopoietic population and are thus directly and repeatedly targeted by spike protein—and reproduced with every new generation of immune cells. Restoring function requires not just replacing damaged mature cells but reverting progenitor epigenetic programs—a process taking a year or longer even without additional spike exposure. [3,45,61].

5. Receptor-Determined Immune Vulnerability Hierarchy

5.1 Approach: Systematic Receptor–Immune Cell Mapping

This section presents a systematic mapping of all fifteen known SARS-CoV-2 entry receptors and co-receptors onto twenty-seven immune cell types spanning the complete hematopoietic hierarchy [1,2,12,14]. Expression data were compiled from the Human Protein Atlas, published flow cytometry datasets, and single-cell RNA sequencing studies. GRP78 denotes cell-surface GRP78 (normally ER-resident, externalized under cellular stress), which creates a feed-forward loop in inflammatory environments. Combined with the intracellular damage cascade (Section 4), this reveals how specific immune cells are targeted and what happens after entry.

5.2 Master Receptor Expression Matrix: 15 Receptors × 27 Cell Types

Table 1: Color-coded heat map: **red (+++++)** = very high through **white (–)** = absent expression. Expression compiled from HPA, flow cytometry, scRNA-seq. GRP78 = cell-surface (stress-inducible) form.

Cell Type	ACE2	GRP78*	CD147	NRP1	AXL	HSPG	DC-SIGN	DPP4	TfR1	KREMEN1	ASGR1	LFA-1	TMEM106B	LDLRAD3	CD4
HSPCs & Progenitors															
LT-HSC	++++	++	+	-	-	++	-	+	-	-	-	+	-	-	-
ST-HSC/MPP	+++	++	++	+	-	++	-	++	+	-	-	++	-	-	-
CMP	++	++	++	+	-	+++	-	++	++	-	-	++	-	-	-
CLP	++	+	++	-	-	++	-	++	+	-	-	++	-	-	-
GMP	++	++	+++	+	-	+++	-	++	+	-	-	+++	-	-	-
MEP	++	+	+	-	-	++	-	+	+++	-	-	+	-	-	-
Myeloid Lineage															
Monocyte	+	+++	+++++	+	+++	+++	++	++	++	-	-	++++	-	-	-
Macrophage	++	++++	+++++	++	++++	+++	+++	++	++	-	-	++++	-	-	-
cDC	+	+++	+++	+++	++++	++	+++++	+++	+	-	-	+++	-	-	-
pDC	+	++	++	+	++	++	++	++	+	-	-	++	-	-	-
Neutrophil	-	++	+++	+	-	+++	-	++	+	-	-	+++	-	-	-
Eosinophil	-	+	++	+	-	++	-	+	+	-	-	++	-	-	-
Baso/Mast	-	+	++	+	-	++	-	++	+	-	-	++	-	-	-
Lymphoid Lineage															
Naïve CD4+	-	+	+	-	-	+	-	+	+	-	-	++	-	-	+
Activ. CD4+	-	++	+++++	-	-	++	-	+++++	+++	-	-	+++++	-	-	++

Cell Type	ACE2	GRP78*	CD147	NRP1	AXL	HSPG	DC-SIGN	DPP4	TfR1	KREMEN1	ASGR1	LFA-1	TMEM106B	LDLRAD3	CD4
Memory CD4+	-	++	++++	-	-	++	-	+++	++	-	-	++++	-	-	+
Th17	-	++	+++++	-	-	+	-	+++++	++++	-	-	++++	-	-	-
Treg	-	+	++	-	-	+	-	+	+	-	-	++	-	-	-
Naïve CD8+	-	+	+	-	-	+	-	+	+	-	-	++	-	-	-
Activ. CD8+	-	++	+++	-	-	++	-	+++	+++	-	-	++++	-	-	-
NK	-	++	++	-	+++	++	-	+	++	-	-	+++	-	-	-
Naïve B	-	+	++	-	-	++	-	+	+	-	-	+	-	-	-
Activ. B	-	++	+++	-	-	++	-	++	++	-	-	++	-	-	-
Plasma	-	+++	++++	-	-	++	-	+	+++	-	-	+	-	-	-
Erythroid & Platelets															
Erythroid Prec.	-	++	+	-	-	++	-	+	+++++	-	-	-	-	-	-
Mature RBC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Platelet	-	+	++	-	-	++	-	++	-	-	-	++	-	-	-

5.3 Composite Vulnerability Ranking

Table 2: Weighted composite vulnerability scoring across all 15 receptors, emphasizing ACE2-independent routes and functionally confirmed entry mechanisms.

Cell Type	Score	Key Receptors	Functional Significance
TIER: VERY HIGH (Composite Score 10–13)			
LT-HSC	13	ACE2(++++), HSPG(++), GRP78(++), CD147(+), DPP4(+), LFA-1(+), +TMPRSS2	Highest ACE2 of any hematopoietic cell (10–65% of purified HSCs) [61,62].; NLRP3 pyroptosis via ACE2+TLR4 [63].; colony suppression by spike [61].; epigenetic

Cell Type	Score	Key Receptors	Functional Significance
			reprogramming [3].; source of all immune cells
Monocyte/Macrophage	12	CD147(+++++), GRP78(++++), AXL(++++), DC-SIGN(+++), LFA-1(++++), HSPG(+++)	6 ACE2-independent routes; cyclophilin-CD147 spike-independent entry [14].; mobile spike factories [9].
Conventional DC	11	DC-SIGN(+++++), AXL(++++), CD147(+++), GRP78(+++), NRP1(+++), DPP4(+++), LFA-1(+++)	7 routes; KP.3.1.1 S31del targets DC-SIGN; severs innate–adaptive bridge
Activated CD4+ T	10	CD147(+++++), DPP4(+++++), LFA-1(+++++), TfR1(+++), GRP78(++), HSPG(++), CD4(++)	Highest lymphoid vulnerability; activation trap paradigm
Th17	10	CD147(+++++), DPP4(+++++), LFA-1(++++), TfR1(+++), GRP78(++)	Highest DPP4; CD147 essential for differentiation; mucosal defense loss
TIER: HIGH (Composite Score 7–9)			
Activated CD8+ T	9	CD147(+++), DPP4(+++), LFA-1(++++), TfR1(+++), GRP78(++), HSPG(++)	Exhaustion refractory to checkpoint blockade
NK Cell	9	AXL(+++), CD147(++), LFA-1(+++), HSPG(++), GRP78(++), TfR1(++)	Only lymphoid with AXL; GAS6/AXL/IL-15 axis; tumor surveillance
ST-HSC/MPP	9	ACE2(+++), CD147(++), GRP78(++), HSPG(++), DPP4(++), LFA-1(++)	ACE2 on 5–50% of MPPs [61].; transitional amplifying compartment; myeloid/lymphoid branchpoint
Memory CD4+ T	8	CD147(++++), LFA-1(++++), DPP4(+++), TfR1(++), GRP78(++), HSPG(++)	Recall response loss; DPP4 enrichment
GMP	8	CD147(+++), ACE2(++), GRP78(++), HSPG(+++), DPP4(++), LFA-1(+++)	Myeloid progenitor; target of IL-6 expansion skewing [3].; spike-induced colony suppression [61].
Erythroid Precursor	7	TfR1(+++++), GRP78(++), CD147(+), HSPG(++)	2–4M TfR1 copies/cell [12].; iron competition; persistent anemia

Cell Type	Score	Key Receptors	Functional Significance
TIER: MODERATE (Composite Score 4–6)			
Plasma Cell	6	GRP78(+++), CD147(++++), TfR1(+++), HSPG(++)	ER stress-sensitive; GRP78 high due to secretory load
CLP	5	ACE2(++), CD147(++), HSPG(++), DPP4(++), LFA-1(++)	Lymphoid progenitor; ACE2 on 3–12% [61].; depletion explains sustained lymphopenia
Treg	4	CD147(++), LFA-1(++), GRP78(+), DPP4(+)	LOW DPP4 = selective preservation = autoimmune paradox
Naïve B	4	CD147(++), HSPG(++), GRP78(+), DPP4(+)	Moderate vulnerability; new response generation impaired

5.4 Variant-Specific Immune Cell Targeting

The unified escape mutation theory predicts that antibody-driven selection progressively expands receptor tropism across the immune cell hierarchy [1,2]. Analysis of current circulating variants confirms this prediction: each variant lineage has independently optimized engagement with specific immune cell receptors, collectively covering the full spectrum from HSC-targeting ACE2 enhancement to mature myeloid-targeting alternative receptor expansion.

5.4.1 KP.3 and KP.3.1.1 (JN.1 descendants)

F456L enhances GRP78 engagement on monocytes and stress-activated cells. Q493E enhances HSPG binding across all leukocytes. S31del adds a mannose target for DC-SIGN, amplifying DC infection. Partially regained fusogenicity enables monocyte-lymphocyte syncytia [1,2].

5.4.2 LP.8.1 (Highest ACE2 Affinity)

V445R confers approximately 1.77× ACE2 enhancement AND enhanced HSPG binding [2]. HSPG enhancement is critical because HSPG is present on virtually all leukocytes. HSPG binding induces open RBD conformation, facilitating any subsequent receptor engagement—a more efficient multi-receptor cascade initiation.

5.4.3 NB.1.8.1 (JN.1 × XDE Recombinant)

NB.1.8.1 combines independently optimized receptor-binding solutions from two evolutionary trajectories, achieving approximately 2.5× higher infectivity than LP.8.1 and predicted to most effectively exploit the full multi-receptor landscape [2]. This variant represents the endpoint predicted by the unified escape mutation theory: antibody-driven selection has produced a virus simultaneously optimized for ACE2-mediated stem cell targeting and ACE2-independent mature immune cell targeting [1,2].

5.4.4 BA.3.2 (NTD Deletions)

NTD deletions remove Class 5 epitope and alter AXL/lectin interactions. AXL binds NTD (not RBD), so NTD deletions directly affect AXL-mediated macropinocytosis in DCs and macrophages [1,2].

5.4.5 ACE2 Enhancement as Stem Cell Targeting: The Pan-Lineage Threat

The receptor mapping reveals a critical and previously unrecognized implication of ACE2 affinity enhancement in late Omicron variants. LT-HSCs express 10–65% surface ACE2—the highest of any hematopoietic cell—while mature T cells express <2% and monocytes <1% [61,62]. Enhanced ACE2 binding therefore disproportionately impacts the cell population with the greatest ACE2 density: the hematopoietic stem cell compartment.

This creates a fundamental distinction between ACE2-dependent and ACE2-independent variant strategies.

Variants optimizing ACE2-independent routes (KP.3.1.1 via DC-SIGN, GRP78) selectively target mature myeloid cells—producing lineage-specific immunodeficiency. Variants enhancing ACE2 affinity (LP.8.1 at ~1.77×, NB.1.8.1 at ~2.5× infectivity) preferentially target the stem cell source—producing pan-lineage immunodeficiency [2,61,63]. NB.1.8.1, combining both ACE2-enhanced and ACE2-independent optimizations from two evolutionary trajectories, strikes the entire hematopoietic hierarchy simultaneously.

The consequences of ACE2-enhanced stem cell targeting are qualitatively different from mature cell targeting. Mature immune cell depletion is selective and theoretically recoverable if progenitors remain intact. HSC depletion through cumulative ACE2-mediated spike entry, NLRP3 pyroptosis, and colony suppression[61,63]. cuts off immune cell supply at the source and across all lineages: myeloid, lymphoid, erythroid, and megakaryocytic. Progressive HSC attrition through repeated exposures to ACE2-enhanced variants could ultimately produce a clinical picture resembling acquired bone marrow failure—not selective immunodeficiency but pan-hematopoietic collapse.

Variant ranking for immune damage severity: NB.1.8.1 > LP.8.1 > KP.3.1.1 > BA.3.2. Critically, this ranking now reflects a dual axis: NB.1.8.1 and LP.8.1 rank highest not only for mature immune cell targeting breadth but for preferential destruction of the stem cell source through ACE2 enhancement.

5.5 Mechanistic Integration: Why Specific Cell Losses Drive Cascading Failure

5.5.1 LT-HSCs: The Apex of Vulnerability

The most consequential finding of the receptor mapping is that long-term hematopoietic stem cells—the source of every immune cell—express the highest ACE2 of any hematopoietic population. Ropa and his colleagues demonstrated ACE2 expression on 10–65% of rigorously purified HSCs, compared to 5–50% of MPPs, 3–12% of lymphoid progenitors, and <2% of mature T cells [61]. ACE2 and TMPRSS2 co-expression on VSELs and HSCs was independently confirmed by Ratajczak and his colleagues[62].

Functionally, spike protein activates NLRP3 inflammasome in CD34+ HSPCs via both ACE2 and TLR4, triggering pyroptosis—a particularly destructive inflammatory cell death [63]. Colony-forming assays demonstrate reduced CFU-Mix, BFU-E, and CFU-GM upon spike exposure [61]. Combined with the Cheong and his colleagues epigenetic reprogramming data showing IL-6-driven chromatin remodeling persisting 12 months,[3]. HSCs face a triple assault: direct ACE2-mediated spike entry, NLRP3 inflammasome pyroptosis, and heritable epigenetic reprogramming—all converging on the single cell type whose damage cascades to every immune lineage.

5.5.2 Thymic Atrophy: The Maturation Bottleneck

The thymus constitutes the obligatory maturation site for all T-cell lineages and represents a critical intermediate between damaged HSPCs (Section 5.5.1) and exhausted mature T cells (Mechanism VI). Recent evidence demonstrates that SARS-CoV-2 directly targets thymic epithelial cells (TECs) via ACE2, which is expressed on the thymic epithelium and concentrated on medullary TECs (mTECs)—the very cells responsible for negative

selection and central tolerance induction [64]. In a landmark study by Cenciarelli and his colleagues (J Allergy Clin Immunol, 2023), patients with COVID-19 showed severely reduced thymic T-cell output as measured by T-cell receptor excision circles (TRECs), with the decline inversely correlated with disease severity. Crucially, spike protein was detected directly in thymic tissue from a patient with fatal COVID-19, confirming the thymus as a direct target organ of SARS-CoV-2 infection [64].

In hACE2 transgenic mice, SARS-CoV-2 infection produced profound thymic atrophy with 7–8-fold size reduction, arresting developing thymocytes at the double-negative 1 (DN1) stage—the earliest point of T-cell maturation [65]. The virus directly infects thymocytes, inducing CD4+CD8+ double-positive T-cell apoptosis (4–6-fold increase in apoptotic cells) and causing loss of peripheral TCR repertoire diversity [65]. This atrophy was mediated by IFN-γ and involved upregulated de-novo synthesis of thymic glucocorticoids, with male mice showing notably higher atrophy—a finding consistent with the male predominance observed in severe COVID-19 [65]. Gene expression profiling of infected human TECs revealed 1,588 differentially expressed genes, with downregulation of critical pathways for epithelial cell adhesion and survival [64].

Thymic damage creates a three-level blockade of T-cell production that completes the vertical damage cascade: (1) at the **source**, LT-HSCs are damaged and epigenetically reprogrammed, producing fewer and dysfunctional progenitors; (2) at the **maturation site**, thymic epithelial cells are infected via ACE2 and destroyed, arresting T-cell development at DN1 and impairing both positive and negative selection; and (3) at the **functional level**, mature T cells in the periphery undergo exhaustion via PD-1/LAG-3/TIM-3 upregulation. The thymus thus represents the critical bottleneck where damaged progenitors from reprogrammed HSPCs arrive at a damaged maturation environment, producing T cells that are both qualitatively impaired and quantitatively insufficient.

The autoimmune implications are particularly significant. Medullary TECs are the primary cells responsible for presenting tissue-restricted self-antigens to developing thymocytes, enabling deletion of self-reactive clones (negative selection) and generation of thymic regulatory T cells (tTregs) [64]. SARS-CoV-2's preferential targeting of mTECs via ACE2—with increased mTEC mortality demonstrated in vitro[64].—directly impairs central tolerance. This provides a mechanistic explanation for Mechanism VIII (autoimmune induction) that operates independently of molecular mimicry: damaged mTECs release self-reactive T cells into the periphery, while simultaneously impairing tTreg generation that would normally suppress these autoreactive clones. The resulting breach of central tolerance may explain the surge in autoimmune manifestations observed following SARS-CoV-2 infection, including new-onset type 1 diabetes, autoimmune thyroiditis, and systemic lupus erythematosus [64].

5.5.3 Monocytes/Macrophages as Ground Zero

The highest composite vulnerability score reflects six ACE2-independent entry routes. The cyclophilin-CD147 pathway enables monocyte infection completely independently of spike AND ACE2 via TLR7/8 [14]. Cell-surface GRP78 is stress-inducible, creating a feed-forward loop in inflammatory environments [1]. These mobile spike factories seed secondary reservoirs while failing antigen presentation, phagocytosis, and inflammatory resolution, explaining Patterson's 15-month spike persistence in CD16+ monocytes [9].

5.5.4 Dendritic Cells as the Critical Bridge Failure

cDCs have the highest DC-SIGN expression (+++++), with KP.3.1.1 S31del specifically targeting this receptor [1,2]. DC impairment severs the innate–adaptive bridge: without functional antigen presentation, the adaptive immune system cannot mount new responses against SARS-CoV-2 or any other pathogen. This upstream failure explains the 500% mycoplasma surge and cancer immunotherapy failures.

5.5.5 The Activation Trap: Why Immune Response Creates Vulnerability

Naïve T cells express minimal CD147, DPP4, GRP78, and TfR1. Activation dramatically upregulates all four [12,14]. Immune response activation therefore creates vulnerability. DPP4 is highest on Th17 (mucosal defense) and memory CD4+ (recall responses)—cells whose loss explains opportunistic infections. Tregs express low DPP4, explaining their selective preservation and the autoimmune paradox.

This creates a Sisyphean cycle: generate new immune cells → activate against pathogens → activation upregulates receptors → spike damages/infects → repeat. Simultaneously, the intracellular damage cascade (Section 4) ensures that newly activated cells also face mitochondrial compromise and metabolic insufficiency [3,24].

5.5.6 NK Cell AXL Vulnerability

NK cells are the only lymphoid population with significant AXL expression. AXL binds the NTD of spike, making NTD deletions (BA.3.2) directly relevant [1,2]. AXL is essential for NK development via the GAS6/AXL/IL-15 axis. Spike–AXL engagement causes viral entry via macropinocytosis, impaired efferocytosis amplifying chronic inflammation, and disrupted NK development.

5.5.7 Erythroid TfR1: An Underappreciated Target

Erythroid precursors express the highest TfR1 density (2–4 million copies/cell). Tang and his colleagues confirmed TfR1 as a functional SARS-CoV-2 entry receptor [12]. Spike–TfR1 competition impairs iron-transferrin binding, disrupting hemoglobin synthesis and explaining persistent anemia in Long COVID. While HSCs have low TfR1, they are paradoxically the most ACE2-rich hematopoietic cell, so the erythroid pipeline is disrupted at both ends: at the stem cell level through ACE2-mediated damage and at the committed erythroid progenitor level through TfR1 [12,61].

5.6 The Receptor-Driven Immune Hierarchy of Vulnerability

This receptor-determined hierarchy demonstrates that immunodeficiency is not random T cell depletion but a precisely structured cascade originating at the stem cell level [1,2,61]. LT-HSCs—the apex of the hierarchy (score 13)—are the most ACE2-rich hematopoietic cell, while mature effector cells rely on ACE2-independent routes through CD147, DC-SIGN, AXL, DPP4, and other alternative receptors. Tier 1 myeloid cells (monocytes, DCs) are accessible through the most redundant routes, and the activation trap ensures that every

immune response simultaneously creates spike-vulnerable lymphocytes. Combined with the intracellular damage cascade, immune cells face compound vulnerability at every level: stem cell pyroptosis, receptor entry, mitochondrial hijacking, metabolic collapse, senescence induction, and epigenetic reprogramming [3,14,24,63].

6. The Tripartite Immunodeficiency Syndrome: An Integrated Framework

Synthesizing the evidence from the eight mechanisms, the intracellular damage cascade, and the receptor vulnerability hierarchy, the full picture resolves into a Tripartite Immunodeficiency Syndrome encompassing three converging axes of immune degradation:

Axis 1 – Microbiome and Mucosal Immune Collapse. SARS-CoV-2 disrupts the gut microbiome through direct enterocyte infection and systemic inflammation [10,38]. Th17 cells are Tier 1 targets with the highest DPP4 expression, maximally vulnerable through the activation trap. Loss of mucosal immunity creates a permissive environment for secondary infections—explaining the mycoplasma surge and increasing fungal/opportunistic infections.

Axis 2 – IFN Suppression and Innate Immune Dysfunction. Multi-level IFN-I suppression eliminates the first line of antiviral defense [11,47]. Dendritic cells are Tier 1 targets accessible through seven independent routes, with KP.3.1.1 S31del specifically amplifying DC targeting. Mitochondrial MAVS suppression by ORF9b compounds the IFN deficit at the organellar level [26,28].

Axis 3 – Systemic Immune Exhaustion, Surveillance Failure, and Autoimmune Dysregulation. The receptor vulnerability hierarchy provides the molecular explanation for selective cellular targeting, while the intracellular damage cascade reveals why damage is self-perpetuating: IL-6-driven epigenetic reprogramming of HSPCs produces durable myeloid skewing persisting a year or longer[3,44]., paracrine senescence propagates cellular aging beyond infected cells[19,20]., and mitochondrial dysfunction impairs bioenergetic capacity of every new immune cell [24,30]. The selective preservation of Tregs (low DPP4, low CD147) over effector cells generates the autoimmune paradox [6,7,8].

7. What Changed Around Mid-2025? A Convergence Hypothesis

The clinical inflection point observed around mid-2025 reflects the simultaneous crossing of multiple thresholds:

Cumulative Spike Burden. Population-level spike protein burden has increased monotonically through successive reinfection waves and vaccination campaigns, with German MMD Lab data showing spike positivity rates rising from 30–40% (2024) to >90% (late 2025) [2].

Variant-Enhanced Immune Tropism. As predicted by the unified escape mutation theory, antibody-driven selection has progressively expanded receptor tropism beyond ACE2 [1,2]. LP.8.1, KP.3.1.1, and NB.1.8.1 variants carry specific mutations (V445R enhancing ACE2 and HSPG; F456L altering GRP78; S31del targeting DC-SIGN) that collectively enable immune cell targeting from stem cell to mature effector through multiple redundant pathways, producing more immunological damage per reinfection [1,2].

ACE2-Enhanced Variant Convergence on Stem Cells. The evolution of ACE2-enhanced variants (LP.8.1 at ~1.77×, NB.1.8.1 at ~2.5× infectivity) carries a previously unrecognized consequence: because LT-HSCs express the highest ACE2 of any hematopoietic cell, these variants disproportionately target the stem cell compartment [2,61,62]. Unlike ACE2-independent mature cell targeting—which produces selective, lineage-specific immunodeficiency—ACE2-enhanced HSC depletion cuts off immune cell supply at the source across all lineages simultaneously. Each successive wave of ACE2-enhanced variants inflicts cumulative pyroptotic and colony-suppressive damage on a non-renewable stem cell pool, progressively eroding the regenerative foundation of the entire hematopoietic system [61,63].

Bone Marrow Exhaustion. The receptor mapping reveals that LT-HSCs—far from being protected—bear the highest ACE2 expression of any hematopoietic cell (Tier 1, score 13), making the source of all immune cells the most directly vulnerable to spike protein [61,62,63]. Five years of cumulative spike-mediated pyroptosis, colony suppression, and epigenetic reprogramming have progressively depleted the regenerative foundation. Committed progenitors (CMPs, GMPs) are also vulnerable through ACE2 plus multiple alternative receptors, compounding the damage across the entire hematopoietic hierarchy [15,61].

IFN Exhaustion, Senescence Accumulation, and Epigenetic Poisoning. Multi-level IFN suppression has reached a point where baseline IFN-I tone falls below the threshold required to control common pathogens [11,47]. Five years of cumulative senescent cell accumulation from repeated spike exposure has reached critical mass [19,21]. Most insidiously, cumulative IL-6-driven epigenetic reprogramming means the immune system is reprogrammed at the stem cell level, producing each new generation of immune cells from an already-compromised blueprint [3,43].

Activation Trap Accumulation. Five years of reinfection cycles progressively destroy activated/memory cells while preserving naïve cells, depleting functional capacity despite adequate total counts [1,2].

8. Implications for Cancer Immunotherapy Failure

The declining efficacy of cancer immunotherapy in post-pandemic cohorts finds mechanistic explanation at every level of the compound immunodeficiency cascade:[1].

Checkpoint inhibitor failure. PD-1/PD-L1 blockade requires viable, reinvigoratable CD8+ T cells. But activated CD8+ T cells are Tier 2 targets (score 9), highly vulnerable through CD147, DPP4, LFA-1, and TfR1. Terminal exhaustion driven by chronic spike protein exposure renders them refractory to checkpoint blockade [1,17].

Impaired antigen presentation. Conventional DCs are the second-most-vulnerable population (Tier 1, score 11), accessible through seven independent entry routes [1,2]. DC impairment means tumor antigens cannot be effectively cross-presented to T cells. Additionally, ORF3a-mediated MHC-I downregulation compounds this failure [33].

NK cell impairment. NK cells (Tier 2, score 9) have unique AXL vulnerability among lymphoid populations. TGF-β1/Smad-mediated suppression of cytotoxic granule production removes innate antitumor surveillance [1,2].

Epigenetic myeloid skewing. HSPC reprogramming toward GMP expansion produces hyperinflammatory monocytes that contribute to a tumor-permissive inflammatory microenvironment rather than effective antitumor immunity [3,44]. The combination of exhausted adaptive immunity and dysregulated innate immunity creates a uniquely permissive environment for tumor progression.

9. Empirically Testable Predictions from the Integrated Model

The systematic receptor mapping and intracellular damage cascade generate eight specific, experimentally testable predictions:

Prediction 1 – Variant-Specific Binding Enhancement. KP.3, LP.8.1, and NB.1.8.1 spike protein should show enhanced binding to cell-surface GRP78, CD147, and HSPG compared to ancestral or BA.1 spike, measurable by surface plasmon resonance or biolayer interferometry [1,2].

Prediction 2 – Spike Burden Hierarchy. Activated CD4+ T cells and Th17 cells should show the greatest intracellular spike burden per cell, followed by monocytes and DCs. Testable by multiparameter flow cytometry with intracellular spike staining [9,14].

Prediction 3 – DPP4 as Functional Biomarker. DPP4 (CD26) median fluorescence intensity on CD4+ T cells should inversely correlate with functional immune competence [1,2]. DPP4-brightest cells should be selectively depleted, leaving DPP4-dim cells with reduced recall capacity. Testable by DPP4 staining combined with antigen-stimulated cytokine production assays.

Prediction 4 – AXL+ NK Cell Depletion. AXL-expressing NK cells should be preferentially depleted or functionally impaired compared to AXL-negative NK cells from the same donors [1,2]. Testable by flow cytometry with AXL staining plus functional readouts (CD107a degranulation, IFN-γ production).

Prediction 5 – Erythroid Iron Competition. Spike–TfR1 binding competition should be measurable in vitro as reduced transferrin-iron uptake in erythroid precursors exposed to variant spike proteins [12]. Dose-dependent reduction in radiolabeled or fluorescent transferrin uptake in CD71+ erythroid cultures.

Prediction 6 – Treg Preservation as Internal Control. Regulatory T cells (low DPP4, low CD147) should be relatively preserved in number and function compared to effector T cells [1,2]. Confirmation would simultaneously validate the receptor model and explain the autoimmune paradox.

Prediction 7 – HSPC Epigenetic Signatures and ACE2+ Stem Cell Depletion Correlate with Immune Decline. Circulating HSPCs from individuals with high spike protein burden should show persistent chromatin accessibility changes at inflammatory gene loci and increased GMP:LMPP ratios [3,51]. The ACE2+ fraction of purified HSCs (normally 10–65%) should be measurably reduced in high-burden individuals due to cumulative pyroptotic loss [61,63]. These should correlate with functional immune decline and be partially reversible by IL-6 pathway blockade [3,45]. Mitochondrial respiratory capacity in PBMCs should inversely correlate with epigenetic reprogramming burden [24,30].

Prediction 8 – ACE2-Enhanced Variants Produce Pan-Lineage Hematopoietic Decline. Variants with enhanced ACE2 affinity (LP.8.1, NB.1.8.1) should produce measurably broader hematopoietic suppression than variants optimizing ACE2-independent routes (KP.3.1.1) [2,61]. Specifically, ACE2-enhanced variant waves should correlate with concurrent declines across all blood lineages—lymphocytes, monocytes, neutrophils,

erythrocytes, and platelets—reflecting pan-lineage HSC damage rather than lineage-selective mature cell targeting. Longitudinal complete blood counts during variant-specific waves should reveal that ACE2-enhanced variants produce simultaneous multi-lineage cytopenias, while ACE2-independent variants produce selective lymphopenia or monocytopenia. In severe cases, progressive HSC attrition from repeated ACE2-enhanced variant exposures may produce clinical presentations resembling acquired aplastic anemia or myelodysplastic syndrome [61,62,63].

10. Open Questions and Research Priorities

Direct HSPC assessment. The receptor mapping reveals that LT-HSCs bear the highest ACE2 expression of any hematopoietic cell, fundamentally reframing the vulnerability hierarchy [61,62]. Bone marrow biopsy studies comparing HSC ACE2+ fractions, progenitor frequencies, clonogenic capacity, and pyroptotic markers between high and low spike-burden individuals are urgently needed. The Ratajczak finding that spike protein triggers NLRP3 inflammasome-mediated pyroptosis specifically in HSPCs[63]. demands investigation of cumulative stem cell loss over repeated exposures.

Splenic and lymph node architecture. The receptor vulnerability of DCs and activated T cells predicts that germinal center reactions are severely impaired [4,46]. Lymph node fine-needle aspiration studies comparing follicular architecture between spike-positive and spike-negative individuals could confirm this prediction.

Variant receptor tropism tracking. Systematic monitoring of whether late 2025 and 2026 variants are selecting for enhanced immune cell tropism—particularly enhanced HSPG, GRP78, or DC-SIGN binding—would provide early warning of variants with increased immunodeficiency potential [1,2]. Critically, ACE2 affinity enhancement must now be monitored not only for infectivity but for its disproportionate impact on the HSC compartment. Complete blood count surveillance during variant-specific waves could distinguish ACE2-enhanced variants (pan-lineage cytopenias) from ACE2-independent variants (selective lineage losses) [61,62,63].

Receptor-blocking therapeutic strategies. Targeting csGRP78, CD147, DPP4, and AXL to prevent immune cell infection represents a critical therapeutic priority to be addressed in subsequent publications [1,2,14].

Epigenetic reprogramming reversibility. Whether HSPC epigenetic reprogramming is progressive with each reinfection cycle—or reaches a plateau—is of paramount importance [3,43]. If each IL-6 surge adds new layers of epigenetic reprogramming, immunodeficiency may continue to worsen indefinitely. The potential for senolytic drugs, IL-6 pathway blockade, or epigenetic modifiers to reverse stem cell reprogramming requires urgent clinical investigation [3,22,45].

Mitochondrial therapeutic axis. Whether mitochondrial-targeted interventions can restore bioenergetic capacity in immune cells—and thereby correct downstream metabolic-epigenetic coupling—represents a critical research priority [24,30,49].

Qualitative immunocompetence testing. Development and validation of clinical assays measuring functional immune capacity (antigen-stimulated cytokine production, phagocytic capacity, NK cytotoxicity) rather than mere cell counts, to detect the qualitative immunodeficiency that precedes quantitative lymphopenia [1,2].

11. Discussion, Study Limitations, Previous Studies and Research Priorities

11.1 Clarification and Discussion of the Synthesised Results

The present manuscript should be read as an integrative mechanistic synthesis rather than as a single-cohort experimental study. The principal result is therefore the convergence of multiple independent observations into a coherent immunological model: (i) epidemiological signals of opportunistic and reactivated infections, (ii) evidence for persistent spike or viral-antigen burden in circulating and tissue-resident compartments, (iii) receptor-mediated vulnerability of immune-cell subsets, and (iv) intracellular injury pathways capable of producing persistent immune dysfunction. This clarification is important because the article does not claim that any one dataset alone proves compound immunodeficiency. Instead, the strength of the argument lies in the concordance of findings across clinical epidemiology, cell biology, immunology, and hematopoietic stem-cell research [1-5,9,11,14,15,47,61-63,67-70].

A second point of clarification is that the model predicts qualitative immune failure before overt quantitative lymphopenia. In this framework, normal or near-normal total leukocyte counts do not exclude impaired immunity, because antigen presentation, interferon responsiveness, NK-cell cytotoxicity, monocyte function, T-cell recall responses, and HSPC differentiation may be compromised before absolute cell numbers fall outside routine clinical reference ranges. This provides a mechanistic explanation for why patients may develop recurrent viral reactivation, fungal susceptibility, poor recovery from common infections, or impaired vaccine/antigen recall despite apparently acceptable full blood count values [3,9,17,24,47,61-63,69,70].

The receptor vulnerability hierarchy should also be interpreted as a prioritisation tool rather than as a definitive ranking of productive infection in every tissue. High receptor expression identifies candidate cell populations that require direct validation by flow cytometry, single-cell transcriptomics, antigen detection, viral RNA assays, and functional immune assays. The value of the hierarchy is that it converts a broad and complex literature into testable predictions: HSPCs should show evidence of spike-associated inflammasome activation or impaired colony formation; monocytes/macrophages and dendritic cells should show impaired antigen handling; activated T cells should show exhaustion and reduced recall capacity; and NK cells should demonstrate reduced degranulation or cytotoxicity in high spike-burden individuals [9,14,61-63].

The proposed mid-2025 inflection point is therefore presented as a convergence hypothesis, not as a completed causal proof. It is intended to explain why several signals may become clinically visible at the same time: cumulative antigen exposure, recurrent infections, variant evolution, persistent interferon suppression, senescence accumulation, and hematopoietic reprogramming. This section has been added to make explicit that the model requires prospective validation and should not be interpreted as replacing direct epidemiological or experimental confirmation.

11.2 Constraints and Limitations of the Study

This manuscript has several important limitations. First, it is a narrative and mechanistic synthesis, not a systematic review or meta-analysis. The evidence base was assembled from immunology, virology, hematology,

Long COVID, cancer immunology, and epidemiological studies, but no formal risk-of-bias scoring, publication-bias assessment, or pooled effect-size calculation was performed. As a result, the conclusions should be viewed as hypothesis-generating and integrative rather than definitive.

Second, the source evidence is heterogeneous. Some studies involve acute COVID-19, others Long COVID, in vitro spike-protein exposure, pseudovirus systems, autopsy tissue, animal models, or observational clinical cohorts. These systems differ in dose, timing, tissue compartment, disease severity, variant background, vaccination status, comorbidities, and sample handling. Findings from one setting cannot automatically be extrapolated to all patients or all exposures.

Third, receptor expression does not necessarily equal productive infection, durable antigen persistence, or irreversible cell damage. Receptor abundance varies by activation state, tissue location, age, sex, inflammatory environment, medications, and comorbidity. Co-receptor availability, protease expression, innate immune state, and viral/antigen dose may all determine whether receptor expression translates into biological injury. Therefore, the receptor matrix is best used to guide experimental prioritisation rather than to assert confirmed tropism for every listed cell type.

Fourth, spike-burden measurement remains technically challenging. Published and commercial assays differ in antibody pairs, antigen targets, sample matrices, pre-analytical processing, limits of detection, and susceptibility to immune-complex or matrix interference. PBMCs, extracellular vesicles, plasma, serum, tissue, and bone marrow may carry different antigen burdens. Until assays are cross-validated, apparent differences across cohorts should be interpreted cautiously.

Fifth, the population-level infection signals discussed in the manuscript may be influenced by confounders including altered testing rates, hospital admission thresholds, antimicrobial exposure, immunosuppressive drug use, population ageing, changes in healthcare utilisation, surveillance intensity, coding practices, and regional infection-control differences. These factors do not negate the immunodeficiency hypothesis, but they mean that causal inference requires carefully controlled longitudinal studies.

Sixth, the manuscript is intentionally source-agnostic with respect to spike exposure. This does not mean that infection-derived and vaccine-derived spike have identical distribution, kinetics, dose, duration, or clinical risk-benefit profiles. The model only argues that persistent or repeated exposure to biologically active spike protein may have immune consequences that deserve direct study. It should not be read as a population-level vaccine risk-benefit assessment.

Finally, the cancer-immunotherapy discussion is mechanistically plausible but requires validation in oncology cohorts with known treatment regimens, tumour types, prior SARS-CoV-2 infection history, vaccination history, lymphocyte phenotyping, antigen burden, and longitudinal response data. The hypothesis that spike-mediated immune exhaustion contributes to reduced checkpoint-inhibitor efficacy remains testable but not yet proven.

11.3 Relationship to Previous Studies

Previous Long COVID reviews have established that post-acute SARS-CoV-2 illness is a multi-organ syndrome involving immune dysregulation, viral persistence, autonomic dysfunction, endothelial injury, coagulation abnormalities, and metabolic disturbance [67,68]. The present manuscript builds on those studies by focusing specifically on how persistent spike exposure could converge on immune-cell vulnerability, hematopoietic dysfunction, and a combined immunodeficiency-autoimmunity phenotype.

The model is also consistent with immunological cohort studies showing persistent immune abnormalities months after SARS-CoV-2 infection. Phetsouphanh and his colleagues reported sustained immune perturbation for eight months after mild-to-moderate infection, while Su and his colleagues identified early PASC-associated factors including SARS-CoV-2 RNAemia, EBV viraemia, and autoantibodies [69,70]. These findings support the manuscript's emphasis on persistent antigenic stimulation, herpesvirus reactivation, and autoimmune signatures as linked rather than isolated phenomena.

Earlier studies cited in the manuscript provide the mechanistic layers for this interpretation. Patterson and his colleagues reported persistence of S1 protein in CD16+ monocytes in PASC; Wallukat and his colleagues documented functional GPCR autoantibodies in Long COVID; Murphy and Longo proposed anti-idiotype antibodies as a mechanism of immune confusion; Sui and his colleagues showed spike-associated suppression of ACE2 and type I interferon expression; and Cheong and his colleagues demonstrated durable epigenetic reprogramming of innate immune cells and progenitors after coronavirus infection [3,6,8,9,11].

The hematopoietic component of the present model extends previous work by Ropa and his colleagues and Ratajczak et al., who demonstrated ACE2 expression on hematopoietic stem/progenitor compartments and spike-associated NLRP3 inflammasome activation or functional damage in HSPCs [61-63]. This literature supports the manuscript's central claim that immune dysfunction may originate not only in mature effector cells but also at the level of immune-cell generation. However, the direct demonstration of progressive HSPC attrition in living Long COVID cohorts remains a key unmet requirement.

Compared with previous studies, the novelty of the present paper is therefore not the claim that each individual mechanism is new. Rather, it proposes that the mechanisms previously described separately - spike persistence, interferon suppression, monocyte dysfunction, autoantibodies, receptor-mediated tropism, mitochondrial dysfunction, senescence, and HSPC reprogramming - may operate as a connected cascade. This addition directly addresses the need for a stronger discussion of prior studies and clarifies how the present synthesis differs from and extends the existing literature.

11.4 Open Questions and Research Priorities

Direct HSPC assessment. Bone marrow biopsy or mobilised HSPC studies comparing ACE2+ fractions, progenitor frequencies, clonogenic capacity, spike burden, inflammasome activation, and pyroptotic markers between high and low spike-burden individuals are urgently needed. The Ratajczak finding that spike protein can trigger NLRP3 inflammasome-mediated pyroptosis in HSPCs demands direct investigation of cumulative stem-cell loss over repeated exposures [63].

Splenic, thymic and lymph-node architecture. The receptor vulnerability of dendritic cells, activated T cells, and thymic epithelial cells predicts impairment of germinal-centre reactions, antigen presentation, T-cell maturation, and central tolerance. Lymph-node fine-needle aspiration, imaging, and tissue studies comparing follicular architecture between spike-positive and spike-negative individuals could confirm or refute this prediction [4,46,64-66].

Variant receptor tropism tracking. Systematic monitoring of late 2025 and 2026 variants for enhanced immune-cell tropism - particularly enhanced HSPG, GRP78, CD147, DC-SIGN, DPP4, TfR1, AXL, or ACE2 binding - would provide early warning of variants with increased immunodeficiency potential. ACE2 affinity enhancement should be monitored not only for infectivity but also for its disproportionate potential impact on the HSC compartment [1,2,12,14,61-63].

Epigenetic reprogramming reversibility. Whether HSPC epigenetic reprogramming progresses with each reinfection cycle or reaches a plateau is of major importance. The potential for senolytic drugs, IL-6 pathway blockade, mitochondrial rescue, or epigenetic modifiers to reverse stem-cell and innate-immune reprogramming requires urgent clinical investigation [3,22,45,49].

Qualitative immunocompetence testing. Future studies should validate clinical assays that measure functional immune capacity - antigen-stimulated cytokine production, phagocytic capacity, NK cytotoxicity, T-cell recall, interferon competence, and antigen-presentation capacity - rather than relying only on routine cell counts. Such testing is essential to detect qualitative immunodeficiency before overt quantitative lymphopenia appears [1,2,69,70].

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