BeyondMold

CLINICAL SCIENCE MONOGRAPH · II

THE CELL DANGER RESPONSE SERIES

From Haplotype to Healing Cycle

A Cell Danger Response Counter-Model of Individual Vulnerability in Biotoxin-Associated Illness

A positive, mechanistic alternative to the HLA susceptibility narrative: differential vulnerability after biotoxin exposure read as an acquired, exposome-dependent state — not a fixed inheritance of antigen-presentation genotype.

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Clinical Science Monograph II

This monograph develops a positive, mechanistic alternative to the HLA susceptibility narrative. It argues that the differential vulnerability clinicians observe after biotoxin exposure is better understood as an acquired, exposome-dependent state — written into innate immune memory, perpetuated by the mitochondrial integrated stress response, broadcast as symptom by mitokines, and compounded by metabolic suppression of adaptive clearance — than as a fixed inheritance of antigen-presentation genotype.

ABSTRACT

The counter-model in brief

The chronic inflammatory response syndrome (CIRS) construct attributes individual susceptibility to biotoxins to inherited HLA-DR/DQ haplotypes. This paper first defines what HLA molecules are and how they legitimately participate in disease, then shows that the haplotype claim rests on a single unrefereed source and is mechanistically mismatched to the genuine HLA-restricted environmental diseases from which it borrows authority — before advancing a constructive alternative. Within Naviaux's Cell Danger Response (CDR) framework, susceptibility is reframed as a property of the danger-response threshold and its persistence rather than of antigen presentation.

Four interlocking mechanisms are developed. **Trained immunity** — epigenetic and metabolic reprogramming of myeloid cells and their marrow progenitors by β-glucans, chitin, and muramyl peptides characteristic of water-damaged buildings — provides a durable, exposure-history-dependent lowering of the activation threshold: a mechanistically defined account of molecular scarring and of the echoing by which each successive exposure lands harder. **ATF4 and the mitochondrial integrated stress response (ISRmt)**, entered through the OMA1–DELE1–HRI relay, supply a self-sustaining perpetuation loop whose transcriptional readouts are the mitokines GDF15 and FGF21; GDF15 acting on brainstem GFRAL offers a presentation-independent explanation for symptoms out of proportion to structural findings. **Adaptive suppression** — the same eIF2α–ATF4 axis running with opposite sign inside T-helper cells, reinforced by IDO/GCN2 tryptophan restriction, arginase, and adenosine–A2A signaling — produces the antibody-negative persistence the HLA model invokes a presentation defect to explain, with no such defect required.

Because this state is acquired and metabolically maintained, it is in principle re-trainable; treatment solutions are mapped accordingly. The model accounts for dose-response, recovery, re-exposure sensitization, symptom disproportion, and treatment responsiveness that a fixed-haplotype model cannot, and it yields falsifiable predictions on instruments already in clinical use.

SECTION 1

Two theories of why one person falls ill

Co-exposure is the natural experiment that motivates every susceptibility theory in this field. Two people occupy the same water-damaged building; one develops a disabling, multi-system, years-long illness and the other does not. Any adequate model must explain that divergence. Shoemaker's answer is inheritance: the

vulnerable individual carries an HLA-DR/DQ haplotype that cannot present and clear the biotoxin, defaulting into chronic innate activation [3]. The answer developed here is different in kind. It locates the divergence not in a fixed birthright of antigen-presentation genotype but in an *acquired state* — a danger-response configuration shaped by each person's prior exposome, written into the regulatory machinery of innate immunity and mitochondrial signaling, and maintained by self-reinforcing metabolic loops.

The distinction is not academic. A fixed-haplotype model predicts that susceptibility is stable across the lifespan, untreatable at its root, and concentrated in carriers of particular alleles. An acquired-state model predicts that susceptibility is dynamic, dose- and history-dependent, in principle reversible, and distributed according to cumulative biological exposure rather than a single locus. These predictions diverge sharply, and the clinical phenomena — sensitization on re-exposure, recovery with treatment, symptoms far exceeding objective findings — fall consistently on the acquired-state side of the ledger.

SECTION 2

What HLA is: its normal role and its participation in disease

Because the entire susceptibility debate turns on what HLA molecules actually do, they must be defined precisely before we can ask whether they can carry the explanatory weight the CIRS construct places on them. A clear account of normal HLA biology is not a detour; it is the yardstick. It is precisely what reveals which uses of HLA in disease are legitimate and which are not, and it is the standard against which the haplotype claim is measured in Section 3.

2.1 The molecules and the locus

The human leukocyte antigen (HLA) system is the human version of the major histocompatibility complex (MHC), encoded in a gene-dense cluster on the short arm of chromosome 6 (6p21). It is the most polymorphic region of the human genome: thousands of alleles exist at the principal loci, and that diversity is concentrated, tellingly, in the residues that line a single structure — the peptide-binding groove [39,40]. Two classes matter here. **Class I** molecules (HLA-A, -B, -C) are expressed on virtually all nucleated cells and present short peptides of roughly eight to ten residues, sampled from the cell's own interior, to $CD8^+$ cytotoxic T cells. **Class II** molecules (HLA-DR, -DQ, -DP) are expressed on professional antigen-presenting cells — dendritic cells, macrophages, B cells — and present longer peptides, typically thirteen to twenty-five residues, derived from the extracellular environment, to $CD4^+$ helper T cells [41,42]. Because the polymorphic groove residues determine which peptides can be bound and displayed, an individual's HLA type sets their personal peptide-binding repertoire. The loci are inherited together as haplotypes in strong linkage disequilibrium, which is why HLA is discussed in haplotype blocks rather than single alleles — and why disease associations are often with a haplotype rather than a resolved causal allele.

2.2 The normal job: immune surveillance and self / non-self discrimination

Under normal conditions HLA molecules are the platform of immune surveillance [42]. Every nucleated cell continuously displays, via class I, a shifting census of its own internal proteome; antigen-presenting cells display, via class II, a sampling of the extracellular milieu. T cells are educated in the thymus to be self-MHC-restricted yet self-tolerant — positive selection retains those that can read self-HLA, negative selection deletes those that react too strongly to self-peptide. The mature result is a system that flags infected or transformed cells for cytotoxic attack and marshals $CD4^+$ help for antibody and inflammatory responses, while ordinarily ignoring healthy self [39,40]. The defining principle is *MHC restriction*: a T cell recognizes its antigen only in the context of a particular HLA molecule, so HLA type shapes the entire adaptive repertoire an individual can mount. This is the legitimate power of HLA — and every disease role below is a variation on it.

2.3 How HLA participates in disease — the legitimate routes

Five decades of work have shown HLA to be central not only to protective immunity but to disease, and the mechanisms are now reasonably well specified [41,42,43]. They are worth enumerating because each is defined at the level of a molecule, a groove, and a T-cell consequence — the precision that legitimizes an HLA claim. **Direct presentation driving autoimmunity:** a particular allele binds a self or modified-self peptide and drives a pathogenic T-cell response, as with the HLA-DRB1 "shared epitope" in rheumatoid arthritis and HLA-DQ in coeliac disease and type 1 diabetes — the best-mapped route. **Molecular mimicry:** HLA presents a microbial peptide that cross-reacts with a self-peptide, generating post-infectious autoimmunity, as in antibiotic-refractory Lyme arthritis [6]. **Hapten and altered-self presentation:** a small non-peptide modifies the peptide or the groove itself to create a neoantigen — the mechanism of chronic beryllium disease, where beryllium presented in the HLA-DPB1 Glu69 groove drives a $CD4^+$ response [5], and of abacavir hypersensitivity, where a drug reshapes the HLA-B*57:01 binding repertoire. **Altered thymic selection:** an allele shapes which self-reactive or protective clones survive education, tuning the repertoire toward or away from disease. **Infectious-disease control:** HLA alleles determine the success of responses to pathogens (certain HLA-B alleles and HIV control are the classic example), and the same polymorphism that protects against an infection may predispose to autoimmunity — the balancing selection that maintains HLA diversity in the first place.

2.4 The standard this sets

Across all five routes, the disease mechanism is always exercised the same way: through specific presentation of a defined antigen by a defined molecule, producing a defined T-cell consequence — whether protective, or pathogenic by excess. A serious HLA claim must therefore name the antigen, the groove, and the T-cell outcome. That is the bar. Section 3 asks whether the CIRS haplotype claim clears it.

SECTION 3

The limits of the HLA narrative

Measured against the standard Section 2 sets, the Shoemaker HLA assertion separates into three things that are routinely conflated: the direct literature offered in its support, the borrowed literature on genuinely HLA-

restricted disease from which it draws plausibility, and the structural problems that divide a defensible susceptibility concept from a validated genotype-to-biotoxin mechanism.

3.1 The direct evidentiary base is thin

The primary citation for the genetic claim is not a peer-reviewed paper but a poster presented at the American Society for Tropical Medicine and Hygiene in 2002 [3] — a legitimate vehicle for a preliminary signal, but one carrying no published methods, no disclosed control population, no correction for population structure, and no independent replication. The haplotype taxonomy that propagated through two decades of practice traces, in its original form, to this single unrefereed source. Shoemaker's genuinely peer-reviewed work characterizes the *phenotype* of biotoxin illness rather than its genetics: the time-series and clinical-trial papers describe a multi-system syndrome and a treatment effect [44], and the early dinoflagellate work, including the 1998 *Lancet* Pfiesteria report, established the clinical reality of a post-exposure neurocognitive syndrome [45]. These describe the illness the genetic claim is meant to explain, not the claim itself. The most rigorous genomic work in the lineage, the 2015 ciguatoxin transcriptomic study, reported differential expression of HLA-region genes including HLA-DQB1 and HLA-DQB2 [37] — an important but often-misread result, since differential expression in the disease state is a downstream, state-dependent observation, logically distinct from the germline claim that an inherited haplotype predisposes to acquiring the illness in the first place.

3.2 The borrowed paradigm: beryllium, Lyme, and ABPA

The plausibility of the claim rests not on Shoemaker's data but on analogy to a real literature in which inherited HLA variation demonstrably gates the response to an environmental agent. Three precedents are invoked, and the precision each carries is exactly what the CIRS claim lacks. **Chronic beryllium disease** is the exemplar: a glutamate at position 69 of HLA-DPB1 marks susceptibility, carried by roughly 97% of cases versus about 30% of unaffected individuals, refined to specific Glu69-bearing alleles and quantified at an odds ratio near nine with a gene-dose effect [5,46,47] — and the mechanism is fully specified, beryllium acting as a hapten presented in the Glu69 groove to drive a $CD4^+$ response. **Antibiotic-refractory Lyme arthritis**, directly relevant because Lyme is a named biotoxin source, shows an HLA-DRB1 association — but with two features the borrowing ignores: the association emerges only when patients are stratified by outcome (overall haplotype frequencies resemble controls), and the risk alleles confer it by binding the OspA antigen well and mounting a vigorous, mimicry-driven autoimmune response, not by failing to present it [6,48]. **Allergic bronchopulmonary aspergillosis** is the closest organism-level analogue — HLA-DR-restricted hypersensitivity to *Aspergillus* [49,50] — yet it is an IgE- and Th2-driven hypersensitivity to fungal antigens, the very mechanism the CIRS construct defines itself against. The precedent closest in organism is therefore furthest in mechanism.

3.3 Five structural problems

Set against those precedents, the assertion exhibits five problems, none fatal to the clinical intuition but each disqualifying for a claim presented as established mechanism. **No independent validation:** the beryllium and Lyme associations were established by independent investigators with defined controls and replicated across cohorts; no equivalent case-control study, still less a genome-wide study, confirms the "dreaded" CIRS haplotypes. **The base-rate problem:** the designated susceptible haplotypes are common and vary by ancestry [4], so a high prevalence among patients is expected even absent any causal link, and without ancestry-matched con-

trols the observation is close to uninformative — a concern raised from within the CIRS community itself, where HLA testing has correspondingly lost favor [51]. **Mechanistic inversion:** every legitimate route in Section 2 is a *gain* of presentation; Shoemaker's model posits the opposite — a failure to present and clear, producing antibody-negative persistence — borrowing the credibility of the HLA-restriction paradigm while reversing its causal logic, and the inverted mechanism has never been demonstrated for any biotoxin. **The undefined, largely non-peptide antigen:** no binding study exists for any mold toxin, and many candidate mycotoxins (the trichothecenes, for example) are small non-peptide molecules not presented in the class II groove at all; the beryllium hapten model fits better, but beryllium maps to HLA-DP, not to the DR haplotypes of the Rosetta Stone, and no analogous hapten chemistry has been shown for mycotoxins. **Circularity:** the haplotype categories were derived by observing which haplotypes recurred among already-diagnosed patients and then used to support further diagnoses — a circularity only an external, prospectively controlled study can break.

3.4 What a counter-model must therefore supply

The susceptibility phenomenon is genuine; the haplotype explanation is not validated against the standard its own borrowed precedents set. A successful counter-model must therefore do three things the HLA narrative cannot: explain individual vulnerability without relying on antigen presentation, account for persistence and symptom-amplification, and be falsifiable on instruments already in use. The Cell Danger Response framework, developed from here, meets each requirement.

SECTION 4

A state, not a birthright: the Cell Danger Response frame

Naviaux's Cell Danger Response describes a conserved, metabolically encoded program triggered when a cell's threat surveillance — oxidative, infectious, toxic, or physical — exceeds a threshold [1]. On activation, the cell shifts away from oxidative phosphorylation and cooperative function toward a defensive posture: hardened membranes, altered redox, extracellular ATP release as a danger signal, and a staged inflammatory and repair sequence. Recovery requires progressing through the phases of a healing cycle — CDR1 (innate, glycolytic, antimicrobial), CDR2 (proliferative, anabolic, M2-skewed repair), and CDR3 (differentiation and reintegration) — and then standing the response down [2]. Chronic illness, in this account, is not the persistence of the original injury but the failure to complete and exit the cycle: the danger response remains switched on after the threat is gone.

This reframes susceptibility precisely. The question is no longer "which peptide can this person present?" but "at what threshold does this person enter the danger response, and how readily do they exit it?" Both parameters are set by metabolic and signaling machinery — mitochondrial reserve, purinergic tone, the integrated stress response, the epigenetic state of innate immune cells — and both are shaped by prior exposure rather than fixed at conception. The sections that follow specify the machinery: trained immunity sets the entry threshold and writes it into durable memory; ATF4/ISRmt perpetuates the response and resists exit; mitokines

translate the persistent metabolic state into felt symptoms; and adaptive suppression prevents the clearance that would otherwise end the episode.

SECTION 5

Trained immunity: the molecular substrate of acquired susceptibility

5.1 Innate memory is real, and it lowers the threshold

The classical division of labor held that only lymphocytes remember. That view is now obsolete. Monocytes, macrophages, and NK cells — and, decisively, the hematopoietic progenitors that produce them — can acquire a durable, heightened functional state after an initial stimulus, responding more rapidly and more intensely to subsequent, even unrelated, challenges. Netea and colleagues named this *trained immunity*, and established that it is mediated not by gene rearrangement but by epigenetic reprogramming and metabolic rewiring [7,8]. Trained immunity is the mechanistic key to acquired susceptibility because it is, by definition, a memory of past exposure that makes the next response stronger — a lowered danger-response threshold inscribed in chromatin.

5.2 Water-damaged buildings are an ideal training stimulus

The canonical inducers of trained immunity are precisely the molecular constituents of a water-damaged building. Fungal β-glucans signaling through the dectin-1 receptor are the prototypical training agent, first characterized with *Candida albicans* and β-glucan, which reprogram monocytes to a hyper-responsive state on heterologous rechallenge [9]. Chitin from fungal cell walls, and muramyl dipeptide from bacterial peptidoglycan signaling through NOD2, are additional established inducers. A mold-contaminated indoor environment therefore delivers a sustained, polymicrobial training stimulus to the innate system — not a single antigenic insult but a repeated, multi-ligand education of myeloid cells and their progenitors. This is the substrate the HLA model has no language for: the relevant exposure trains the innate system regardless of which peptides any HLA molecule can present.

5.3 The epigenetic and metabolic engine

Training is written through histone modifications that render pro-inflammatory loci more accessible — notably H3K4 trimethylation and H3K27 acetylation at the promoters and enhancers of cytokine genes — so that on restimulation transcription is faster and larger. These marks are installed and maintained by a metabolic shift. Cheng and colleagues showed that an mTOR–HIF-1α axis driving a switch to aerobic glycolysis is the metabolic basis of trained immunity [10]; Arts and colleagues extended this to glutaminolysis and the accumulation of fumarate, which inhibits KDM5 histone demethylases and thereby stabilizes the activating methylation marks [11]. The significance for CIRS is direct: the same metabolic features that define the Cell Danger Response — glycolytic shift, altered TCA-cycle flux, accumulation of signaling metabolites — are the features that establish and lock in trained immunity. Trained immunity is, in effect, the CDR remembered.

5.4 Central training: why the scar outlasts the cell

A monocyte lives days to weeks; a susceptibility that lasts years cannot reside in the peripheral cell alone. The resolution is *central* trained immunity: the reprogramming reaches bone-marrow progenitors. Mitroulis and colleagues demonstrated that modulation of myelopoietic progenitors is an integral component of trained immunity [12], and Kaufmann and colleagues showed that BCG educates hematopoietic stem cells to generate functionally altered progeny [13]. Once the progenitor compartment is reprogrammed, it exports successive cohorts of pre-activated myeloid cells long after the inciting exposure, giving the durability that the clinical picture demands and that a short-lived peripheral state could never provide. This is the cellular location of the "scar."

5.5 When training becomes maladaptive — and an honest caveat

Trained immunity is adaptive by design — the basis of heterologous vaccine protection. But the same machinery can be pathological when the training stimulus is chronic or sterile: Christ and colleagues showed that a Western diet triggers NLRP3-dependent innate immune reprogramming that persists after the stimulus is withdrawn [14], a clean proof of principle that maladaptive trained immunity exists and drives chronic inflammatory disease. Intellectual honesty requires the caveat that maladaptive trained immunity in specific chronic human illnesses remains better supported as association than as proven causation; the protective arm of the literature is the more secure. For CIRS this should be held as a strong, mechanistically grounded working hypothesis — not as settled fact — and it is, importantly, a testable one (Section 10).

SECTION 6

Molecular scarring and echoing

"Molecular scarring" earns its place only if it names something specific. Defined loosely — "things stayed changed" — it becomes an unfalsifiable catch-all, and would deserve exactly the skepticism we direct at the HLA Rosetta Stone. Defined rigorously, it is the durable record left by trained immunity: the H3K4me3/H3K27ac marks at inflammatory loci, the metabolic set-points that maintain them, and the reprogrammed progenitor compartment that propagates them [10–13]. A scar, in this precise sense, is a heritable-at-the-cellular-level change in regulatory state that alters the response to future stimuli without altering the genome. The discipline this imposes is the same we would demand of any genetic claim: specify which loci, which cell types, and which progenitor compartment carry the mark.

"Echoing" is the functional consequence of the scar across time. Because the threshold has been lowered and the progenitor pool pre-activated, each subsequent exposure — a new building, a viral illness, a surgical stress, a re-exposure that a naïve individual would clear silently — elicits a disproportionate and faster danger response. The clinical correlate is the familiar history of stepwise worsening: patients who date their decline to a cascade of insults, each apparently smaller than the last yet each producing a larger reaction. This is not sensitization of an antigen-specific memory; it is the echo of an innate system whose baseline has been reset. The HLA model, positing a static defect, has no natural account of why exposures should compound; the trained-immunity model predicts it.

SECTION 7

ATF4 and the mitochondrial ISR: the perpetuation engine

7.1 The integrated stress response in brief

If trained immunity sets the entry threshold, the integrated stress response (ISR) governs persistence. The ISR is a conserved signaling hub in which four kinases — PERK, GCN2, PKR, and HRI — converge on phosphorylation of the translation initiation factor eIF2α in response to distinct stresses (ER stress, amino-acid limitation, viral RNA, and heme/mitochondrial stress, respectively) [15]. Phosphorylated eIF2α attenuates global cap-dependent translation while paradoxically increasing translation of select mRNAs bearing upstream open reading frames — chief among them ATF4, the master transcription factor of the response. ATF4, normally degraded within minutes, accumulates and reprograms transcription toward amino-acid synthesis, redox defense, autophagy, and — critically for this argument — the mitokines [15,18].

7.2 How mitochondrial stress enters the loop: OMA1–DELE1–HRI

The mechanistic discovery that makes the ISR central to CDR biology is the identification of the relay by which mitochondrial dysfunction triggers the response. Two 2020 *Nature* papers established that mitochondrial stress activates the inner-membrane protease OMA1, which cleaves the protein DELE1; cleaved DELE1 accumulates in the cytosol, binds the kinase HRI, and activates eIF2α phosphorylation and ATF4 — the OMA1–DELE1–HRI pathway [16,17]. ATF4 was independently confirmed by multi-omic analysis as the principal regulator of the mammalian mitochondrial ISR (ISRmt) [18], with the specific defects that trigger it depending on the cell's metabolic state [19]. A parallel mTORC1–ATF4 input feeds the same node. The upshot is a defined molecular circuit linking the metabolic core of the Cell Danger Response to a transcriptional program with measurable outputs.

7.3 Why the loop perpetuates

A stress response that resolves is healthy; the pathology is a loop that will not reset. Several features of the post-exposure state conspire to keep ISRmt engaged after the inciting toxin is gone. Mitochondrial reactive oxygen species and mtDNA stress are themselves ISRmt triggers, so a response that damages mitochondria can sustain its own input. Extracellular ATP released during the danger response maintains purinergic signaling that reinforces the metabolic shift. Trained, hyper-responsive myeloid cells continue to generate inflammatory and oxidative load. The result is a self-licensing circuit: ATF4 activity begets the conditions that re-activate ATF4. This is the molecular form of "failure to exit the healing cycle" — not a missing antigen response, but a stress loop that has lost its off-switch.

7.4 ATF4 as the bridge between metabolism and symptom

ATF4 is the hinge of the whole model. Upstream it integrates mitochondrial, redox, and nutrient stress; downstream it drives a transcriptional program whose most clinically legible products are the mitokines. It is

therefore the point at which a metabolic state becomes, by a defined molecular route, a measurable signal and a felt symptom — the subject of the next section.

SECTION 8

Mitokines: how a metabolic loop becomes a symptom

Two ATF4-driven secreted factors — growth differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21) — are the circulating readouts of the ISRmt, and they convert an intracellular stress state into a systemic, perceptible one. They are the most direct answer the model gives to the central clinical puzzle of CIRS: symptoms grossly out of proportion to objective findings.

8.1 GDF15–GFRAL: a presentation-independent malaise signal

GDF15 is induced by the integrated stress response and rises across a wide range of mitochondrial, inflammatory, toxic, and gestational stresses [24]. In 2017 four groups independently deorphanized its receptor, GFRAL, and found its expression restricted to the area postrema and nucleus tractus solitarius of the hindbrain — circumventricular structures outside the blood-brain barrier, exquisitely positioned to sample circulating distress signals [20–23]. Acting through GFRAL–RET, GDF15 drives anorexia, nausea, conditioned taste aversion, and the broader sickness-behavior repertoire [25,26]. This is a mechanistically complete, antigen-free explanation for the malaise, food aversion, and profound fatigue of biotoxin illness: a mitochondrial stress loop in the periphery broadcasts a hormone that the brainstem reads as “we are poisoned,” producing sickness behavior without any structural lesion and without any requirement for antigen presentation. Where the HLA model is silent on why patients feel as ill as they do, the GDF15 axis supplies a direct route from metabolism to symptom.

8.2 FGF21 and the biomarker logic

FGF21 is the second ATF4-dependent mitokine, long validated as a serum biomarker of muscle-manifesting mitochondrial disease [27], and FGF21 and GDF15 together now function as first-line, minimally invasive indicators of mitochondrial dysfunction, frequently outperforming muscle histology [28]. For the present argument their value is twofold. First, they corroborate that an ISRmt state is present and quantifiable. Second — and this is the decisive contrast with HLA — they are dynamic: they rise with mitochondrial burden and fall with recovery. A susceptibility marker that moves with treatment is the signature of an acquired, modifiable state; a fixed haplotype, by construction, cannot track symptom burden or recovery at all. This is precisely the biomarker logic on which the Beyond Mold GDF15/FGF21 program is built, and it is testable today.

SECTION 9

Adaptive suppression: the CDR2-immune face

The model so far explains threshold, persistence, and symptom. It must also explain clearance failure — the antibody-negative persistence that the HLA narrative invokes a presentation defect to explain. The answer is the most elegant turn in the framework: the same eIF2α–ATF4 axis that is pro-symptom in tissue is, inside the T-helper cell, immunosuppressive. One signaling axis, two opposite valences, partitioned by cell type.

9.1 The sign-flip

Effector T-cell commitment is bioenergetically expensive: it requires an mTORC1/Myc-driven glycolytic and glutaminolytic switch to fuel clonal expansion. A sustained ISR does the opposite — eIF2α phosphorylation attenuates the very translation that proliferation demands, biasing cells toward anergy and a regulatory phenotype. The classic physiological triggers are exactly what a hot innate environment produces. IDO-driven tryptophan depletion is sensed in T cells by GCN2, which Munn and colleagues showed mediates IDO-induced proliferative arrest and anergy [29]; arginase-driven arginine depletion arrests the T-cell cycle and downregulates the CD3ζ chain [30]. So the identical stress axis that amplifies symptoms in parenchyma starves the adaptive response in the lymph node. CDR2 — the proliferative, M2-skewed, TGF-β– and IL-10–rich repair phase — is immunologically a Th2/Treg-tilted milieu with blunted Th1 help and impaired follicular help, which predicts weak high-affinity, class-switched antibody. That is the “antibody-negative persistence,” produced with no presentation defect required.

9.2 Reciprocity with trained immunity

Trained immunity and adaptive suppression are not competing stories; they are reciprocal. Chronically activated, β-glucan/NOD2-trained myeloid cells are themselves the source of the suppressive machinery — IDO, arginase, PD-L1, and an MDSC-like program. The louder and more “scarred” the innate compartment, the more tryptophan- and arginine-starved and metabolically constrained the T cell becomes. “Worn-Out Defender” is an apt name precisely because the adaptive failure is not a quiet immune system but the tax imposed by a loud, persistently trained innate one. The clinical signature — reactivated herpesviruses, intracellular bacterial persistence, MARCoNS-type colonization — is the footprint of adaptive underperformance layered on innate hyperreactivity.

9.3 Purinergic and neuropeptide brakes

Two further axes, already central to the CDR intervention scheme, make the suppression over-determined. CD39/CD73-generated adenosine acting on the A2A receptor is among the most potent physiological brakes on T cells, raising cAMP, dampening TCR signaling, and reinforcing Treg differentiation [32,33]; a microenvironment that cannot clear extracellular ATP and adenosine is, by construction, T-suppressive — which means anti-purinergic intervention is simultaneously an adaptive-disinhibition lever. Vasoactive intestinal peptide, the Phenotype D anchor, is genuinely tolerogenic, Th2-skewing and Treg-inducing while suppressing Th1/Th17 [34].

This is a tension to hold openly rather than smooth over: the same VIP biology that resolves a stalled CDR3 is, at the wrong time or dose, itself a T-suppression signal.

9.4 Honest caveats

Three flags keep this from overreaching. First, the GCN2–tryptophan link in T cells, though foundational, has been contested: Van de Velde and colleagues found GCN2-independent effects in some antigen-specific systems [31], so amino-acid restriction is one mechanism among several, not the whole story. Second, ATF4 in T cells is genuinely bidirectional — activated T cells require a transient ATF4 pulse to acquire amino acids — so the suppressive reading specifically requires chronic, unresolved ISR, not a physiological transient. Third, a direct immunosuppressive action of GDF15 on T cells is emerging but mixed, and should be held as a plausible feedback limb rather than a load-bearing claim. The same discipline applies here as to molecular scarring: pin each effect to a signal, a cell type, and a timecourse.

SECTION 10

Why the CDR model explains vulnerability better than HLA

Set side by side, the two models are not equally matched against the clinical facts. The table below summarizes the contrast; the argument is that the CDR model earns explanatory credit on exactly the phenomena where the HLA model is silent or contradicted.

Clinical phenomenon	HLA / haplotype model	CDR / acquired-state model
Co-exposure divergence	Carrier vs non-carrier of a fixed allele	Different danger-response thresholds set by prior exposome and innate training
Dose–response & cumulative exposure	Not predicted; genotype is static	Predicted directly; training and ISRmt accumulate with exposure
Sensitization on re-exposure (echoing)	No natural account	Core prediction: lowered threshold + primed progenitors
Symptoms out of proportion to findings	Unaddressed	GDF15–GFRAL malaise signaling; ISRmt sickness behavior
Antibody-negative persistence	Attributed to presentation failure	ISR-mediated T-helper suppression; no presentation defect needed
Recovery with treatment	A fixed defect should not resolve	Acquired, re-trainable state; mitokines fall with recovery
Non-peptide toxins (trichothecenes)	Not presentable in the class II groove	Act as metabolic/innate stressors; no presentation required

Clinical phenomenon	HLA / haplotype model	CDR / acquired-state model
Falsifiability	Base-rate confounded; no matched-control validation	Ex-vivo and biomarker predictions on existing instruments

The decisive point is falsifiability on instruments already in use. The HLA model predicts antigen-specific adaptive signatures and ancestry-matched haplotype enrichment, neither of which has held up. The CDR model predicts, in patients versus matched controls: monocyte hyper-responsiveness to heterologous TLR challenge ex vivo; activating epigenetic marks at inflammatory loci; a Seahorse XF signature of depressed spare respiratory capacity with a shifted OCR/ECAR ratio; CD4 hyporesponsiveness to recall antigen with a raised Treg/effector ratio; and GDF15/FGF21 that track symptom burden and fall with recovery [27,28]. Each is measurable; each would, if negative, weaken the model. That is the standard the haplotype taxonomy never met.

SECTION 11

Treatment solutions mapped to mechanism

The clinical payoff of an acquired-state model is that an acquired state can be changed. Where a fixed HLA defect would be untreatable at its root, a trained, ISR-locked, mitokine-broadcasting, adaptively suppressed state offers a defined set of levers — each tied to a mechanism above. The table maps them; the text adds rationale and honest evidence grading. None of this is offered as a protocol; it is a mechanistic rationale for a sophisticated clinical readership, and the evidence base for several arms is early.

Intervention arm	Mechanistic target	CDR phase	Evidence grade
Antipurinergic (e.g. low-dose suramin)	Lowers eATP/purinergic drive; releases the danger loop and A2A T-cell brake	CDR1→exit	Hypothesis / early trial in other CDR disease
Vagal / cholinergic (VNS, breathwork)	Cholinergic anti-inflammatory reflex dampens myeloid output	CDR1–CDR2	Mechanism established; CIRS data limited
VIP (timed)	Resolves stalled CDR3; neuroendocrine restoration	CDR3	CIRS observational; timing caveat
Mitochondrial / metabolic support	Restores spare respiratory capacity; lowers ISRmt input	CDR2–CDR3	Rational; heterogeneous evidence
Re-training the innate system	Reverses maladaptive epigenetic/ metabolic marks	Upstream of all	Preclinical proof of principle
Limbic / brain retraining	Top-down modulation of central danger response	All phases	Plausible; RCT evidence thin
Exposure removal first	Removes the training/ISRmt stimulus	Prerequisite	Strong rationale; foundational

11.1 Reset the danger loop: antipurinergic and vagal arms

If extracellular ATP and purinergic signaling help perpetuate both the CDR and the A2A-mediated T-cell brake, then lowering that drive should simultaneously release the danger loop and disinhibit adaptive clearance. This is the logic of antipurinergic therapy, for which the proof of concept is Naviaux's low-dose suramin work in a CDR-framed disorder [35]; its application to CIRS is, candidly, extrapolation rather than established practice, and belongs in the hypothesis column. The vagal/cholinergic arm rests on firmer general ground — the cholinergic anti-inflammatory reflex is a well-characterized brake on myeloid cytokine output [36] — even if CIRS-specific trial data are limited; it is low-risk and mechanistically coherent.

11.2 Re-train the trained: the upstream lever

The most distinctive therapeutic implication of this model has no analogue in the HLA frame: if susceptibility is written as maladaptive innate memory, it can in principle be un-written. Trained states are reversible — β-glucan can reverse LPS-induced tolerance, and the metabolic inputs that sustain training (the glycolytic shift, glutaminolysis/fumarate, the mTOR–HIF-1α axis) are druggable targets [10,11]. Reversing maladaptive central training — at the progenitor level — is the upstream lever that would, if achieved, raise the danger-response threshold itself rather than merely damping its outputs. This is preclinical, but it is the direction the model points, and it reframes "re-training" from metaphor to molecular program.

11.3 Resolve and re-integrate: VIP, metabolic support, and sequencing

VIP addresses the stalled-CDR3 phenotype, restoring neuroendocrine tone and supporting reintegration [34]; the tolerogenic caveat from Section 9.3 makes timing matter — it is a resolution signal once danger drive is controlled, not a tool to deploy into an actively hot, suppressed state. Mitochondrial and metabolic support targets the ISRmt input directly by restoring spare respiratory capacity, which the Seahorse signature can track. Across all arms, sequencing is not optional: the exposure must be removed first (it is the training and ISRmt stimulus), and a readiness construct — the Readiness to Heal Index — properly gates whether a patient can tolerate resolution-phase intervention or must first have danger drive lowered. The HLA model offers no sequencing logic because a fixed defect has no phases; the CDR model is intrinsically staged.

11.4 Why these work where an HLA defect could not

The common thread is that every arm targets a modifiable state — a trained epigenome, a perpetuating stress loop, a purinergic tone, a suppressed but recoverable T-cell compartment. A susceptibility that is genuinely a fixed antigen-presentation genotype would be inert to all of them; the observed responsiveness of patients to exposure removal, danger-loop modulation, and resolution-phase support is itself evidence against the fixed-defect model and for the acquired-state one.

SECTION 12

Integration with the four-phenotype framework

The mechanisms map cleanly onto the four-phenotype CDR scheme, which is where the model earns its clinical keep — by predicting which lever a given patient needs.

Phenotype	Dominant mechanism	Primary lever
A — Stuck Alarm (CDR1-dominant)	Trained-immunity hyper-reactivity; high eATP/ purinergic drive	Antipurinergic; vagal; exposure removal
B — Drained Battery (CDR2-mitochondrial)	ISRmt/ATF4 perpetuation; depressed respiratory capacity; high mitokines	Metabolic/mitochondrial support; track GDF15/FGF21
C — Worn-Out Defender (CDR2-immune)	Adaptive suppression (IDO/GCN2, arginase, A2A); antibody-negative persistence	Disinhibit adaptive arm; treat persistent colonizers; antipurinergic
D — Closed Gate (CDR3-blocked)	Failure to complete/exit healing cycle; neuroendocrine deficit	VIP (timed); resolution-phase support

Read this way, the phenotypes are not four diseases but four dominant positions within one danger-response process, and the Readiness to Heal Index gates movement between resolution and de-escalation strategies. Trained immunity and echoing predominate in A; ISRmt/ATF4 and mitokines in B; adaptive suppression in C; and stalled reintegration in D — with most patients carrying a blend whose center of gravity shifts during recovery. This is a fundamentally different object from a haplotype: a trajectory through a process, not a fixed seat in a genotype.

SECTION 13

Conclusion

The HLA narrative answers the co-exposure question with a fixed inheritance the evidence does not support and the mechanism cannot bear. The Cell Danger Response answers it with an acquired state whose machinery is now specifiable in detail: trained immunity sets and durably records a lowered danger threshold; molecular scarring and echoing are that record and its consequence across time; the ATF4-driven mitochondrial integrated stress response perpetuates the danger loop and resists exit; GDF15 and FGF21 broadcast the persistent state as measurable signal and felt malaise; and the same stress axis, inverted inside T-helper cells and reinforced by purinergic and neuropeptide brakes, suppresses the adaptive clearance that would end the episode — producing antibody-negative persistence with no presentation defect required.

The model explains what the haplotype model leaves unexplained, predicts what it cannot, and — because the state is acquired and metabolically maintained — implies a therapeutics of re-training and resolution where

the fixed-defect model implies resignation. It is also, unlike the Rosetta Stone, falsifiable on instruments already in the clinic.

The susceptibility difference between two co-exposed individuals is real; it is simply not, in the main, a difference of antigen presentation. It is a difference of danger — how readily it is entered, how stubbornly it persists, and how completely it can be resolved.

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Note on sources and evidence grading. Bibliographic details for the HLA-biology, immunology, ISR, and mitokine literature were verified against primary records (PubMed, journal pages, publisher metadata); the HLA primer in Section 2 draws on standard reference reviews (refs 39–43), and the environmental-disease precedents in Section 3 (refs 44–51) are the established beryllium, Lyme, and ABPA literature. Mechanistic landmark citations are well established; page-level details should be confirmed before formal submission. The treatment section grades evidence explicitly: several arms (antipurinergic, innate re-training, limbic retraining) are mechanistic rationale or preclinical/early-trial rather than established CIRS practice, and are presented as such for a clinical-scientific readership, not as a protocol.