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Hypothesis

Endocrine–Immune Conditioning and NET-Mediated Dormancy Awakening in ER+ Breast Cancer

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Abstract

Late distant recurrence in estrogen receptor-positive (ER+) breast cancer raises the question of how disseminated tumor cells resume proliferation years after primary tumor resection. We propose two coupled processes: endocrine–immune conditioning of the local niche and neutrophil extracellular trap (NET)-mediated dormancy awakening. In the first, ERα-associated signaling is proposed to alter neutrophil recruitment and activation, favoring NET formation and local persistence near dormant cells. In the second, NET-associated proteases remodel basement-membrane laminin, generating matrix signals that activate integrin α3β1-dependent signaling and intracellular YAP in adjacent tumor cells, promoting cell-cycle reentry. Estrogen-dependent neutrophil reprogramming and NET-mediated awakening have experimental support in separate systems, including mammary involution and a postresection breast cancer dormancy model in the lung. Distant perivascular niches support dormancy. We propose that endocrine–immune conditioning engages NET-mediated awakening of dormant ER+ cells within these niches. PER2 loss is proposed to reinforce endocrine–immune conditioning through ERα stabilization, while local estrogen production, complement and coagulation shape niche permissiveness. Spatial analysis of primary tumors can test spatial organization and its association with subsequent recurrence. Distant-site studies and functional dormancy models are needed to test local endocrine–immune conditioning and NET-dependent reactivation after resection. This model links host endocrine–immune conditions to dormant tumor-cell awakening.

Keywords: ER-positive breast cancer; tumor dormancy; neutrophil extracellular traps; laminin remodeling; complement; coagulation; YAP

1. Introduction

Late distant recurrence in ER+ breast cancer raises a mechanistic question: what causes disseminated tumor cells (DTCs) to resume proliferation after years of clinical dormancy? In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis, distant recurrence continued during years 5–20 among women who were disease-free after five years of scheduled endocrine therapy, with risk related to original tumor diameter and nodal status [1].

The distant perivascular niche provides an anatomical setting for this question. Ghajar and colleagues localized dormant breast tumor cells alongside microvessels in lung, bone marrow and brain and showed that endothelial signals regulate quiescence and outgrowth [2]. Albrengues and colleagues subsequently demonstrated inflammation-induced, NET-dependent awakening, including after spontaneous MCF-7 dissemination and primary-tumor resection [3]. We propose two coupled processes: endocrine–immune conditioning

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of the distant niche, followed by NET-mediated matrix remodeling and awakening of resident ER+ DTCs. The hypothesis concerns local reactivation after the primary tumor has been removed.

Postpartum breast cancer illustrates the relevance of physiological tissue remodeling to metastatic risk. In a cohort of women aged 45 years or younger, diagnosis within ten years of childbirth was associated with increased metastatic risk, particularly in stage I or II disease, including ER+ and ER− cancers [4]. Mammary involution combines immune-cell recruitment with extensive extracellular-matrix remodeling and has been proposed to mediate this association [5]. Involution is relevant here because it couples endocrine responsiveness to immune-cell recruitment and matrix remodeling, the host processes proposed to condition a dormancy niche (Figure 1).

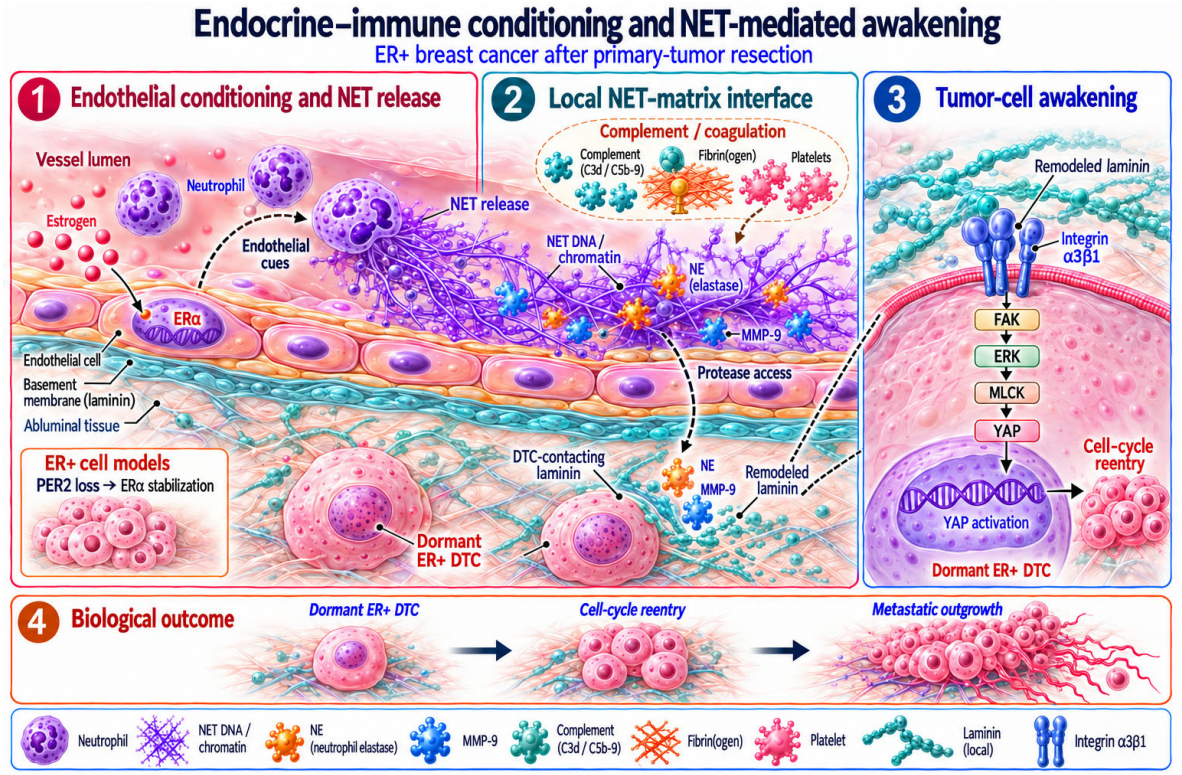


Figure 1. Endocrine–immune conditioning and NET-mediated dormancy awakening in ER+ breast cancer after primary-tumor resection. (1) Estrogen-responsive endothelium and luminal neutrophils depict conditioning at the vascular interface. The inset summarizes PER2 loss and ERα stabilization in ER+ cancer-cell models. (2) NET DNA/chromatin localizes NE and MMP9. Complement activation products (C3d/C5b–9), fibrin(ogen) and platelets illustrate experimentally established interactions with NETs. The dormant disseminated tumor cell (DTC) lies in abluminal tissue beside laminin undergoing local remodeling. (3) Remodeled laminin engages integrin α3β1-dependent FAK/ERK/MLCK signaling and intracellular YAP, promoting cell-cycle reentry. (4) Dormant-cell awakening progresses to metastatic outgrowth. Dashed arrows indicate modeled effects on NET activity and protease access in the ER+ dormancy niche. Diagonal dashed connector lines indicate the enlarged matrix–receptor view in panel 3. Sequential NE-then-MMP9 proteolysis was characterized on laminin-111; awakening on laminin-211, -411 and -511 was demonstrated in vitro. Local substrate identity is organ-specific. NET, neutrophil extracellular trap; NE, neutrophil elastase; MMP9, matrix metalloproteinase 9; FAK, focal adhesion kinase; ERK, extracellular signal-regulated kinase; MLCK, myosin light chain kinase; PER2, period circadian regulator 2; YAP, yes-associated protein.

2. Endocrine–Immune Conditioning of the Niche

The conditioning process concerns how estrogen-responsive signaling changes the local immune environment. Chung and colleagues showed that estrogen promoted neutrophil infiltration, inflammatory reprogramming and tumor growth during murine mammary involution; neutrophil depletion attenuated these responses. Estrogen also increased cyclooxygenase-2 (COX2) and tissue-remodeling gene expression in isolated mammary neutrophils. Because the implanted tumor was ER−, these experiments identify a host-mediated estrogen effect [6]. Lim and colleagues showed that an ERα agonist reproduced relevant inflammatory responses and that C-X-C chemokine receptor 2 (CXCR2) signaling contributed to neutrophil recruitment. Estrogen reduced neutrophil infiltration in nulliparous mammary tissue, with several inflammatory genes responding in the opposite direction to involuting tissue [7]. These findings identify local tissue state as a determinant of endocrine–immune conditioning.

Human neutrophil studies identify receptor-dependent control of activation and NET production. Circulating neutrophils express ERα and ERβ [8,9], and selective antagonists of these receptors reduced phorbol 12-myristate 13-acetate (PMA)-induced NET production in primary human neutrophils [9]. The G protein-coupled estrogen receptor (GPER) agonist G1 (10–100 μM) altered human neutrophil activation and survival [10]. In neutrophil-like HL-60 cells, estradiol and the GPER agonist G-1 enhanced A23187-induced NET formation and increased peptidylarginine deiminase 4 (PAD4) and citrullination endpoints; GPER antagonism partially reduced the estradiol response [11].

Giaglis and colleagues showed that estradiol promoted NET formation in primary human neutrophils under gestational conditions, while progesterone restrained NET release despite histone citrullination [12]. Yan and colleagues demonstrated GPER1-dependent estrogen signaling in pancreatic tumor cells that promoted neutrophil recruitment and NET formation [13]. These findings support endocrine regulation of NET activity; their application to dormant ER+ breast cancer requires testing in the relevant niche.

ERα-associated conditioning refers to signaling within identified tumor, stromal, endothelial and immune compartments of the niche. Receptor abundance, local estrogen exposure and downstream activity define the endocrine state of each compartment.

Local estrogen production provides an intercellular route for conditioning. Human breast tissue and cell-model studies support aromatase expression and stromal–parenchymal interactions, while broader work describes aromatase regulation in hormone-responsive tumors [14,15]. In human adipose stromal cultures, prostaglandin E2 (PGE2) increased aromatase expression or activity [16,17]. We propose that inflammatory PGE2 production stimulates stromal estrogen synthesis, linking a local inflammatory input to receptor-responsive cells that regulate the neutrophil environment.

PER2 regulates ERα stability. Gery and colleagues demonstrated that PER2 promotes ERα degradation and that reducing PER2 stabilizes ERα in ER+ cancer-cell models [18]. We propose that PER2 loss stabilizes ERα in responsive niche cells and thereby favors neutrophil activation and NET formation. Cell-specific PER2 perturbations can distinguish neutrophil-intrinsic regulation from signals provided by other niche cells.

3. Thromboimmune Organization and Local NET Activity

NETs provide a scaffold for platelet and coagulation interactions. Fuchs and colleagues demonstrated platelet adhesion and aggregation on NETs in blood-perfusion experiments, and fibrinogen binding to NETs in plasma. Recalcified blood perfusion produced thrombin-dependent fibrin deposition [19].

Martins-Cardoso and colleagues found that NET exposure induced epithelial–mesenchymal changes in human breast cancer cells [20]. Their subsequent

study showed increased tissue-factor (TF) expression and procoagulant activity; inhibiting TF/protease-activated receptor 2 (PAR2) signaling attenuated selected NET-induced pro-tumor gene responses [21]. These experiments identify a route by which NET exposure changes the local coagulation and signaling environment. Its contribution to dormancy awakening can be assessed with the reentry assays described below.

NETs also provide a surface for complement activation. Wang and colleagues showed that NETs generated after PMA or lipopolysaccharide (LPS) stimulation activated the alternative complement pathway in human serum [22]. Yuen and colleagues demonstrated properdin deposition and terminal complement complex formation on NETs; properdin blockade inhibited activation under alternative-pathway-selective conditions [23]. Niculescu and colleagues localized C5b–9 deposits to tumor-cell membranes and necrotic regions in human breast carcinoma [24]. We propose that local interactions among NETs, complement and coagulation modify the availability or duration of proteolytic signals near dormant cells.

Coagulation signaling and matrix mechanics offer additional routes to intracellular YAP regulation. Thrombin activated PAR1–G12/13–Rho signaling, inhibited LATS1/2 and activated YAP/TAZ in cell models [25]. Dupont and colleagues identified YAP/TAZ as nuclear mediators of extracellular-matrix rigidity and cell geometry [26]. Dorfleutner and colleagues showed that phosphorylation of the TF cytoplasmic domain relieved suppression of α3β1-dependent migration on laminin-332 [27]. Fibrin-dependent mechanical effects and TF action in the response to NET-remodeled laminin remain specific questions for the proposed niche.

The duration of NET exposure depends on formation and clearance. Plasma studies in patients with thrombotic microangiopathy associated impaired degradation with increased NET burden, while experimental DNase studies showed protection against NET-related vascular obstruction [28,29]. Impaired clearance therefore provides a mechanism for extending local exposure. At a perivascular dormancy niche, the relevant measurements are NET turnover, protease activity and access to DTC-contacting matrix, with vessel-lumen deposits distinguished from abluminal proteolysis.

4. NET Mediated Laminin Remodeling and Dormancy Awakening

Albrengues and colleagues established a NET-dependent mechanism of inflammation-induced dormancy awakening. Sustained lung inflammation induced outgrowth of dormant breast cancer cells. In a spontaneous MCF-7 dissemination experiment, LPS-induced NETs awakened cells after primary-tumor resection (Figure S5D–H of Ref. [3]). NET DNA bound laminin, positioning its associated proteases at the substrate. Laminin-111 cleavage proceeded first through NE and then MMP9. Protease inhibition, NET-DNA digestion and targeting remodeled laminin interfered with awakening [3].

Preincubating Matrigel with NET-containing conditioned medium before cancer-cell plating was sufficient to induce subsequent outgrowth. Both NE and MMP9 were required during matrix remodeling; inhibiting these proteases after remodeling did not prevent outgrowth (Figure S9L–M of Ref. [3]). These experiments establish the remodeled matrix as a mediator of awakening without requiring continued protease activity during cancer-cell culture [3].

Genetic and pharmacological interference with tumor-cell integrin α3β1 and FAK/ERK/MLCK/YAP signaling inhibited NET-induced awakening, placing intracellular YAP within the recipient-cell response to remodeled matrix. The study also demonstrated NET-induced awakening on laminin-211, -411 and -511 in vitro (Figure S11E of Ref. [3]), extending substrate compatibility beyond the detailed laminin-111 experiments [3].

NET proteolysis also affects a perivascular quiescence signal. Ghajar and colleagues identified endothelial-derived thrombospondin-1 (TSP-1) as a mediator of dormancy [2].

Albrengues and colleagues showed that NET-associated NE and MMP9 degraded TSP-1 in vitro and observed TSP-1 degradation after LPS-induced lung inflammation in vivo. Intact TSP-1 suppressed awakening induced by remodeled laminin, and NET-mediated degradation overcame this inhibition [3]. These findings connect loss of a quiescence signal with laminin-dependent awakening. Ghajar also identified transforming growth factor β1 (TGF-β1) and periostin at sprouting vascular tips as promoters of outgrowth, providing a distinct vascular context for comparison [2].

The response to laminin depends on its isoform, structural state and recipient receptor. Nishiuchi and colleagues characterized purified integrin binding to intact laminin isoforms [30], complementing the functional remodeling assays. In brain dormancy models using triple-negative HMT-3522-T4-2 and MDA-MB-231 breast cancer cells, astrocytic laminin-211/dystroglycan signaling maintained DTC quiescence through intracellular YAP sequestration [31]. This brain-niche result demonstrates how a laminin-rich environment can maintain dormancy in a different receptor context. Organ-specific studies should identify the local substrate and determine how remodeling changes its effect on the dormant cell.

In the proposed ER+ niche, endocrine–immune conditioning generates NET-associated proteolysis near dormant cells. Matrix remodeling changes laminin-dependent integrin signaling, and intracellular YAP promotes cell-cycle reentry. The two processes connect a change in the host microenvironment to a proliferative response in the DTC through an extracellular-matrix signal.

5. Local Initiation and Maintenance After Resection

After resection, conditioning arises around a DTC already present at the distant site. We propose that changes in host endocrine conditions, local estrogen metabolism or the responses of vascular, stromal and immune cells alter neutrophil recruitment, activation or NET clearance. The vascular interface supplies circulating hormones and immune mediators, while endocrine-responsive niche cells determine the local response. Matrix-directed proteolysis then engages the awakening pathway in an adjacent dormant cell.

Continued neutrophil recruitment, increased NET formation or impaired clearance can extend exposure to local proteolytic signals. Complement and coagulation interactions are proposed to modify this exposure. The timing and duration of the permissive state determine the opportunity for awakening and are variables for longitudinal niche studies. The prolonged clinical recurrence interval [1] motivates examining these local dynamics after resection.

6. Discussion

The hypothesis predicts that perturbing ERα-associated signaling changes NET formation, laminin remodeling and cell-cycle reentry in dormant ER+ DTCs. Table S1 records experimental support and remaining questions for each connection. Spatial mapping and functional perturbation provide complementary tests of this mechanism.

6.1. Spatial Organization and Clinical Association

Archived primary breast tissue can identify spatial organization at resection and its association with later recurrence. Whole-section imaging with long clinical follow-up can compare ER+ recurrent and nonrecurrent cases, ER− tumors, and benign or normal tissue. These comparisons assess spatial organization and ER+ enrichment. Distal tissue studies and functional models address the initiation and causal activity of a niche that develops after resection.

The spatial panel should locate tumor cells, endothelium, basement membrane and relevant immune/stromal compartments. Extracellular DNA with neutrophil markers

such as CD66b, myeloperoxidase (MPO) or NE, and appropriately controlled citrullinated histone H3 (citH3) staining can support NET identification. The analysis should resolve NET-associated proteases and the relevant laminin substrate relative to resident DTCs, distinguishing lumen from abluminal space. Tumor-cell YAP localization should be paired with proliferation/quiescence measures. Complement, coagulation and PER2 measurements assess their contributions to local conditioning and awakening.

Tissue analysis should control for block age, fixation, antibody performance and sampling time. Field selection and compartment positivity thresholds should be prespecified, with sparse or absent compartments reported explicitly and thresholds validated against functional responses. Resolving laminin chain composition distinguishes laminin-511 from -521. Testing ERα stability requires PER2 protein measurements, cell assignment of ERα signals and assessment of receptor activity.

6.2. Functional Tests of Distal Coupling

A postresection dormancy model should establish resident quiescent DTCs before perturbing local estrogen availability or ERα signaling in defined niche cells. Measurements should follow receptor activity, neutrophil recruitment, NET formation and degradation, laminin remodeling and cell-cycle reentry in DTCs. Inhibiting NET formation, protease activity and tumor-cell integrin/YAP signaling tests the order of these events. DTC-only endocrine-exposure controls and compartment-specific perturbations distinguish direct tumor-cell responses from neutrophil-mediated effects. Interpretable negative results require target engagement, effective blockade and viable DTCs capable of reentry in a positive control. Downstream rescue can help separate pathway disruption from effects on cell survival.

PER2 experiments should distinguish regulation within neutrophils from signaling through another receptor-responsive niche cell. An intercellular mechanism requires identification of the extracellular mediator and recipient response. ERα, ERβ and GPER perturbations distinguish the receptor contributions identified by the component studies. Testing the PGE2–aromatase route requires separate perturbation and measurement of source-cell COX2/PGE2, stromal aromatase, local estrogen exposure and the neutrophil response.

Complement, coagulation and matrix mechanics can be evaluated by measuring whether their perturbation changes NET persistence, proteolytic access or the magnitude of DTC reentry. Coiled-coil domain-containing protein 25 (CCDC25)-mediated sensing of NET DNA promotes tumor-cell migration and metastatic behavior [32]. Testing CCDC25 in a resident-DTC assay would determine whether this additional NET-sensing mechanism also affects dormancy awakening.

6.3. Mechanistic Interpretation

The model couples estrogen-responsive neutrophil conditioning with NET-dependent matrix remodeling and dormancy awakening. The involution studies identify the endocrine-sensitive immune response, while the lung dormancy experiments establish matrix-dependent reactivation. Demonstrating this coupling requires perturbation of local ERα-associated signaling alongside measurements of NET activity, laminin remodeling and cell-cycle reentry within the same distant niche. ER− comparators can determine whether the conditioning response is enriched in ER+ disease.

Abenza and colleagues showed that YAP/TAZ–TEAD activity altered fibroblast clock oscillations, including reduced Per2 amplitude [33]. This circadian result motivates time-resolved PER2 protein measurements and cell-specific ERα activity measurements when evaluating endocrine–immune conditioning.

YAP can also suppress growth in established ER+ disease. Li and colleagues showed that YAP disrupted TEAD–ERα cooperation, inhibited ERα signaling and suppressed growth in ER+ cell and xenograft models; MST1/2 inhibition also reduced proliferation in tumor explants. Higher YAP expression was associated with longer relapse-free survival [34]. In dormant ER+ DTCs, the critical test is whether NET-remodeled matrix induces YAP-dependent cell-cycle reentry while ERα activity is measured in the same cells.

Human tissue studies inform the selection of complementary measurements. Lesicka and colleagues identified clock-gene transcript differences between breast tumors and paired adjacent tissue [35]. Cha and colleagues associated nuclear YAP1 with hormone receptor negativity and identified an independent association with poor distant metastasis-free survival in triple-negative disease [36]. Relating these measurements to local cell identity, quiescence and cell-cycle reentry would establish their relevance to the proposed ER+ dormancy setting.

In an exploratory breast-tissue study with three biological replicates per group, Tillotson and colleagues found higher PAD2–PAD4 abundance in ER− tumors. They also identified ER-stratified citrullinated-protein profiles involving extracellular-matrix proteins, with blood-clotting enrichment in ER+ tissue [37]. These observations support examining matrix and coagulation features together. Assignment of citrullinated proteins to NET structures requires paired extracellular-DNA and neutrophil-marker localization.

TSP-1 provides a further testable connection. Estradiol transiently reduced TSP-1 in human umbilical vein endothelial cells [38], but increased its production in ER+ breast cancer cells [39]. TSP-1 inhibited alternative complement activation and complement-dependent NET formation in vasculitis models [40]. Endocrine regulation of TSP-1 could therefore alter both quiescence signaling and local NET activity, a connection requiring testing in the distant niche. Proteolysis also requires functional assessment: neutrophil processing generated a TSP-1 fragment with enhanced platelet-adhesion activity [41], so cleavage alone does not establish loss of all TSP-1 functions.

Late recurrence in this model depends on the interaction between a dormant ER+ cell and host conditions at its distant niche. Endocrine-sensitive immune conditioning engages a NET-dependent matrix signal that promotes tumor-cell reentry. Spatial studies can identify the relevant anatomy and its association with recurrence; distal functional models can determine when and how this coupling produces awakening after primary-tumor resection.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijtm6040051/s1, Table S1: Mechanistic evidence and testable connections.

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