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A senescent-immune reserve niche model for incomplete lobular involution in the aging breast

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This Review delineates postmenopausal age-related lobular involution (ARLI) in the breast that remains only partially resolved. In contrast to the conventional view of persistent lobules as passive residual structures, this work defines them as an actively maintained senescence-immune reserve niche. Inclusion of operational definitions for the reserve state in human breast tissue would strengthen the article. The work will be of interest to scientists working in the fields of breast disorders.

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Abstract

Breast cancer incidence rises with age and peaks across the menopausal transition, yet why some postmenopausal lobules persist, and why that persistence predicts cancer risk, remains unresolved. Incomplete age-related lobular involution is one of the strongest tissue-level predictors of subsequent breast cancer, but it is still commonly viewed as passive failure of hormonally driven regression. This Review proposes a different framework: persistent lobules are maintained by an active reserve niche that outlasts its reproductive function. By integrating breast epidemiology, mammary stromal biology, cellular senescence, immune surveillance, and comparative reserve systems in skeletal muscle, hematopoiesis, and postmenopausal endometrium, we argue that menopause is a biological control point at which tissue fate diverges. Efficient clearance of senescent cells permits lobular regression to complete, whereas impaired immune surveillance may allow inflammatory paracrine signaling, macrophage reprogramming, and immune evasion to create a self-sustaining senescent-immune niche lock. This framework explains why persistent lobules are biologically active, shifts attention from epithelial quantity to microenvironmental state, and identifies the perimenopausal window as a promising interval for biomarker-guided risk stratification and prevention.

Introduction

Breast cancer is largely a disease of aging: incidence rises steeply with age, the median age at diagnosis is approximately 62 years, and roughly 84% of cases occur in women over 50 (Giaquinto, Sung et al. 2024 [↗](#)); age alone explains more of the incidence curve than any other single variable, and approximately half of all breast cancers occur in women without identifiable genetic or lifestyle risk factors (Lue and Radisky 2025 [↗](#)). Age-related lobular involution (ARLI) is the defining structural aging event of the breast: the progressive regression of terminal duct lobular units (TDLUs), the primary functional and cancer-susceptible epithelial structures of the gland. This process begins in the fourth decade, accelerates around the menopausal transition, and continues variably for decades into postmenopause (Figueroa, Pfeiffer et al. 2014 [↗](#), Radisky, Visscher et al.

2016 [↗](#)). Its completion carries direct clinical significance. Postmenopausal women with incomplete ARLI face up to a threefold elevated risk of subsequent breast cancer compared to women whose lobular regression was complete, independently of parity, body mass index, and family history (Milanese, Hartmann et al. 2006 [↗](#)), and stagnation of the involution process, the failure to progress toward completion, is itself a significant predictor of elevated risk (Radisky, Visscher et al. 2016 [↗](#)).

What has resisted explanation is why. The dominant interpretation is essentially quantitative: more residual epithelial tissue means more target cells. But this framing has important limitations. Breast cancer risk does not scale continuously with residual lobular density; instead it bifurcates around a completion threshold, with partial and absent involution conferring substantially greater risk than even modest degrees of completion (Milanese, Hartmann et al. 2006 [↗](#)). Involution status is independent of other markers of breast density and epithelial content, suggesting it carries biological information beyond tissue quantity (Milanese, Hartmann et al. 2006 [↗](#), Radisky, Visscher et al. 2016 [↗](#)). Most directly: local inflammatory proteins in histologically normal breast tissue from breast cancer patients are inversely associated with complete involution, with higher levels of pro-inflammatory markers IL-6, TNF- α , CRP, COX-2, leptin, SAA1, and IL-8, and notably the immunosuppressive cytokine IL-10, all correlating with less complete lobular regression after age adjustment (Hanna, Dumas et al. 2017 [↗](#)). The microenvironment of persistent lobules is biologically active, not neutral. The more fundamental question is therefore not what prevents involution from occurring, but what actively maintains the tissue that fails to involute.

This review proposes that incomplete ARLI represents the persistence of an adaptive reserve tissue program, an actively maintained, locally sustained epithelial state supported by microenvironmental signaling, rather than a passive default arising from incomplete hormonal withdrawal. A conceptual clarification is necessary from the outset: we use “adaptive” in its evolutionary rather than its functional sense; the program that maintains residual lobular tissue was shaped by selection during reproductive years, when episodic involution and potential late pregnancy created genuine biological value for keeping some lobular capacity in reserve. Menopause represents a context this program was never designed to resolve; the maintenance machinery persists, but the hormonal resolution signal that would normally terminate it does not arrive. What is adaptive in origin can therefore be maladaptive in consequence, and understanding that distinction is central to understanding both the biology of incomplete ARLI and the timing of its cancer risk. We develop this argument in four steps: establishing the conceptual framework of adaptive reserve programs by cross-tissue comparison; applying that framework to ARLI using the published breast biology literature; proposing the senescent-immune niche as the mechanistic basis of reserve maintenance in the postmenopausal breast; and identifying the menopausal transition as the control point that determines whether the niche resolves or locks.

Reserve tissue programs: Conceptual framework

Definition and core properties

Adult tissues that must sustain regenerative capacity across decades face a fundamental problem: the cells that supply regeneration cannot divide continuously without exhausting themselves or accumulating transformative mutations, yet they must remain available on timescales longer than any single remodeling event. Reserve tissue programs are the biological solution. Operationally, a reserve tissue program maintains a latent regenerative module in a poised state, supported by specialized niches, immune-stromal signaling, and intrinsic molecular restraints, in a manner that enables recovery when conditions improve, while potentially increasing long-term pathology risk if the program remains chronically engaged (de Morree and Rando 2023 [↗](#)). This definition distinguishes reserve programs from two superficially similar states: passive quiescence, in which cells simply fail to receive proliferative signals, and terminal differentiation, in which cells have permanently exited the regenerative pool. Reserve programs are actively maintained: their

constituents remain metabolically engaged, stress-resistant, and primed for deployment. The apparent stillness of the reserve conceals ongoing molecular activity: suppression of mRNA translation through post-transcriptional mechanisms, metabolic rewiring toward oxidative phosphorylation that reduces DNA damage accumulation, whose purpose is readiness rather than rest (Tumpel and Rudolph 2019 [↗](#), de Morree and Rando 2023 [↗](#)).

Reserve programs operate across a spectrum of quiescence depth, from shallow states in which cells are one or two signals from re-entering the cell cycle to deep states requiring more substantial reprogramming for reactivation. Under chronic stress or loss of niche support, reserve cells progress toward the deep end of this spectrum, which merges with irreversible senescence-like arrested states from which reactivation is no longer possible. This quiescence-to-senescence continuum is critical to the ARLI hypothesis: the p16^{INK4a}/Rb axis that enforces poised quiescence can become permanently engaged when the signals maintaining its reversibility are withdrawn or overwhelmed. Incomplete ARLI may initially represent a shallow reserve state, but its trajectory under chronic aging and immune remodeling is toward deeper entrenchment and eventual senescent conversion (Tumpel and Rudolph 2019 [↗](#), de Morree and Rando 2023 [↗](#)).

The resilience–risk tradeoff as organizing principle

Reserve tissue programs are Janus-faced. The persistence and molecular poising that enable a tissue to survive chronic stress and regenerate after injury are the same properties that create long-term pathology risk. Long-lived progenitor pools accumulate DNA damage through oxidative stress, mitochondrial dysfunction, and epigenetic drift even without dividing (Tumpel and Rudolph 2019 [↗](#)). Their maintenance in a proliferation-competent poised state means that the cellular machinery required for transformation, including cell cycle progression, apoptosis evasion, growth factor responsiveness, is already partially engaged. None of these risks require prior neoplastic conversion of the reserve cells; they are consequences of reserve architecture rather than defects within it.

This tradeoff is the conceptual key to understanding why incomplete ARLI elevates breast cancer risk without requiring persistent lobules to be pre-malignant at the time the epidemiologic association is measured. The elevated risk is a property of the reserve state itself, a maintained, proliferation-competent tissue unit with a chronic inflammatory microenvironment, rather than evidence of transformation already underway. Aging can drive reserve programs toward the risk side through two distinct failure modes: by depleting the reserve too rapidly, so the progenitor pool is exhausted before malignancy can be selected for; or by failing to resolve a reserve that was shaped by selection for a prior biological context, allowing it to become a chronic substrate for pathology once that context no longer obtains. In the aging breast it is the second failure mode that operates: a program selected during reproductive years, now running without the resolution signal that menopause was never reliably shaped to provide, and the comparator systems below illuminate both why that is and what it predicts mechanistically.

Cross-tissue comparators

Skeletal muscle satellite cells

Muscle satellite cells are the canonical quiescent reserve stem cell population of adult mammalian tissues. These PAX7-positive cells reside between the plasma membrane and basal lamina of individual myofibers, maintained in G0 by niche-derived signals, including Notch ligands, extracellular matrix cues, and paracrine inputs from vasculature, that enforce quiescence while preserving reactivation competence (de Morree and Rando 2023 [↗](#)). In young individuals, satellite cells respond to injury with rapid activation, asymmetric division, and fiber fusion, followed by return to quiescence after repair (Fig. 1 [↗](#), Zone 1).

With aging, this cycle breaks down through a mechanism defined with unusual precision. Resting satellite cells progressively lose active suppression of the p16^{INK4a}/Rb axis, transitioning into an irreversible pre-senescent state even without injury. When challenged, they undergo geroconversion, accelerated entry into full senescence, even after transplantation into a young

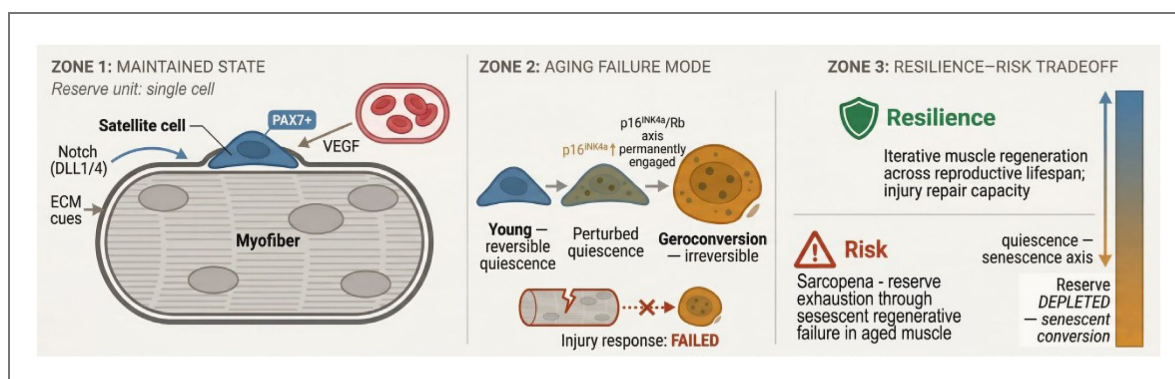


Figure 1. Skeletal muscle satellite cells establish the cellular reserve program logic: quiescence, niche maintenance, and aging-driven senescent conversion.

PAX7⁺ satellite cells (steel blue) reside between the myofiber sarcolemma and basal lamina, maintained in reversible G0 quiescence by Notch ligands, extracellular matrix cues, and paracrine VEGF from adjacent vasculature (**Zone 1**). Niche-enforced quiescence preserves reactivation competence across multiple cycles of injury and repair. With aging, progressive engagement of the p16^{INK4a}/Rb axis drives an irreversible transition through perturbed quiescence to geroconversion, a cell-intrinsic senescent state from which reactivation is no longer possible and injury-induced regeneration fails (**Zone 2**). The quiescence-to-senescence spectrum (right axis) illustrates this progression: young satellite cells occupy the deepquiescence end; aging drives movement toward irreversible senescence, depleting the reserve. **Zone 3** encodes the resilience-risk tradeoff: iterative regenerative capacity across the reproductive lifespan, at the cost of sarcopenic reserve exhaustion through senescent conversion in aged muscle. The core molecular logic, p16^{INK4a}/Rb-dependent quiescence maintenance, niche-enforced reversibility, and aging-driven senescent conversion, recurs across reserve tissue programs and is directly applicable to the breast ARLI system.

host, demonstrating cell-intrinsic failure. Silencing p16^{INK4a} is sufficient to restore reversible quiescence and regenerative function, establishing quiescence-to-senescence conversion as the causal mechanism of sarcopenic muscle's regenerative deficit (Sousa-Victor, Gutarra et al. 2014 [Fig. 1](#), [Zone 2](#)). The breast reserve program follows the same spectrum in the opposite direction: whereas aged muscle loses its reserve through senescent conversion, incomplete ARLI retains a reserve maintained in an increasingly senescence-prone state ([Fig. 1](#), [Zone 3](#)).

Hematopoietic stem cells

Hematopoietic stem cells illustrate the risk consequence of long-lived reserve maintenance. HSCs are maintained in stable quiescence within the endosteal niche across decades; unlike satellite cells, aging does not drive senescent conversion, and the reserve persists morphologically unchanged ([Fig. 2](#), [Zone 1](#)), and the compartment persists as a long-lived progenitor system into later life (Tumpel and Rudolph 2019 [Fig. 2](#), [Zone 2](#)). Risk accumulates instead through somatic evolution within the maintained pool. Large population sequencing studies showed that age-associated clonal hematopoiesis becomes increasingly detectable in individuals without overt hematologic disease, and that these clones are associated with increased subsequent hematologic cancer risk (Genovese, Kahler et al. 2014 [Jaiswal, Fontanillas et al. 2014](#), Steensma, Bejar et al. 2015 [The key principle is that risk is architectural rather than cellular: because the reserve is maintained across decades, rare advantageous mutations have an extended opportunity for selection and clonal propagation, independent of any pre-malignant transformation in the reserve cells themselves \(\[Fig. 2\]\(#\), \[Zone 3\]\(#\)\).](#)

Postmenopausal endometrium

The postmenopausal endometrium is the closest hormonal analog to the breast in the reserve program framework. Basalis stem and progenitor cells that drive cyclic endometrial regeneration persist in quiescence after menopause, without hormonal stimulation or regenerative demand, maintained for years to decades in atrophic but architecturally intact tissue (Cousins, Filby et al. 2021 [Fig. 3](#), [Zone 1](#)). The functional competence of this dormant reserve is demonstrated clinically: exogenous estrogen administered to women with decades of postmenopausal atrophy rapidly restores pre-menopausal endometrial thickness, establishing that reactivation capacity is fully retained regardless of time elapsed since menopause (Cousins, Filby et al. 2021 [Risk arises not from transformation during dormancy but from aberrant reactivation. Unopposed estrogen exposure — from obesity-associated aromatization or exogenous hormone regimens — triggers abnormal proliferation from the maintained reserve, driving endometrial hyperplasia and carcinoma \(Nees, Heublein et al. 2022 \(\[Fig. 3\]\(#\), \[Zone 2\]\(#\)\). The endometrium thus illustrates passive reserve dormancy: the progenitor pool awaits an external hormonal signal, and pathology requires that signal to arrive in unbalanced form. This contrast with the breast is the conceptual hinge of the ARLI hypothesis. In the postmenopausal breast, the equivalent failure is not aberrant reactivation by an external signal but paracrine maintenance without hormonal input; the reserve would, under the reserve niche model proposed in Section 4, be actively sustained by a senescent-immune niche rather than resolved by it \(\[Fig. 3\]\(#\), \[Zone 3\]\(#\)\).](#)

What distinguishes ARLI from canonical reserve programs and what it shares

Reserve maintenance requires niche integrity, cell-intrinsic quiescence programs, and active regulation along the quiescence-to-senescence continuum (Tumpel and Rudolph 2019 [de Morree and Rando 2023](#)). The failure modes differ instructively: in aged muscle, the reserve is depleted through senescent conversion of satellite cells ([Fig. 1](#)); in the hematopoietic system, the stably maintained reserve becomes a substrate for somatic evolution and clonal malignant risk ([Fig. 2](#)); in the postmenopausal endometrium, the reserve persists in passive dormancy awaiting an external reactivation signal ([Fig. 3](#)). In each case, niche integrity is either lost or passively held. In the postmenopausal breast, the pathology runs in the opposite direction: niche integrity is aberrantly sustained, and that maintenance is itself the problem ([Fig. 4](#)).

Figure 2. Hematopoietic stem cells establish the somatic evolutionary horizon principle: cancer risk without pre-malignant conversion in a long-lived maintained reserve.

HSCs (deep violet) are maintained in stable quiescence within the endosteal niche by CXCL12/CXCR4 retention signals from CAR cells and SCF/c-Kit signaling from sinusoidal endothelium (**Zone 1**). Unlike skeletal muscle satellite cells, aging does not drive HSCs toward senescent conversion, the reserve persists in stable quiescence across decades with no morphological change. Risk accumulates instead through somatic evolution within the maintained progenitor pool: clones bearing driver mutations in DNMT3A, TET2, and ASXL1 expand gradually to clonal dominance without producing overt disease (CHIP; **Zone 2**). Clonal dominance is invisible at the cellular level; risk is architectural, not cellular. **Zone 3** encodes the resilience-risk tradeoff: lifelong hematopoiesis across the entire lifespan, at the cost of hematologic malignancy risk through an extended somatic evolutionary horizon operating within the stably maintained reserve. The principle is directly applicable to incomplete ARLI: a maintained, proliferation-competent tissue unit confers cancer risk through the extended opportunity it provides for somatic evolution, independent of pre-malignant conversion of reserve cells themselves.

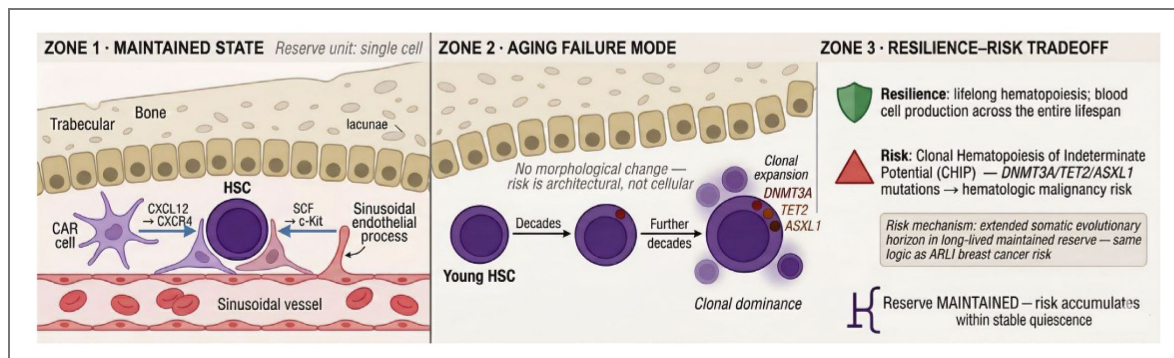
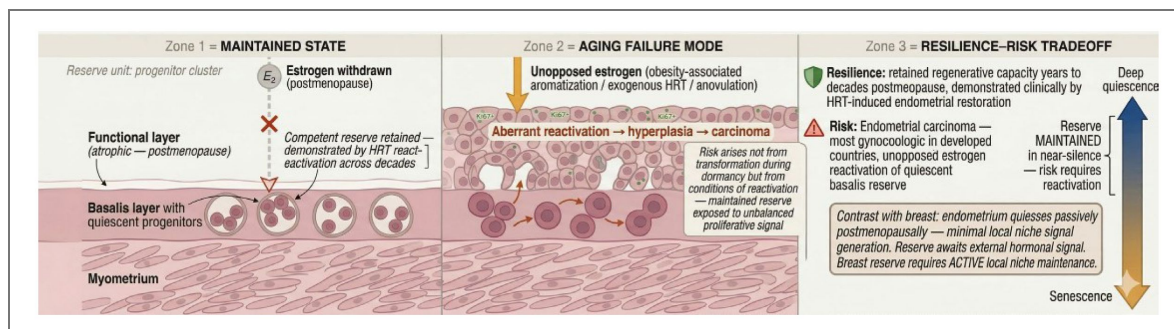


Figure 3. The postmenopausal endometrium illustrates passive reserve dormancy and risk through aberrant reactivation.

Basalis progenitor cells clustered in gland bases at the myometrium interface persist in deep quiescence following menopause, maintained without hormonal stimulation in atrophic but architecturally intact tissue for years to decades (**Zone 1**). The functional competence of this dormant reserve is demonstrated clinically by the rapid restoration of pre-menopausal endometrial thickness following exogenous estrogen administration, as the quiescent reserve retains full reactivation capacity regardless of time elapsed since menopause. Risk arises not from transformation during dormancy but from aberrant reactivation: unopposed estrogen from obesity-associated aromatization or exogenous hormone regimens triggers abnormal proliferation from the maintained reserve, driving endometrial hyperplasia and carcinoma (**Zone 2**). The quiescence-to-senescence spectrum (right axis) positions endometrial progenitors at the deep-quiescence end with minimal aging-driven movement; the reserve awaits an external hormonal signal rather than generating internal niche dynamics. **Zone 3** encodes the resilience-risk tradeoff: retained regenerative capacity years to decades postmenopause, at the cost of carcinoma risk through unopposed estrogen reactivation of the quiescent basalis reserve. Critically, the postmenopausal endometrium quiesces passively; minimal active local niche signal generation is required, and the reserve awaits an external hormonal cue. This is in direct contrast to the breast reserve, which requires active local paracrine maintenance in the absence of systemic hormonal input and is sustained rather than resolved by its immune-stromal microenvironment.



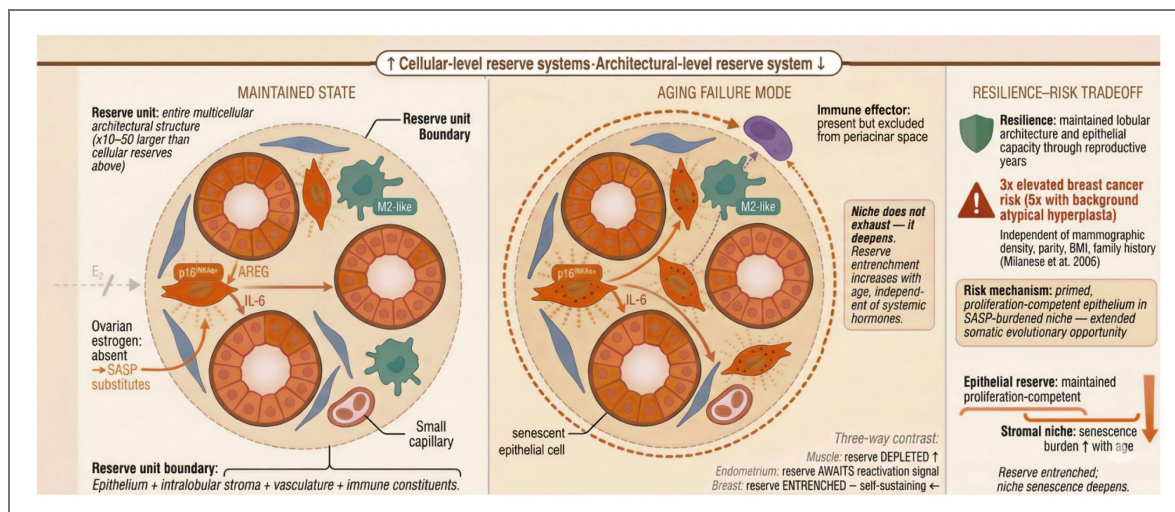


Figure 4. The breast TDLU reserve operates at architectural rather than cellular scale, requiring active local niche maintenance in the absence of systemic hormonal input.

The unit of reserve in incomplete ARLI is an entire functional terminal duct lobular unit: epithelium, intralobular stroma, vasculature, and immune constituents together (dashed boundary), rather than a single stem-cell compartment. This architectural scale implies a requirement not dependent on canonical cell-level reserves: active local paracrine signal generation is needed to sustain the unit after systemic ovarian input has withdrawn. In the maintained state (left), senescent stromal cells are proposed to substitute in part for withdrawn endocrine support through SASP-derived epithelial maintenance signals such as AREG and IL-6, while macrophages and other immune/stromal components contribute to a trophic microenvironment. The aging failure mode (right) is distinct from the comparator systems: rather than reserve depletion through senescent collapse or passive dormancy awaiting reactivation, the breast niche becomes progressively self-sustaining as senescent burden accumulates and immune clearance fails despite continued immune-cell presence. The resilience-risk tradeoff is maintenance of lobular architecture and epithelial capacity across reproductive years at the cost of a chronically survival-permissive microenvironment that extends the somatic evolutionary horizon of the tissue unit.

Incomplete ARLI shares the core reserve logic but differs from all three comparators in one architecturally decisive respect (Fig. 4). In every canonical reserve system, the unit of reserve is individual cells or small subpopulations within otherwise differentiated tissue. In incomplete ARLI, the reserve unit is an entire functional tissue structure: a TDLU with organized acinar architecture, specialized intralobular stroma, and a spatially distinct paracrine signaling environment. Sustaining it requires not merely keeping cells in a particular molecular state but maintaining the organized multicellular assembly of epithelium, stroma, vasculature, and immune constituents together, without systemic hormonal support. This architectural scale implies a requirement absent from all cell-level reserve systems: the local paracrine environment within and around the TDLU must itself actively generate the maintenance signals that estrogen withdrawal has removed from the systemic circulation.

ARLI as reserve tissue: Evidence from the published literature

Having established the reserve program framework through three comparator systems, we now apply it to ARLI directly. The defining question is whether persistent lobular tissue is passively maintained, cells that simply failed to regress, or actively sustained by microenvironmental signaling in the absence of systemic hormonal input. Two converging lines of evidence favor the latter.

Epidemiologic anchors

The natural history of ARLI exhibits the hallmarks of a reserve tissue program: individual variability, biological determination, and clinical consequence independent of standard risk covariates. Quantitative TDLU metrics establish that lobular regression is a lifelong process already underway during reproductive years, well before the menopausal transition (Hutson, Cowen et al. 1985, Figueroa, Pfeiffer et al. 2014, Radisky, Visscher et al. 2016). Regression then continues variably for decades, with heterogeneity unexplained by menopausal timing, parity, BMI, or family history (Radisky, Visscher et al. 2016). This constitutes a field-level phenotype: within-woman quadrant concordance in involution scoring is high, supporting ARLI as a whole-breast biological state rather than a focal observation (Vierkant, Hartmann et al. 2009). Critically, involution stasis, the failure to progress across sequential biopsies, carries elevated breast cancer risk independent of absolute involution degree at any single time point, demonstrating that biological trajectory rather than elapsed time governs outcome (Radisky, Visscher et al. 2016).

The magnitude of the risk association is substantial. Postmenopausal women with no involution face approximately threefold elevated risk compared women with complete involution, rising to fivefold with background atypical hyperplasia (Milanese, Hartmann et al. 2006). These effects are independent of mammographic density: the joint phenotype of dense breasts combined with absent involution confers an incidence rate approximately four times that of nondense tissue with complete involution (Ghosh, Vachon et al. 2010). Standardized quantitative TDLU measures replicate this risk gradient with an independent measurement approach: higher TDLU density, span, and acini per TDLU each predict subsequent cancer, with effect estimates ranging from approximately twofold to threefold across extreme quartile contrasts (Figueroa, Pfeiffer et al. 2016). Involution status also intersects with germline risk: a 313-variant polygenic risk score for breast cancer is positively associated with higher TDLU counts, positioning ARLI as a plausible intermediate phenotype linking inherited susceptibility to tissue architecture (Bodelon, Oh et al. 2020). These associations already have clinical applicability: involution extent is incorporated into the BBD-BC absolute risk prediction model with substantial point assignments for absent and partial involution, enabling ARLI-informed risk stratification in women with benign biopsies (Pankratz, Degnim et al. 2015).

One important caveat deserves acknowledgment. The epidemiologic literature is mixed, and not reducible to a simple Mayo-versus-Nurses' Health split. In a nested case-control study within the Nurses' Health Studies, women whose benign biopsies showed a more involuted lobule-type pattern had lower subsequent breast cancer risk, although the association was attenuated after adjustment for benign histologic category (Baer, Collins et al. 2009 [\[1\]](#)). By contrast, a later large nested case-control analysis in the same parent cohorts using automated wholeslide quantitative TDLU measures found no material association between involution metrics and subsequent breast cancer risk (Kensler, Liu et al. 2020 [\[2\]](#)). Taken together, these results suggest that the epidemiologic signal of ARLI may be method-sensitive: it likely depends on how involution is sampled, operationalized, and quantified across cohorts. Involution status captures microenvironmental information not proxied by established risk covariates, but the conditions under which that signal is most reliably captured remain an active area of investigation.

The biological activity of persistent lobules

A passive target-tissue model cannot account for these patterns. Postmenopausal breast tissue shows two lobular fates within the same adipose field: a collapsed hypocellular remnant representing complete ARLI alongside an architecturally intact, cellularly active TDLU representing incomplete ARLI (Fig. 5A [\[3\]](#)). The most direct functional evidence comes from inflammatory protein profiling of histologically normal breast tissue obtained from pre- and postmenopausal breast cancer patients: elevated levels of IL-6, TNF- α , CRP, COX-2, leptin, SAA1, IL-8, and IL-10 were all inversely associated with complete lobular involution, persisting after age adjustment (Hanna, Dumas et al. 2017 [\[4\]](#)) (Fig. 5B [\[5\]](#)). This result does not by itself establish mechanism, but it shows that less involuted lobular tissue is accompanied by a distinct inflammatory and immune-regulatory milieu rather than a neutral excess of residual epithelium. Complementary histologic work likewise argues against passivity. In normal breast tissue, immune cells are predominantly localized to lobules rather than interlobular stroma, with CD8⁺ cells and dendritic cells closely apposed to the basal epithelial layer; lobules with lobulitis contain significantly higher densities of CD4⁺, CD8⁺, CD20⁺, and CD45⁺ cells, and in this series, lobulitis was present in 70% of noninvolved lobules, 43% of partially involuted lobules, and only 3% of completely involuted lobules (Degnim, Brahmabhatt et al. 2014 [\[6\]](#)). Single-cell transcriptomic and epigenomic profiling of the aging murine mammary gland provides the broader cellular correlate: stromal fibroblasts shift toward senescence-associated and cancer-associated states, M2-like macrophages expand as cytotoxic competence declines, and spatial transcriptomics confirms co-localization of aged immune and epithelial cells in situ, with signatures conserved in human breast tumor transcriptomes (Angarola, Sharma et al. 2025 [\[7\]](#)) (Fig. 5B [\[5\]](#)). The aged mammary microenvironment is not depleted; it is dynamically reorganized within precisely the cellular constituencies, including fibroblasts, macrophages, immune cells, that the reserve niche model identifies as maintenance signals.

Subtype associations provide a second line of support that poorly involuted tissue is biologically distinctive rather than simply more abundant. Among breast cancer cases, reduced involution in adjacent or surrounding normal tissue is preferentially associated with triple-negative and core basal phenotype tumors compared with luminal A cancers, a pattern reported in Polish, Chinese, and Black study populations (Yang, Figueroa et al. 2012 [\[8\]](#), Guo, Sung et al. 2017 [\[9\]](#), Davis Lynn, Lord et al. 2022 [\[10\]](#)). This subtype specificity is consistent with a biologically distinct niche state in which inflammatory remodeling, immune regulation, and stromal signaling differ from the microenvironment surrounding fully involuted lobules.

The postpartum involution analog

Postpartum mammary involution provides mechanistic proof-of-concept that the senescence-immune axis is operative and functionally consequential during mammary tissue regression. By contrast with ARLI, postpartum involution is rapid, hormonally triggered, and largely reversible, but the cellular machinery engaged appears homologous, making it the most direct available analog for the niche biology of age-related involution. Postpartum involution has been established

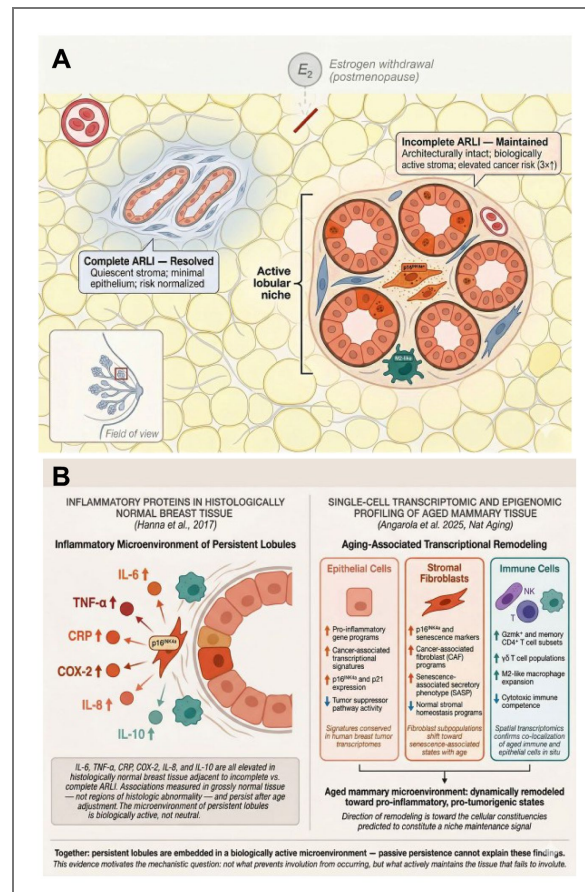


Figure 5. Schematic summary of evidence that incomplete age-related lobular involution is a biologically active maintained tissue state.

(A) Wide-field cross-section of postmenopausal breast tissue showing two lobular fates within the same adipose field. Complete ARLI (left): a collapsed, hypocellular lobular remnant with quiescent stroma embedded in interlobular fat. Incomplete ARLI (right): an architecturally intact terminal duct lobular unit with organized acinar profiles and a biologically active intralobular stroma containing senescent fibroblasts, quiescent fibroblasts, macrophages, and persistent epithelial structures. Ovarian estrogen withdrawal is indicated above; the lobular niche persists despite it. Anatomical inset indicates field of view within the mammary ductal tree. **(B)** Two lines of evidence that persistent lobules are embedded in a biologically active microenvironment rather than passively persisting. Left: in histologically normal breast tissue from breast cancer patients, pro-inflammatory markers IL-6, TNF- α , CRP, COX-2, leptin, SAA1, and IL-8, together with IL-10, were inversely associated with complete involution after age adjustment. Right: single-cell transcriptomic and epigenomic profiling of aged murine mammary tissue reveals coordinated remodeling across stromal, immune, and epithelial compartments, with spatial co-localization of aged immune and epithelial cells.

as a tumor-promotional microenvironment in which collagen remodeling and COX-2 activity are not incidental correlates but functional mediators of progression, thereby framing involution itself as a biologically consequential tissue state rather than a neutral return to baseline (Lyons, O'Brien et al. 2011 [\[4\]](#)). Macrophages are required executors of the epithelial clearance program: conditional CSF1R⁺ macrophage depletion prior to weaning impairs epithelial cell death and alveolar regression, and reconstitution with wild-type or M2-differentiated macrophages fully rescues involution (O'Brien, Martinson et al. 2012 [\[4\]](#)). A transiently immunosuppressive milieu accumulates during mid-involution; neutralizing IL-10 reduces tumor growth in postpartum breast cancer models, and these immune infiltrates are documented in post-lactational human breast tissue, establishing their functional relevance beyond rodent models (Martinson, Jindal et al. 2015 [\[4\]](#), Jindal, Narasimhan et al. 2020 [\[4\]](#)). The postpartum analog therefore supports the central premise of the ARLI hypothesis: mammary involution can proceed through an immune-stromal program that is transient and resolving in youth, yet biologically potent enough to shape later cancer-relevant tissue states.

The molecular overlap between postlactational and age-related involution is further supported by the observation that plasminogen and phospho-STAT3, biomarkers of active postlactational remodeling, are independently associated with progressive ARLI in serial biopsy tissue, establishing shared signaling nodes between the two processes (Stallings-Mann, Heinzen et al. 2017 [\[4\]](#)). Most directly, recent work shows that p16^{INK4a}-dependent senescence is induced in alveolar luminal cells during the irreversible phase of postpartum involution and contributes to normal tissue remodeling; in a postpartum cancer model, eliminating these involution-associated senescent cells extended tumor latency, indicating that the same senescent program that supports physiologic remodeling can be co-opted when oncogenic events coincide with involution (Chiche, Djoual et al. 2026 [\[4\]](#)). If this axis operates during postpartum remodeling in young tissue, it is the natural candidate mechanism for ARLI, with the biology of aging providing the reasons why the resolution that normally follows postpartum involution may instead fail.

Menopause as a control point: microenvironmental remodeling and the niche lock

Menopause does not simply remove hormonal stimulation from breast tissue; it actively remodels the immune and stromal landscape. The conventional framing, that estrogen withdrawal drives lobular regression, and incomplete regression is its consequence, is inconsistent with the natural history of ARLI. Involution is detectable before the final menstrual period, accelerates around the menopausal transition, continues variably for decades afterward, and shows individual heterogeneity that menopausal timing alone cannot explain (Milanese, Hartmann et al. 2006 [\[4\]](#), Radisky, Visscher et al. 2016 [\[4\]](#)). Menopause is better understood as a control point: a transition that shifts immune competence, remodels macrophage polarization, and reorganizes endocrine inputs to breast stromal biology in ways that determine whether the programs capable of completing involution remain operative.

The immune remodeling that accompanies menopause is more complex than a simple loss-of-immunity model. Postmenopause is associated with increased pro-inflammatory tone and reduced cytotoxic immune function, with contributions from estrogen deprivation in addition to chronological aging (Gameiro, Romao et al. 2010 [\[4\]](#)). More recent primary human data sharpen and complicate that picture: postmenopausal women show higher circulating IL-6 and TNF- α , higher total lymphocyte and monocyte counts, and increased exhausted, senescent, and memory T-cell subsets rather than a uniform decline across lymphocyte compartments (Abildgaard, Tingstedt et al. 2020 [\[4\]](#)). Postmenopause is accompanied by increased systemic inflammation and altered immune-cell composition/function, with NK activity and lymphocyte-abundance findings varying across studies (Gameiro, Romao et al. 2010 [\[4\]](#), Abildgaard, Tingstedt et al. 2020 [\[4\]](#)). Immune surveillance capacity may therefore degrade not because every immune population monotonically decreases, but because inflammatory tone rises while the balance of effector, memory, and exhausted/senescent states shifts at the same time that breast tissue senescent burden is increasing (Fig. 6 [\[4\]](#), **locking trajectory**). This is compounded by the postmenopausal

shift from estradiol to estrone: estrone stimulates NF κ B-mediated upregulation of CCL2, IL-6, and IL-8 in mammary adipocytes while estradiol opposes this induction, shifting the postmenopausal breast toward a locally pro-inflammatory state that reinforces rather than counteracts SASP-driven niche signaling (Qureshi, Picon-Ruiz et al. 2020 [\[1\]](#)). Secondary support for broader menopause-associated immune-stromal rewiring comes from a recent bioRxiv preprint using ovariectomized-mouse single-cell datasets, which inferred estrogen-responsive macrophages as major signaling hubs across several tissues (Iijima, Yamashita et al. 2025 [\[2\]](#)).

Menopause therefore defines a critical window during which competing signals for clearance and persistence are both active and a niche lock has not yet been established, which is the period of greatest biological plasticity and highest intervention opportunity (Fig. 6 [\[3\]](#), **perimenopausal window**). The WHI trials establish timing-dependent biological responsiveness as a general principle of postmenopausal endocrine biology: hormone therapy initiated within versus beyond ten years of the last menses produces fundamentally different risk-benefit profiles, demonstrating that target tissue state at the moment of intervention determines outcome (Manson, Chlebowski et al. 2013 [\[4\]](#)). The analogous prediction for the reserve niche is that immune clearance restoration will be most effective before the niche achieves a self-sustaining hormone-independent state; after the lock is established, strategies must target the lock directly. This timing logic also converts a longstanding epidemiologic puzzle into a mechanistic prediction: individual variability in ARLI trajectories among women of comparable age and menopausal timing is expected under the reserve niche model, because what determines outcome is not menopausal timing per se but the state of the senescent-immune system at the moment the transition occurs (Fig. 6 [\[3\]](#), **control point**). Women who enter menopause with more intact immune-clearance competence relative to senescent burden retain sufficient capacity to complete involution; women who enter with already-compromised surveillance are more likely to lose that residual capacity, and under this model the reserve niche locks.

The senescent-immune reserve niche hypothesis

Cellular senescence in the aging breast: the published foundation

The cellular machinery of the senescent-immune niche hypothesis has established precedent in the aging mammary gland before any hypothesis is invoked. p16^{INK4a} expression, the most reliable in vivo marker of cellular senescence, increases markedly with age in mammary epithelium and stroma, restricted to well-defined cellular compartments and attenuated by caloric restriction (Krishnamurthy, Torrice et al. 2004 [\[5\]](#)). Single-cell profiling confirms that aged stromal fibroblasts and immune cells specifically upregulate p16^{INK4a} and p21, with fibroblast subpopulations shifting toward senescence-associated and cancer-associated states (Angarola, Sharma et al. 2025 [\[6\]](#)). The aged breast microenvironment contains a demonstrably elevated senescent burden, localized to stromal compartments anatomically positioned to exert paracrine influence on adjacent epithelium.

The functional output of these cells is the SASP, a context-dependent secretome comprising inflammatory cytokines, matrix metalloproteinases, and, critically, EGFR family ligands including amphiregulin (AREG) and epiregulin (EREG) (Basisty, Kale et al. 2020 [\[7\]](#)). Whether SASP is transiently deployed during normal remodeling or chronically sustained in aging tissue determines its functional consequences (Birch and Gil 2020 [\[8\]](#)). This temporal duality maps directly onto the distinction between complete and incomplete ARLI: the postpartum involution niche represents transient, resolving senescent signaling; the aged breast microenvironment represents chronic, non-resolving SASP accumulation (Lue and Radisky 2025 [\[9\]](#)).

The hypothesis: formal statement

We propose that incomplete ARLI represents the postmenopausal persistence of a reserve tissue program that was actively maintained during reproductive life, sustained now not by ovarian hormones but by a senescent-immune niche lock that substitutes local paracrine signaling for the systemic cues that have been withdrawn. The core proposition is as follows: persistent SASP

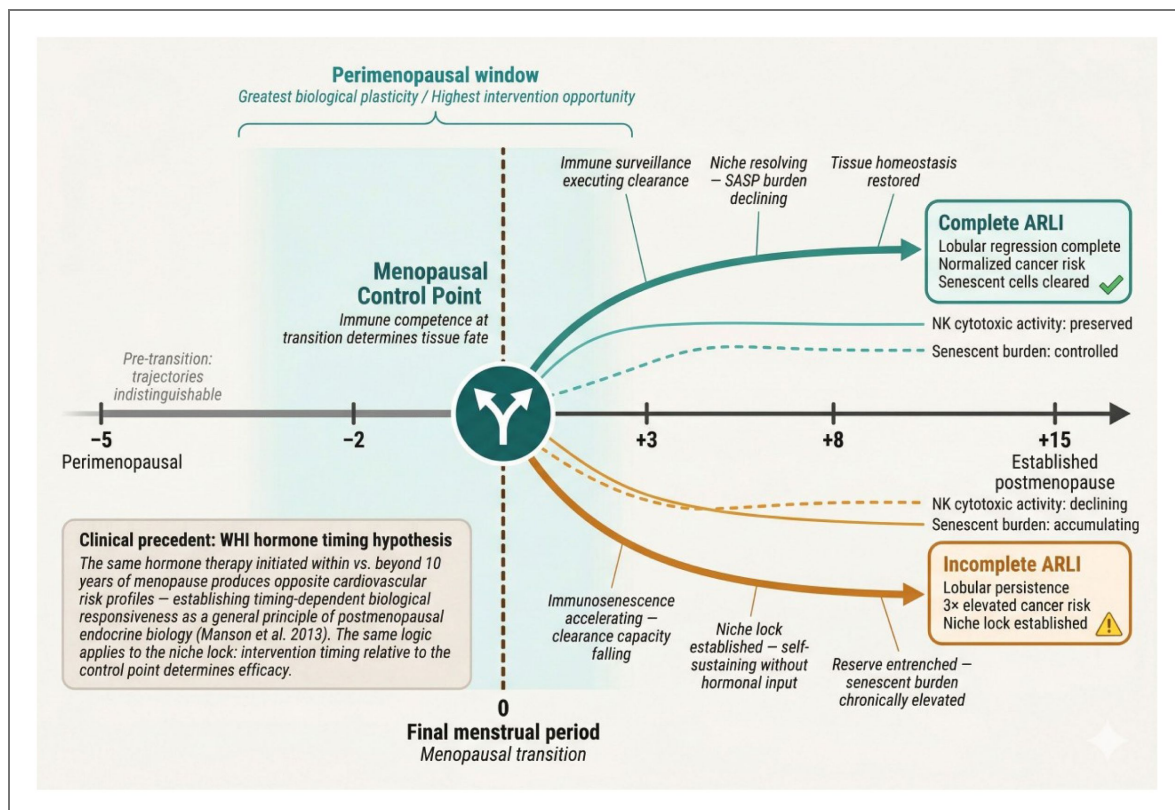


Figure 6. Conceptual model of the menopausal transition as a biological control point for ARLI trajectory.

The x-axis represents years from the final menstrual period, from perimenopause through established postmenopause. Before the transition, tissue fate trajectories are not yet divergent; what matters is immune competence and senescent burden at the control point, not chronological age alone. Two post-transition trajectories are shown: a resolving trajectory (teal), in which senescent cells are cleared, SASP burden declines, and lobular regression completes toward lower risk; and a locking trajectory (amber), in which clearance capacity becomes insufficient, senescent burden rises, and a self-sustaining niche lock is established. Companion traces depict NK cytotoxic activity and senescent burden along each trajectory. The shaded perimenopausal window represents the period of greatest biological plasticity and therefore the period of greatest intervention opportunity. The timing principle has a clinical precedent: responsiveness to menopausal hormone therapy depends on the state of the target tissue at the time therapy is initiated. The same logic is proposed to govern reserve niche interventions.

signaling, combined with menopause- and agethaped immune remodeling, creates a local microenvironment that maintains residual epithelial units in a survival-primed, incompletely involuted state (Fig. 7 [↗](#)). The program is not currently adaptive; the postmenopausal breast is not poised for reactivation, but it is actively maintained, and that distinction has direct mechanistic consequences. Under this model, incomplete ARLI is not a failure to involute but a maintenance program running without its resolution signal, driven by the convergence of SASP accumulation, impaired immune clearance, and macrophage reprogramming in the postmenopausal breast. Three mechanistic arms generate this niche, each independently supported by published evidence and each generating distinct experimental predictions.

Arm 1: SASP as a paracrine maintenance signal for residual epithelium

AREG is among the most consistently elevated factors across SASP profiles (Basisty, Kale et al. 2020 [↗](#)). In the mammary gland, AREG is the primary paracrine mediator of estrogen-driven ductal morphogenesis, functioning through stromal estrogen receptor alpha to drive EGFR-dependent epithelial proliferation (Ciarloni, Mallepell et al. 2007 [↗](#)). Its presence as a canonical SASP factor positions senescent stromal cells as a potential substitute source of epithelial maintenance signal after ovarian hormone withdrawal.

IL-6/STAT3 signaling provides a second paracrine arm with a specifically mammaryrelevant paradox. Acute STAT3 activation is required for epithelial apoptosis during postpartum involution, and conditional Stat3 deletion dramatically delays involution and suppresses cell death, with failure of the downstream survival-signal sequesterant IGFBP-5 to accumulate (Chapman, Lourenco et al. 1999 [↗](#), Hughes, Wickenden et al. 2012 [↗](#)). Yet the same IL-6/STAT3 axis functions as a chronic survival and stemness pathway in cancer and aberrant epithelial states. Under chronic low-level SASP-derived IL-6, without the acute milk-stasis context of postpartum remodeling, STAT3 signaling in residual lobular epithelium may favor survival rather than clearance, a context-dependence consistent with the well-characterized pleiotropy of this pathway.

Arm 2: Convergent mechanisms of immune clearance failure

Four convergent mechanisms are proposed to allow persistent senescent cells to evade immune clearance, all characterized in human tissues or experimental models; their convergent operation specifically within the ARLI lobular niche remains to be demonstrated. First, MMP-dependent shedding of NKG2D ligands (MICA, MICB, ULBPs) by senescent cells removes the activating signal for NK and CD8 T cell killing, while accumulating soluble MICA further downregulates NKG2D in a paracrine feed-forward loop (Munoz, Yannoni et al. 2019 [↗](#)). Second, SASP-derived IL-6 induces HLA-E upregulation on senescent cells, engaging the inhibitory receptor NKG2A on NK cells and terminally differentiated CD8 T cells; an axis reversible by NKG2A blockade (Pereira, Devine et al. 2019 [↗](#)). Third, p16-dependent CDK4/6 inhibition stabilizes PD-L1 by blocking its proteasomal degradation; p16-expressing senescent macrophages thereby create an immunosuppressive environment that amplifies senescent burden through a self-reinforcing loop (Majewska, Agrawal et al. 2024 [↗](#)). Fourth, senescent cells upregulate CD47, the canonical anti-phagocytic signal, suppressing macrophage efferocytosis in a contact-dependent, SASP-independent manner that extends to failure of bystander apoptotic corpse removal (Schloesser, Lindenthal et al. 2023 [↗](#)).

Arm 3: The macrophage as integrating niche hub

The immune evasion mechanisms of Arm 2 converge on macrophages as the primary cellular integrator. Tissue-resident macrophages are the principal executors of epithelial clearance during postpartum involution (O'Brien, Martinson et al. 2012 [↗](#)) and a recent bioRxiv preprint inferred cross-tissue signaling networks from ovariectomized-mouse single-cell datasets and identified estrogen-responsive macrophages as major signaling hubs across multiple tissues (Iijima, Yamashita et al. 2025 [↗](#)). The liver fibrosis system provides a direct mechanistic precedent: NK-mediated clearance of senescent hepatic stellate cells is causally required for fibrosis resolution, and its impairment allows SASP accumulation and progressive fibrotic remodeling (Krizhanovsky,

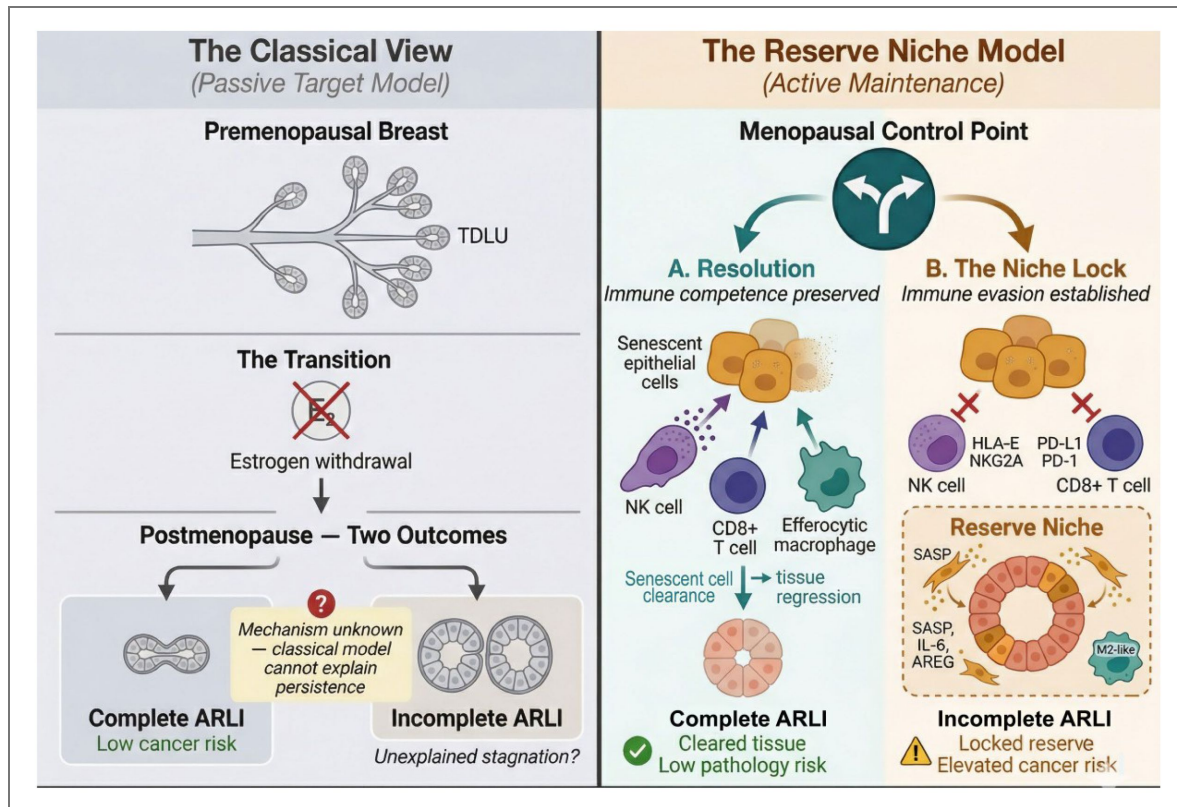


Figure 7. Comparison of classical view and reserve niche model.

The classical passive target model interprets incomplete age-related lobular involution (ARLI) as residual epithelial tissue available for oncogenic transformation, leaving unexplained why persistence stalls at menopause. The reserve niche model proposes that the menopausal transition is a biological control point at which immune competence determines tissue fate. When immune surveillance is preserved, senescent epithelial cells are cleared and lobular regression completes (Resolution, left). When immune evasion is established, senescent cells persist and sustain residual epithelium through SASP-mediated paracrine signaling, EGFR ligands, and an M2-like macrophage niche (The Niche Lock, right). This reframes risk stratification from residual tissue volume toward microenvironmental senescent burden and immune surveillance competence.

Yon et al. 2008 [↗](#)). Under the reserve niche lock hypothesis, postmenopausal macrophage reprogramming shifts mammary tissue-resident macrophages from clearance-executing to niche-sustaining: maintaining close contact with lobular structures while failing to eliminate senescent cells, and instead providing trophic signals that sustain residual epithelium. The immunosuppressive postpartum macrophage phenotype, including IL-10 production, Foxp3⁺ Treg co-recruitment, M2-like polarization (Martinson, Jindal et al. 2015 [↗](#)), may be aberrantly frozen in the aged postmenopausal breast rather than resolving as it normally does.

Experimental predictions and the logic of testing

The three arms generate orthogonal, testable predictions. Arm 1 predicts that senescent cells should be spatially associated with persistent lobular epithelium, and that senolytic clearance should reduce epithelial survival signaling and shift lobular persistence. Arm 2 predicts that senescent cells adjacent to persistent lobules should display immune evasion program upregulation, including HLA-E, PD-L1, CD47, and that targeted clearance restoration should alter lobular trajectory. Arm 3 predicts that macrophage efferocytosis competence and polarization should differ systematically between women with complete versus incomplete ARLI, and that macrophage depletion or repolarization in aged murine mammary tissue should alter residual lobular architecture. These predictions are testable with existing tools: p16-reporter mouse models for senescence visualization and inducible clearance, spatial transcriptomics for lobule-senescent cell co-localization, organoid coculture for paracrine signal dissection, and macrophage depletion or adoptive transfer for niche hub interrogation. The primary experimental gap, and the first-priority test, is spatial association of senescent cells with persistent lobular structures in human tissue correlated with involution status. Its outcome will determine whether the mechanistic arms warrant the more resourceintensive functional models.

Translational implications

Risk stratification: from morphometry to microenvironmental biomarkers

ARLI-based risk assessment currently rests on morphometric parameters, primarily TDLU count, lobular density, degree of involution; these describe tissue architecture but are silent about the mechanisms maintaining it. If incomplete ARLI represents an actively sustained senescent-immune niche state, the informative signal is not the count of persistent lobules but the molecular configuration of the lobular microenvironment: stromal senescent burden, SASP composition, and immune surveillance competence. Candidate tissue biomarkers follow directly from the hypothesis: p16^{INK4a} burden in epithelial and stromal compartments provides spatially resolved senescent cell distribution (Krishnamurthy, Torrice et al. 2004 [↗](#)); SASP cytokine profiles, particularly IL-6, IL-8, AREG, and EREG, report on paracrine epithelial maintenance; and immune markers including NKG2A/HLA-E expression, PD-L1 abundance on senescent populations, and macrophage efferocytosis capacity report on the convergent clearance failure mechanisms of Arm 2 (Munoz, Yannoni et al. 2019 [↗](#), Pereira, Devine et al. 2019 [↗](#), Schloesser, Lindenthal et al. 2023 [↗](#), Majewska, Agrawal et al. 2024 [↗](#)). Non-invasive blood-based proxies are also motivated: GDF15 and SERPINE1 show the strongest associations with biological age in the SASP proteome (Basisty, Kale et al. 2020 [↗](#)), offering longitudinal monitoring in low-burden paradigms. These biomarkers are likely most informative during the perimenopausal window, arguing for risk assessment timed to the transition rather than to fixed postmenopausal intervals.

Therapeutic implications and the primacy of timing

Three mechanistically distinct intervention arms map onto the locking trajectory, and their plausibility is likely to be strongly timing-dependent (Fig. 8 [↗](#)). Senolytics provide the most direct route to disrupting an established niche lock (Fig. 8 [↗](#), Arm 3). Human pilot studies in idiopathic pulmonary fibrosis have established feasibility and tolerability for dasatinib plus quercetin, offering translational precedent for targeting senescent burden in a chronic fibrotic

microenvironment (Justice, Nambiar et al. 2019 [↗](#), Nambiar, Kellogg et al. 2023 [↗](#)). Navitoclax is an additional senolytic candidate with demonstrated activity against several senescent cell types, although its effects are cell-type restricted and its relevance to ARLI remains hypothetical (Zhu, Tchkonja et al. 2016 [↗](#)). A critical caveat applies: transient p16^{INK4a}-dependent senescence is required for normal postpartum mammary involution (Chiche, Djoual et al. 2026 [↗](#)), so poorly timed senolytic therapy risks disrupting this remodeling program in premenopausal women or during the peri-transition period. Senolytics are therefore best viewed as candidates for an already established niche lock, not as indiscriminate preventive agents.

Immune restoration strategies offer complementary approaches tied to specific clearance mechanisms (Fig. 8 [↗](#), **Arm 2**). NKG2A blockade reverses HLA-E-mediated NK and CD8 T cell inhibition of senescent cells (Pereira, Devine et al. 2019 [↗](#)); MerTK agonism or CD47/SIRPα targeting addresses the innate efferocytosis arm (Schloesser, Lindenthal et al. 2023 [↗](#)); NK adoptive transfer could restore cytotoxic surveillance without systemic senolytic off-target risk. SASP attenuation through senomorphics, EGFR pathway modulation, or IL-6/STAT3 axis targeting offers a third strategy: reducing paracrine survival signals to residual epithelium without necessarily eliminating senescent cells (Fig. 8 [↗](#), **Arm 1**).

The central translational principle is that context-dependence is not a complication of trial design: it is the signal (Fig. 8 [↗](#), **footer**). Perimenopausal women are the appropriate population for interventions aimed at preventing niche lock formation; postmenopausal women with established incomplete ARLI are the appropriate population for interventions that seek to break an already self-sustaining lock. Treating menopausal timing as a covariate to adjust for, rather than a primary stratification variable, risks obscuring the very interaction that is most likely to determine efficacy.

The breast as a model system for transition-biology research

ARLI occupies an unusual position among human aging processes: triggered by a defined physiologic event, producing a measurable structural outcome, following a decadal natural history with documented individual variability, and accessible to serial tissue sampling through core biopsy; a combination unavailable for comparable aging questions in liver, lung, bone marrow, or kidney. If perimenopausal immune state can be shown to predict long-term tissue fate in the breast, the principles generated, including critical windows of biological plasticity, context-dependent interpretation of inflammatory signals, timing-dependent responsiveness of tissue fate, are unlikely to be breast-specific, and the findings will carry implications for transition-biology research well beyond breast cancer risk.

Conclusions and future directions

Three questions define the most consequential experimental frontier. The first and most foundational question is what kind of biological state incomplete ARLI actually represents. Throughout this review we have used “adaptive reserve” in an evolutionary rather than a functional sense: the lobular maintenance program was likely selected during reproductive years, when keeping epithelial capacity available across cycles of partial involution had genuine biological value. The postmenopausal breast is not awaiting reactivation for lactation; the program is not serving a current purpose. What persists postmenopausally is more accurately described as a maintenance program running without its resolution signal, the hormonal and immune cues that would ordinarily terminate it having been progressively withdrawn across the menopausal transition. Whether the epithelium retained within that program preserves any meaningful progenitor properties, or whether it has become purely a senescent-adjacent scaffold sustained by niche signaling without functional reserve competence, is the consequential experimental question. The answer matters for therapeutic strategy: progenitor-competent epithelium and inert inflammatory scaffold present different molecular targets, and the reserve niche framework predicts different intervention points depending on which state predominates.

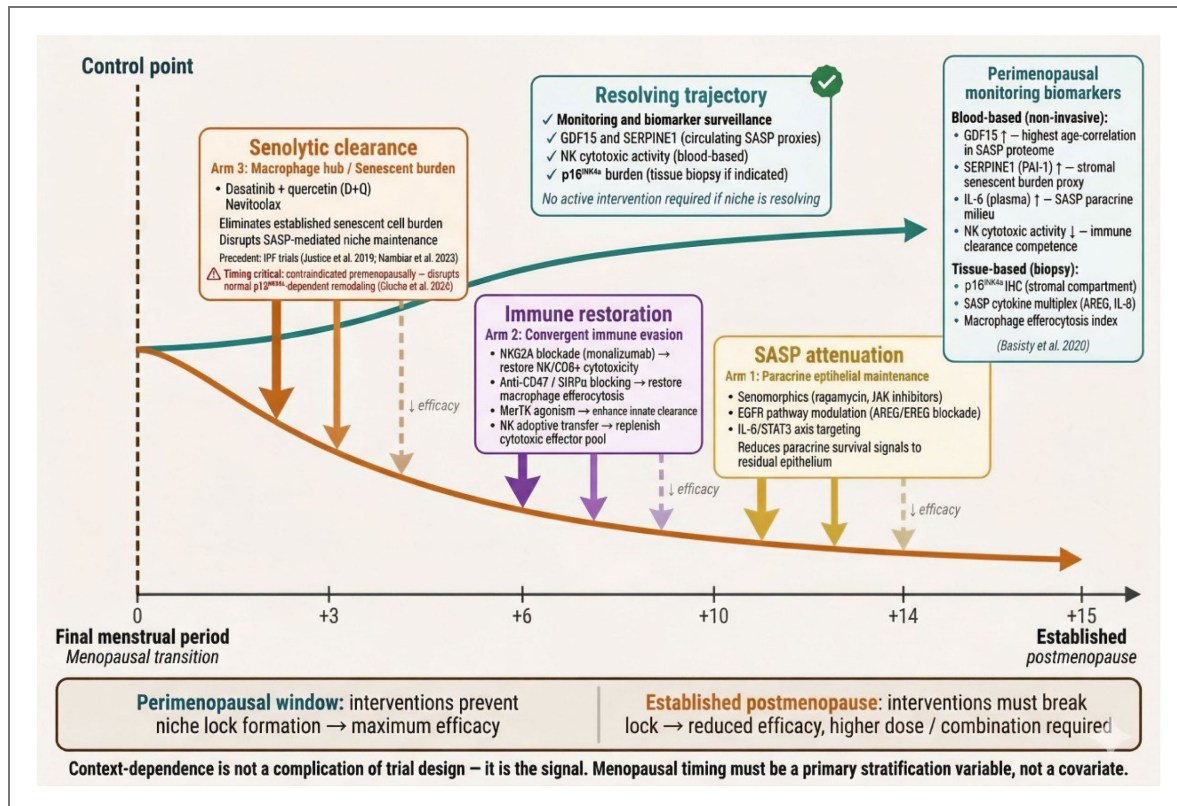


Figure 8. Proposed mechanism-based intervention map for the senescent-immune niche lock.

The x-axis runs from the menopausal control point to established postmenopause. The resolving trajectory (teal) requires monitoring rather than active intervention. The locking trajectory (amber) presents three intervention classes, each mapped to a mechanistic arm of the hypothesis and each expected to show timing-dependent efficacy. Arrow weight encodes predicted timing-dependent efficacy, with earlier intervention expected to be more effective than later intervention once the niche becomes self-sustaining. Senolytic clearance (Arm 3): dasatinib plus quercetin or navitoclax are proposed to reduce established senescent burden and disrupt SASP-dependent niche maintenance; clinical feasibility has been demonstrated for dasatinib plus quercetin in idiopathic pulmonary fibrosis, whereas navitoclax provides primary senolytic precedent in multiple senescent cell models. Immune restoration (Arm 2): NKG2A blockade, anti-CD47/SIRPα approaches, strategies aimed at restoring MerTK-dependent efferocytosis, and NK adoptive transfer are proposed to address the convergent clearance failures of the niche lock. SASP attenuation (Arm 1): senomorphics, EGFR pathway modulation, and IL-6/STAT3 axis targeting are proposed to reduce paracrine survival signals to residual epithelium. Perimenopausal monitoring biomarkers, shown at upper right, represent candidate indicators for identifying women at risk of niche lock formation during the window of greatest intervention opportunity. The footer encodes the central translational principle: menopausal timing relative to the control point is not merely a covariate but a primary stratification variable that is likely to determine intervention efficacy.

The second question concerns which cell types are the primary drivers of the senescent niche. The hypothesis invokes SASP-producing stromal cells as the paracrine maintenance signal for adjacent epithelium, but the dominant senescent population, whether mammary epithelial cell, fibroblast, adipose stromal cell, vascular endothelial cell, or immune cell, has not been established for the aging human breast. The SASP components most relevant to each mechanistic arm, AREG and EREG for epithelial maintenance, MMPs for NKG2D ligand shedding, IL-6 for HLA-E induction, may originate from distinct cellular sources whose spatial relationship to persistent lobules has yet to be mapped.

The third question concerns immune spatial organization within the persistent lobule. The reserve niche model requires that immune surveillance cells fail to access or eliminate senescent cells in the lobular microenvironment, but whether this reflects active exclusion, such as inhibitory ligand expression, ECM barriers to trafficking, or deficient chemokine gradient formation, or passive failure of recruitment is unresolved. The mechanistic answer matters for therapeutic design: strategies targeting cytotoxic effector function (NKG2A blockade, NK transfer) will fail if the primary barrier is physical access rather than functional suppression. Spatial transcriptomics applied to matched complete and incomplete ARLI tissue with multiplexed immune phenotyping is the tool most directly suited to resolving this.

A fourth question extends the reserve niche logic to a connected epidemiologic puzzle: the divergent cancer risk profiles of early versus late pregnancy. Early pregnancy confers durable long-term protection against breast cancer risk, while late pregnancy does not (MacMahon, Cole et al. 1970 [↗](#), Ewertz, Duffy et al. 1990 [↗](#), Collaborative Group on Hormonal Factors in Breast 2002 [↗](#), Albrektsen, Heuch et al. 2005 [↗](#), Lue and Radisky 2025 [↗](#)). The reserve niche model generates a testable mechanistic explanation for this asymmetry. Late pregnancy occurs as women approach the perimenopausal transition; this is precisely the window during which senescent burden is rising and immune clearance capacity beginning to decline. Normal postpartum involution requires transient p16^{INK4a}-dependent senescence for epithelial clearance and tissue remodeling (Chiche, Djoual et al. 2026 [↗](#)); if a woman enters postpartum remodeling against a background of already-elevated senescent burden and compromised immune surveillance, this transient senescent signal may fail to resolve normally. The predicted result is a hybrid state in which elements of postpartum senescent signaling merge with the nascent conditions of an age-related niche lock, impairing completion of postpartum involution and leaving behind a microenvironment with niche lock characteristics. Under this model, the attenuated protective effect of late pregnancy is not simply a function of epithelial differentiation status but reflects the immune-senescent context in which postpartum remodeling must occur, a context that conditions whether the transient senescent program resolves or entrains. This prediction is experimentally testable by comparing postpartum involution trajectory and immune clearance competence in women delivering at different ages, stratified by perimenopausal senescent burden and NK cytotoxic activity at the time of delivery.

If the immune evasion mechanisms already present in the reserve niche, PD-L1 stabilization, HLA-E expression, CD47 upregulation, provide early immune escape scaffolding for emerging tumor cells, the framework will connect ARLI epidemiology to specific breast cancer subtype biology in a mechanistically grounded way, opening new lines of thinking about early interception timed to the niche rather than to established premalignant lesions. The reserve niche hypothesis offers a reorientation of how breast cancer risk is understood: from a static count of persistent tissue to a dynamic, targetable microenvironmental program; one whose most consequential biology unfolds in the perimenopausal window, before the lock is set.

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Peer reviews

Reviewer #1 (Public review):

Summary:

This Perspective proposes a conceptual model in which incomplete age-related lobular involution (ARLI) in the breast reflects an actively maintained senescent-immune "reserve niche," rather than simply passive failure of lobular regression after menopause. The authors aim to integrate breast cancer epidemiology, mammary gland biology, cellular senescence, immune surveillance, and comparative reserve-tissue systems to explain why persistent postmenopausal lobules are associated with increased breast cancer risk. The manuscript is ambitious, creative, and potentially useful in shifting attention from residual epithelial quantity alone toward the microenvironmental state of persistent lobules.

Strengths:

A major strength of the manuscript is its forward-looking synthesis. The authors bring together several areas that are often considered separately: ARLI as a tissue-level risk marker, inflammatory features of incompletely involuted breast tissue, senescence biology, macrophage-mediated remodeling, and the menopausal transition as a potential window of biological plasticity. The model is conceptually interesting and, if supported by future evidence, could stimulate new approaches to risk stratification and prevention focused on the perimenopausal period.

Weaknesses:

However, the current manuscript often presents the proposed model with more certainty than the available evidence supports. The evidence clearly supports associations among incomplete ARLI, inflammatory or immune features, and breast cancer risk, but it does not yet demonstrate that senescent cells maintain persistent lobules, that immune clearance failure causes incomplete involution, or that a self-sustaining senescent-immune "niche lock" exists in human breast tissue. Much of the mechanistic framework is extrapolated from other tissues, postpartum involution, or general senescence biology. These are reasonable sources for hypothesis generation, but the manuscript would be stronger if it more clearly distinguished established observations from inference and speculation.

The senescence component of the model requires stronger and more direct support. Several claims about senescent burden in the aging breast appear to rely on general senescence literature or mammary aging studies that do not directly demonstrate senescence in persistent human TDLUs. This distinction is important because the manuscript's central model depends on senescent cells being spatially and functionally linked to incomplete ARLI.

The epidemiologic evidence also requires a more balanced treatment. Although several studies support incomplete ARLI as a breast cancer risk-associated phenotype, other cohorts and quantitative approaches have reported attenuated or null associations. This mixed evidence is acknowledged, but it is treated largely as a caveat rather than incorporated into the central argument. For readers, this uncertainty is important for interpreting the strength and generalizability of the proposed model.

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Reviewer #2 (Public review):

Summary:

This review constructs a novel theoretical framework to elucidate incomplete postmenopausal age-related lobular involution (ARLI) in the breast. Differing from the conventional view of persistent lobules as passive residual structures, the work innovatively defines them as an actively maintained senescence-immune reserve niche. It

comprehensively integrates multidisciplinary evidence from breast epidemiology, stromal biology, cellular senescence and immune surveillance, as well as cross-tissue research findings, and identifies menopause as a core biological turning point regulating ARLI and relevant breast cancer risk, providing a new theoretical perspective for subsequent breast cancer risk assessment and preventive intervention research.

Strengths:

This study presents an original, logically rigorous, and well-organized research hypothesis. It innovatively breaks through the traditional cognitive perspective of ARLI and adopts a multidisciplinary and cross-tissue analytical approach to sort out relevant biological mechanisms systematically. The proposed theoretical framework is insightful, with good theoretical innovation and potential translational value for guiding breast cancer risk evaluation and targeted prevention strategies.

Weaknesses:

The manuscript currently serves primarily as a conceptual framework rather than a rigorously evidenced synthesis. Its central argument relies heavily on cross-sectional correlations and theoretical analogies to other organ systems, lacking operational definitions for the reserve state in human breast tissue.

<https://doi.org/10.7554/eLife.111667.1.sa1>

Author response:

We thank the editors and reviewers for recognizing the originality and potential value of the proposed framework. The reviews rightly ask us to distinguish three things more sharply: what is established directly in human breast tissue, what is inferred from mammary and aging studies, and what remains hypothesis. We agree, and the revision will make that distinction explicit throughout.

We will define the proposed reserve state operationally and specify the findings that would distinguish active niche maintenance from passive persistence. Throughout, we will treat passive persistence as a legitimate competing hypothesis rather than a settled question. Heterogeneity and immune or inflammatory associations will be presented as consistent with active maintenance and causal directionality, not as establishing them. We will also integrate the mixed epidemiologic evidence more centrally into the argument, rather than treating it as a caveat.

We will reassess the evidence for senescence in the aging breast and describe it more precisely, correcting or narrowing statements that outrun the data. The figures will be revised so that observed inflammatory and immune-regulatory features are clearly separated from proposed senescence- and SASP-mediated mechanisms. We will also clarify the limits of our analogies: postpartum involution and cross-tissue reserve systems will be presented as sources of candidate mechanisms and testable predictions, not as direct evidence for the proposed mechanism in human ARLI. Finally, we will frame the translational implications as contingent. They depend on first demonstrating that senescent cells are enriched near persistent lobules, identifying the relevant cell types and immune states, and establishing causal relevance.

We appreciate the reviewers' constructive suggestions. We believe these revisions will preserve the conceptual contribution of the model while making its evidentiary status, the alternative explanations, and its falsifiable predictions substantially clearer.

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