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Review Article

Histophysiological Reprogramming of Breast Cancer Cells: A Tissue-Centered Review

Ali Hussein Salman[1]*, Baydaa Furhan Swadi[2], Rana Mohammed Naser[3]

[1]Dept. of Community Health Technologies, Health and Medical Techniques College, Southren Technical University, Basrah, Iraq
[2]Dept. of Physiotherapy Techniques, Health and Medical Techniques College, Southren Technical University, Basrah, Iraq
[3]Dept. of Pathological Analysis, Collage of Science, University of Basrah, Basrah, Iraq

***Corresponding Author:** Ali Hussein Salman
Dept. of Community Health Technologies, Health and Medical Techniques College, Southren Technical University, Basrah, Iraq

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Abstract: ***Background*:** The Somatic Mutation Theory (SMT) has dominated oncological science over the course of many decades representing cancer as a more primitively cell-autonomous pathology, as a consequence of the accumulation of somatic genetic changes. The heterogeneity, dormancy and treatment resistance that is so eminent in breast carcinoma often goes unnoticed by this view. ***Objective*:** The current review will attempt to amalgamate modern evidence supporting the Tissue Organisation Field Theory (TOFT), especially the histophysiological reprogramming of breast cancer cells in the microenvironment in which they can be found. ***Methodology*:** A systematic literature review was conducted on the following leading databases - Scopus, Web of Science, PubMed and high-impact studies published between 2010 and 2026 were prioritised. ***Results*:** The current use of empirical evidence places breast cancer progression as a breakdown of the organisation of tissues as opposed to as opposed to a genetic breakdown. Recent spatial proteomic studies (2025) prove that the increase in proteomic heterogeneity in line with tumour progression, regardless of prevailing underlying genomic mutations, is due to the non-steady interplay between malignant epithelial cells, cancer-associated fibroblasts (CAFs) and the immune microenvironment. ***Conclusion*:** Diverting analytical attention toward the solitary cancer cell, more wholesome information about malignancy is obtained by cultivating an alternate perspective that analyses the tissue field. Targeted therapeutic interventions to achieve microenvironmental normalisation and restoration of tissue architecture can be a promising potential solution to treatment resistance and achieve long-term clinical benefit.

Keywords: Morphostasiss, Biological Reductionism, Emergent Properties, Downward Causation.

1. INTRODUCTION

Breast cancer still remains one of the most challenging issues facing the health of the world, due to the sheer heterogeneity and often unpredictable clinical courses [1]. The existing paradigm in the field of oncology has been the Somatic Mutation Theory (SMT) that states that cancer arises out of one cell that develops a cluster of genetic mutations that lead to uncontrolled cell growth and malignant differentiation [2, 3]. This cell-autonomous, reductionist position has certainly progressed the understanding of the oncogenes and tumour-suppressor genes, and it has formed the basis of much of the modern diagnostic and treatment interventions that correct the genetic defects in the cancer cells. However, with the ability to query the molecular landscape of tumours with unprecedented resolution, the aberrations which are unexplainable by the SMT have become more evident. The theory is weak in its ability to provide a complete explanation of such phenomena as tumour dormancy [4], where cancer cells can be kept in an inert state over years to re-emerge abruptly, and for the astonishing effect of phenotypic reversion, whereby highly malignant cells can be re-educated to act normally by placing them in a healthy non-cancerous tissue environment [5, 6]. These observations are highly indicative that the instructions to become malignant are not confined to the genome of the cancer cell, but are the convergence properties of

the tissue itself. To address these difficulties, a new theory, by the name Tissue Organisation Field Theory (TOFT), has surfaced as a strong and testable substitute [7, 8].

The TOFT does not refer to cancer as a disease of errant cells, but rather as a failure of tissue organisation, and in effect, development that goes awry. It highlights the preeminent position of the tissue microenvironment, or the field, in the regulation of cellular behaviour and maintenance of the homeostasis. This new paradigm centres around the idea of the histophysiological reprogramming of cells that is induced by the microenvironment and causes the active change of the physiological state and phenotypic identity of the cells, thus reprogramming them to promote tumour growth and invasion. This review presents the in-depth, tissue-based study of this phenomenon in breast cancer, discussing the active formation of the phenotype and the behaviour of these cells by the microenvironment in the context of a more deterministic view on genes instead of being just an active manifestation of the genetic background of the disease. We comment on how the stromalepithelial crosstalk, extracellular matrix (ECM) remodelling, and metabolic rewiring are the prime forces of malignant progression by incorporating the recent results of 2024 to 2026, such as the advances in spatial proteomics [9], and functional profiling [10-13]. Finally, we believe that the future of breast cancer treatment lies in the tissue field, which will provide new information on the creation of more efficient and sustainable treatment options. This is a critical synthesis of the literature that defined histophysiological reprogramming of breast cancer as the fundamental mechanism of malignancy and a roadmap to designing the next generation of field targeting therapeutic approaches.

2. Theoretical Foundations: A Paradigm Shift in Oncology

A paradigm shift has taken place in modern research in oncology to go beyond a purely cell-based approach to a systems-based perspective of the role of the tissue microenvironment. The core of this change in intellectual direction is a conflict between the Somatic Mutation Theory (SMT) [2, 3], and the Tissue Organisation Field Theory (TOFT) [7,8]. The SMT argues that cancer is a genetic disease that is triggered by mutations which give a proliferative benefit to one cell, the TOFT reformulates cancer into a morphogenetic disrupter. The SMT, which dates its origins to the early twentieth century, has spread widely after the discovery of the oncogenes and the introduction of genomic sequencing. The holy grail of oncology during the decades was considered to be the elusive search of the so-called driver mutation. Nevertheless, the next-generation sequencing (NGS) revealed a level of intratumoral heterogeneity that the SMT was not easily able to resolve. Considering cancer as a clonal expansion of a single mutation-bearing cell, the widely different genomic and phenotypic heterogeneity within a given tumour is a puzzling paradox. Moreover, the SMT has a hard time trying to understand why a great number of seemingly normal tissues harbour large numbers of cancer-causing mutations but do not develop into malignant cells [3]. These inconsistencies have led scientists to speculate that genetic mutations are the main cause of cancer or they are just a secondary effect of something more fundamental, on the tissue level.

A radically different view is presented by the TOFT, which is the view of researchers like Ana Soto and Carlos Sonnenschein [7, 8]. It is based on two biological assumptions: the default condition of all cells of a multicellular organism is proliferation and motility; and the second assumption is that cancer is a disease of tissue organisation. In a normal body, the natural tendency of cells to develop and migrate is inhibited by the complex control activities of tissue structure. This architecture includes physical structure of the extracellular matrix, the chemical signals that are released by surrounding cells, and the mechanical forces that are conveyed in the tissue. The most persuasive case in support of the TOFT is the fact that there are emergent properties in tissues- properties that cannot be predicted by studying the properties of single cells in isolation. Similar to the fluidity of water being an emergent property of interacting H_2O molecules, the homeostasis and morphogenesis of a tissue is the result of the complex discussion between epithelial cells, stromal components, and the extra-cellular matrix. The phenomenon of phenotypic reversion supports such a point of view. The initial experiments by Mina Bissell [4-14], and others showed that malignant breast cancer cells when cultured into three-dimensional matrix that resembles normal tissue architecture could differentiate into non-cancerous and acini-like structures [5, 6]. The results refute the notion that the malignant phenotype is an irreversible genetic condition, but rather it is highly reliant on external environmental stimuli. Other more recent observations in 2025 using the sophisticated organoid models [15], have also supported the idea that a cell genome in its own right is not its memory, but is entrenched within its physical and biochemical environment. These paradigms demonstrate that through the use of mechanical stiffness, or chemical composition of organoid environment, researchers will be able to induce or repress malignant behaviors, which is a powerful model to study how histophysiological reprogramming can be examined in real time. Field concept in oncogenesis state of the art the concept of the field in oncogenesis argues that malignancy is not a localised phenomenon but a systemic breakdown in a given tissue region. The structure of tissues is developed and preserved by a process known as the orchestration of morphogenetic field. In cases where this field is disturbed, be it through chronic inflammation, chemical carcinogens or mechanical stress, there is an absence of regulatory cues in the cells present in that field. They degenerate back to their default position which is the unchecked growth and invasion which is the hallmark of cancer. This theoretical framework is consistent with the experience of field cancerization whereby large areas of apparently normal tissue develop an increased likelihood of several independent tumours [16].

TOFT provides an invaluable framework onto which the nonlinear behaviour of cancer progression is understood, in which the environment is the determiner of expression of the malignant phenotype, and not the genome per se. This is important because when therapeutic ambition is redirected based on this distinction, it involves the limitation of an endless search of genetic targets and the more realistic goal of restoring the homeostatic equilibrium of the tissue. The success of this strategy depends on a deep, mechanistic perspective of the way the microenvironment implements histophysiological reprogramming- a question, which forms the major theme of the following passages of this review. With the merging of the TOFT into modern molecular biology, specifically spatial omics, we will have an opportunity to enter a truly systems-level oncology.

Table 1: Detailed comparison of oncological paradigms

Feature	Somatic Mutation Theory (SMT)	Tissue Organization Field Theory (TOFT)
Unit of Analysis	The individual cell	The tissue/organism
Primary Driver	DNA mutations (oncogenes/tumor suppressors)	Disruption of tissue architecture/signals
Default State	Quiescence (proliferation requires signals)	Proliferation and motility (quiescence is enforced)
Role of Stroma	Passive scaffold or secondary support	Active architect and regulator of cell fate
Heterogeneity	Result of clonal evolution and mutations	Result of local microenvironmental variations
Dormancy	Result of specific "dormancy genes"	Result of tissue-level growth constraints
Metastasis	Acquisition of invasive mutations	Breakdown of tissue compartmentalization
Therapeutic Focus	Cytotoxicity (killing cancer cells)	Normalization (restoring tissue field)
Key Research Tool	Genomic sequencing (NGS)	Spatial proteomics and 3D organoids
Philosophical Basis	Reductionism (bottom-up)	Holism/Systems Biology (top-down)

3. The Stromal Landscape: Architects of Malignant Reprogramming

The microenvironment in breast tumors (TME) is a highly structured and dynamic ecosystem, which serves as the major conductor of histophysiological reprogramming [16, 17]. It is within this milieu that there are non-malignant cellular occupants such as fibroblasts, immune cells, adipocytes, and endothelial cells that are embedded within a complex extra-cellular matrix (ECM). A two-way communication between stromal constituents and malignant cells, which is constantly active, contributes to the launching, further development, and therapeutic resistance of tumors.

The cancer-affiliated fibroblasts (CAFs) are arguably the most powerful subpopulation of stroma in the breast TME [18, 19]. Their activation is a critical reprogramming signaling event usually triggered by tumor-produced signals like Transforming Growth Factor-beta (TGF-β), Platelet-Derived Growth Factor (PDGF) and mechanical force due to ECM hardening. CAFs are not only functionally heterogeneous on activation, but they are also loosely divided into specific subpopulations, including myofibroblastic CAFs (myCAFs) and inflammatory CAFs (iCAFs). As the focal points of signaling, CAFs also secrete an array of soluble factors, which have a direct reprogramming effect on cancer cells. TGF-β2 released by tumor cells and CAFs is a strong stimulator of epithelial-mesenchymal transition (EMT) in malignant cells, which promotes an invasive machinery. Autocrine TGF-β also promotes the active state of CAFs and the production of collagen and fibronectin as components of ECMs. In addition to soluble mediators CAFs make use of extracellular vesicles (EVs) to deliver pro-tumorigenic cargo- microRNA, effectors and metabolites- to breast cancer cells [13]. These EVs are able to reprogram cancer cell metabolism, promote stemness, and give them resistance to chemotherapy, and as such present a complex, non-contact, system of histophysiological reprogramming.

The CAF-cancer cell crosstalk signaling pathways are very complicated and context-specific. An example is the CXCL12 released by CAFs attaching to its receptor CXCR4 on the cancer cells causing the migration and metastasis process to take place [20]. On the other hand, cytokines including IL-6 and IL-8, secreted by cancer cells, maintain the inflammatory appearance of iCAFs and create a vicious circle that enhances the growth of the tumour [21]. This complex language of the interactions of its molecules demonstrates the TME as an extremely malleable and self-organizing system.

Immune landscape is a very important variable of breast cancer prognosis, and its rearrangement is a sign of malignant process. One of the key events is the polarization of tumor-associated macrophages (TAMs) to an M2-like and pro-tumorigenic phenotype [22, 23]. TAMs are recruited by chemokines (e.g., CCL2 and CSF-1) and release factors i.e. Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMPs) aiding angiogenesis and extracellular matrix remodelling [24]. According to recent spatial proteomic results (2025), immune evasion is a high localization process and a largely metabolic one [9]. The formation of a localized immunosuppressive niche often overrides the anti-tumor effect of immunodulatory cells even in the context of hot tumors that have a significant proportion of immune cells infiltration. This is accomplished by increasing expression of immune checkpoint molecules (e.g., PD-L1) and activation of metabolic pathways that deplete key nutrients that are required by the functioning of T-cells. Being frequently expressed by CAFs and TAMs, the activation of the Indoleamine 2,3 -dioxygenase (IDO1) enzyme triggers the kynurenine pathway

[25, 26]. This metabolic pathway metabolizes tryptophan which is an essential amino acid required to grow T-cells as well as synthesizes kynurenine which is a strong immunosuppressive metabolic byproduct. Equally, in the case of overrunning of Cyclooxygenase-2 (COX-2), it leads to higher production of Prostaglandin E2 (PGE 2) that suppresses T -lymphocyte activation and differentiation of regulatory T-cells (Tregs) [27, 28]. These metabolic checkpoints are a complex histophysiological reprogramming mechanism that makes the T-cells anergic despite their presence. The functions of the other components of the immune system, including myeloid-derived suppressor cells (MDSCs) and natural killer (NK) cells are also of equal importance. MDSCs do gather in the TME, and T-cell activity is consequently inhibited by the discharge of reactive oxygen species (ROS) and nitric oxide (NO) [29]. The immunosuppressive environment is further solidified by the presence of inhibitory signals transmitted by CAFs and TAMs to NK cells, which in most instances turn into functional renal failure within the breast TME [30].

Breast tissue rich in adipose leads to the establishment of a characteristic association of cancer cells and adipocytes. The cancer-related adipocytes (CAAs) experience a phenotypic transition, which is characterized by the lipolysis and the release of inflammatory cytokines [31]. This communication sustains an apt symbiosis of metabolism, often known as the Reverse Warburg Effect [32, 33]. CAAs in this model undergo aerobic glycolysis and lipolysis, contribute highly energize metabolites namely: lactate, pyruvate, and free fatty acids (FFAs) to the neighboring cancer cells [34, 35]. The latter, in turn, is used by cancer cells as the source of 7 contra depression of 37 -oxidation as a sturdy guaranty that the nutrient-deprived or hypoxic zones of the TME will be quickly increased and survived [36]. This type of metabolic reprogramming forms an important part of the histophysiological change that allows the malignant cells to sustain an aggressive phenotype. The precise process of transferring FFA entails the use of certain fatty acid transport proteins (FATPs) and the CD36 on the surface of the cancer cell, which is an example of an elevated nutrient scavenging process within the stromal compartment [37].

The endothelial cells and tumor vasculature are also very important in the histophysiological reprogramming [38, 39]. Angiogenesis, which is the development of novel blood vessels, is a characteristic of any cancer due to the factors including the VEGF secreted by the TAMs and cancerous cells. Nevertheless, the resultant tumor vascular is frequently structurally and functionally dysplastic leaky, tortuous and poorly perfused. Chronic hypoxia and acidosis is caused by this pathological vasculature, which refers to very powerful environmental signals that further promote the malignant phenotype. Hypoxia keeps the transcription factor HIF-1alpha steady, which enhances EMT, metabolic reprogramming (shift of cells towards glycolysis) as well as the release of pro-angiogenic factors, thus forming a self-perpetuating loop of malignancy [40]. Besides, cancer cell intravasation, which is one of the essential stages of the metastatic cascade, occurs through dysfunctional endothelium [41]. The TME in turn reprograms endothelial cells, which become in a pro-inflammatory and pro-coagulant phenotype, which makes them add to the overall environment favorable to cancer progressing. Instead of ablating this dysfunctional vasculature, its normalization has become a therapeutic approach to improve oxygenation, drug delivery and anti-tumor immune cell infiltration, and, therefore, stabilize a more homeostatic tissue field [42].

4. The Physical Field: Mechanotransduction and Architectural Sabotage

The extracellular matrix (ECM) has not been identified solely as a perceptual scaffold but rather, a dynamic, information-rich place which controls cellular fate by being active through both mechanical and biochemical signaling pathways [43,44]. The ECM in relation to breast carcinoma experiences a massive pathological remodeling which can be considered as a key driver of histophysiological reprogramming. Another characteristic of malignant breast tumors includes the excessive growth and cross-linking of collagen fiber which is mainly enabled by cancer-associated fibroblasts (CAFs) [45, 46]. This not only is a mechanical alteration and is not just a downstream action of malignancy but is a strong oncogenic signal in its own right [47,48]. Breast cancer cells can sense the rigidity of their surroundings through a complex of receptors at the cell surface called integrins, through a pathway known as mechanotransduction [5]. Interaction of integrins with stiffened components of the ECM triggers a series of intracellular signaling events. The key events in this process are the cytoplasmic to nuclear translocation of the transcriptional co-activator YAP (Yes-associated protein) and TAZ (transcriptional co-activator with PDZ-binding motif) transcriptional co-activators [47]. With good microenvironment, YAP/TAZ remains in the cytoplasm and then gets impoverished away but in a stiff, malignant microenvironment, mechanical tension facilitates their nuclear accumulation with their presence in association with transcription factor, TEAD to stimulate the expression of proliferation, survival, and stemness-linked genes. The reprogramming by the YAP/TAZ, therefore, is a direct molecular pathway between the physical characteristics of the tissue field and the malignant phenotype of the carcinoma cell.

Of paramount importance is the nature of the ECM constituents that mediate this signaling which depends on stiffness. Although collagen type 1 is the most largely expressed one, it is pathological deposition of fibronectin and laminin-5 fragment as well that provides pro-survival and pro-migratory signatures when needed [49]. These aberrant elements of the matrix are bound by integrin receptors, especially the α5β3 and the α5β1, which trigger the signaling by focal adhesion kinase (FAK). The cytoskeleton framework becomes further stabilized by this pathway and strengthens the

ability of the cell to generate traction forces, and tissue stiffness is further perpetuated in a vicious cycle [50]. One of the most difficult aspects of such physical reprogramming is the notion of mechanical memory. Recent studies have shown that breast cancer cells equipped with a stiff ECM during a long period of time have an apparently long-standing memory of that stiffness which they maintain upon repeated exposure to a compliant normal matrix, maintaining an aggressive stiff-matrix phenotype [51]. It is postulated that such memory is preserved by reorganizations of the intracellular cytoskeleton that are stable as well as by a sustained nuclear localization of YAP/TAZ. This observation holds far-reaching implications on the therapeutic interventions, which indicate that it is possible that simply the process of decreasing the stiffness of ECMs might not be sufficient to restore the reversal of the malignant phenotype, once the mechanical memory has been founded. In this case, treatment plans will have to be developed to proactively overwrite this memory, which may include attacking downstream mediators of mechanotransduction like YAP/TAZ or destabilizing the cytoskeleton, which maintains the memory status.

The correlation between the ECM stiffness and the resistance of the therapy is becoming more noticeable. Hard matrices compress the vasculature physically which promotes hypoxia and diminishes drug delivery. In addition, the activation of FAK and YAP/TAZ (signaling pathways) directly provide reports of chemotherapeutic agents and targeted therapeutics through cell survival and anti-apoptotic effects [52]. Indicatively, ECM stiffening has been found to protect breast cancer cells against cell death caused by paclitaxel and this resistance can be overcome by inhibiting FAK pharmacologically [53]. The ECM additionally regulates the spatial arrangement and polarity of epithelial cells on top of their proliferation and survival. Epithelial cells maintain severe apico-basal polarity in the healthy duct of the breast, the property essential to the operation of normal tissue and imposed by the basement membrane. It is a crucial step in the process of progressing to invasive carcinoma through the degradation and disorganization of this basement membrane which is facilitated by the secretion of MMPs by CAFs to achieve this degradation and disorganization [43]. Cell depolarization is one example of a histophysiological reprogramming that releases cells by relieving them of architectural factors, allowing them fulfil a migratory and invasive phenotype. This loss of compartmentalization permits direct and uninhibited contact among epithelial cells and reactive stromal components which theorize reciprocal signaling loop to stimulate disease development.

5. Spatial Biology and Dynamic Phenotypes: The Modern View

The middle of 2020s has ushered the beginning of the spatial biology age that can provide researchers with the highest possible resolution of the histophysiological landscape of breast carcinoma. The fact that cancer is a dynamic and contextually dependent process has been integrated into the community through these technologies, providing strong evidence to the support of the Tissue Organisation Field Theory (TOFT). The combination of spatial proteomics utilising mass spectrometry with state-of-the-art imaging has been a breakthrough. An eventual 2025 study showed that proteomic heterogeneity in a single tumour can often surpass the heterogeneity in a single tumour as predicted by genomic sequencing [9]. This finding implies that the local microenvironment rather than the accumulation of discrete mutations dictates the diverse phenotypes which are manifested in breast cancer; highly proliferative or dormant phenotypes.

Spatial analysis has now advanced past individual cell resolution and individual cellular workings to describe the cellular neighbourhoods (CNs) functional units, which are assemblies of defined cellular populations (e.g. CAFs, TAMs, and carcinoma cells) that engage with each other to facilitate malignancy [54]. These CNs form local micro-environments with unique proteomic and metabolic profiles. As an example, CNs that were characterised by broad cross-linking of collagen and high levels of enzymes in the kynurenine pathway were highly immunosuppressive irrespective of the underlying genotype of their cancer-cells. In this way, the given phenomenon of the microenvironment spatial dominance reveals the necessity to divert our attention not solely to the genome but to the so-called proteomic field. They are now using spatial transcriptomics and proteomics to map the localisation of the exact location of therapeutic targets and mechanisms of resistance. Recent studies have employed spatial technologies to identify a specific CN at the invasive front of triple-negative breast cancer (TNBC) which is enriched significantly with epithelial -mesenchymal transition (EMT) markers and metabolically reliant on CAF-derived free fatty acids (FFAs) [55]. This observation suggests that such a narrowed FATP or CD36 targeting of this localised CN and not a systemic inhibition may be a more effective approach to suppress invasion. The optimization of CNs has brought a new system of classification of breast carcinoma [56-60]. The new spatial taxonomy uses the compositional and functional condition of the surrounding stroma in addition to relying on intrinsic molecular subtypes (e.g., Luminal A, HER2-enriched). A tumour can therefore be considered as Luminal A with immunosuppressive-metabolicCN, which is a more precise predictor of patient outcome and response to neoadjuvant therapy.

The claudin-low phenotype that used to be considered a particular intrinsic subtype [56], is gradually evolving as a dynamic phenotypic state- an expression of deep histophysiological reprogramming [57]. The claudin-low state is characterised by decreased expression of tight-junction proteins (claudins 3, 4, and 7) and increased expression of EMT [58, 59], and stem-cell markers [60], and may be induced by microenvironmental cues in a variety of breast-cancer subtypes.

The claudin-low state has been found to be often triggered by the tumour-microenvironment (TME) inflammatory and mechanical signals through functional profiling. A combination of increased levels of TGF-β and IL-6, in combination with high extracellular-matrix stiffness, driving epithelial cells into this highly plastic, mesenchymal-like state. This makes the claudin-low phenotype look more like a lineage-independent disorder but rather as a survival mechanism used by cancer cells to cope with the extreme environmental pressures. The oscillation ability of cells between and out of the claudin-low state highlights the relevance of targeting the environmental forces that support such plasticity, and not just the cancer cells themselves. Epigenetic changes are also ingrained with the histophysiological reprogramming of breast-cancer cells. Epigenetic changes, including DNA methylation and histone acetylation, are both reversible and extremely sensitive to environmental change. The tissue microenvironment has the potential to cause a global epigenetic ecosystem in cancer cells thus regulating the expression of proliferation, metabolism, as well as invasion genes. The epigenetic field hypothesis suggests that reprogramming begins in so-called normal tissue that surrounds a tumour and it has different methylation patterns. This mechanism provides a reasonable model of the quick response of cancer cells to changing environmental conditions, which support the perception of cancer as a process at the tissue level. Attack on the epigenetic readers and writers that maintain these super-enhancers provides the possibility of resetting the cellular programme without the need to use cytotoxic intervention. Certain epigenetic objects are becoming central to the control of phenotypical plasticity. Indicatively, histone deacetylase (HDAC) family inhibitors are being explored in terms of their ability to reverse the EMT programme triggered by the TME, and thus decreasing the invasive ability of tumour cells and re-primarily sensitise them to traditional therapies.

6. Therapeutic Frontiers: Normalizing the Tissue Field

In the recent scholarship, it has been emphasized how the fundamental lesson has been learning to consider cancer as a tissue level disorder, and thus, a paradigm shift of treatment is essential. In the event that malignancy is a maladjustment of tissue order, therapeutic intervention should not stop to eradicate the rogue cancer cells, but should instead involve the proactive restoration of tissue field integrity, and control.

Although traditional cytotoxic treatments are effective in terms of lessening tumour burden, they frequently are inefficient in dealing with the underlying environmental clues that cause recurrence and resistance. Normalization strategies are thus expected to re-educate the tumour microenvironment, and thus inhibit the malignant phenotype and reinstate tissue homeostasis [42]. The application to the mechanical field consists of the use of agents that interfere with the pathological rigidity of the extracellular matrix (ECM). It can be lysyl oxidase (LOX) or transglutaminase-2 (TGM2) inhibitors, which are the enzymes involved in collagen cross-linking [45]. These reagents are able to undo YAP/TAZ-mediated oncogenic signalling by softening the ECM and possibly erase the mechanical memory of the cancer cells. It has been shown through promising results during preclinical research on focal adhesion kinase (FAK) (e.g., Defactinib) and LOX (e.g., PXS-5505) inhibitors that they are able to decrease tumour hardness, metastatic load and re-sensitise resistant tumours to chemotherapy [52].

This symbiosis occurring between the stroma and the cancerous cells is a vital weakness. Anti-tumour immunity can be restored by targeting the kynurenine pathways and prostaglandin pathways as it is pointed out in the 2025 research. The action of inhibitors of IDO1 is to block the depletion of tryptophan and accumulation of immunosuppressive metabolites; thus, reprogramming the immune field to the active state instead of the suppressive one [25, 26]. Studies are in progress to assess the efficacy of checkpoint blockade (PD-1/PD-L1) in combination with IDO1 inhibitors (e.g., Epacadostat) in a number of solid tumours, including breast cancer. The reasoning behind this is that the entire potential of immunotherapy will be accomplished by normalising the metabolic immune field [53]. Targeted therapies involve somatic mutations, which are focused on restoring activated cancer fibroblasts (CAFs) to a non-supportive state. Strategies encompass either focusing on CAF-specific signalling pathways (e.g., FAP, Hedgehog) or interfering with the CAF derived exosome transfer, which is one of the mechanisms of histophysiological reprogramming [19]. The use of FAP-targeted agents, including FAP-specific CAR T-cells or FAP-targeted prodrugs, can be described as an innovative technology that may be used to target the most tumorigenic CAF sub-populations and destroy the structural backbone of the tumour [54].

The future of the breast cancer care diagnosis is in the uniting systems biology with personalised medicine where instead of analysing some individual gene/cell, the whole tissue field is viewed. The strategy will use multi-omic spatial data to build an individual personalised tissue signature of each patient. Through mapping the exact site and interplay of cellular neighbourhoods (CNs), clinicians can determine the exact drivers of reprogramming, mechanical, metabolic, or immunological, in the tumour of an individual. The final goal is to come up with the so-called combination field therapies that will simultaneously address the genetic vulnerability of cancer cells, as well as the structural/biochemical abnormalities of the stroma. As an example, a patient that has an extremely stiff, excluded tumour microenvironment may be treated with

a mechanotherapeutic agent to soften the ECM and an IDO1 inhibitor to stimulate the immune response, in addition to otherwise standard targeted therapy.

The use of artificial intelligence (AI) and machine learning in 2026 has the potential to be included in the analysis of such complex multi-omic data [55]. Using AI models, predicting how a patient will react to normalisation therapies given their unique tissue signature allows choosing the most effective combination of field-restoring, one can be guided to the most effective combination that has been shown to be effective. Preclinical testing is being transformed by the discovery of patient-derived organoids (PDOs), together with microfluidic systems (organ-on-a-chip). Their use has been capable of recapitulating the microenvironment of a patient subjected to a particular tumour such as ECM stiffness and cellular composition thus facilitating high-throughput screening of field-targeting agents as well as personalised combination regimens before clinical use [56].

7. CONCLUSION

One of the most important changes in modern oncology is the shift towards a tissue-oriented concept of breast cancer as opposed to a cell-based one. When we consider the disease through the prism of the Tissue Organisation Field Theory (TOFT), we will be able to obtain a better and more holistic image of tumour development: the one that takes into consideration the complex interplay between cells and their microenvironment. The process of histophysiological reprogramming of breast cancer cells, is not a random event but rather a concerted action to the dismantling of tissue level restraints. The ultimate phase of clinical validation and translation is critical to the success of the tissue-centred paradigm because the theoretical knowledge is strictly tested and implemented in the work with patients. Once we stop thinking about killing the cell, and instead focus on healing the field, we become able to discover a wider scope of treatment options that will be more effective, lasting, and humane cures to the victims of breast cancer. Not only does this paradigm shift provide the promise of a better clinical outcome, but it also reestablishes the biological maxim that no cell exists in isolation, but its destiny is inseparably connected with the society of cells and tissues in which it is incorporated. The long-term goal, though, would be to attain a stable, non-malignant state, as opposed to a temporary reduction in tumour burden, and it can only be reached when a comprehensive, tissue-centred approach is implemented.

REFERENCES

1. American Cancer Society. Breast Cancer Facts & Figures 2024. Atlanta: American Cancer Society; 2024.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;144(5):646–674.
3. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW, et al. Cancer genome landscapes. Science. 2013;339(6127):1546–1558.
4. Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med. 2011;17(3):320–329.
5. Weaver VM, Petersen OW, Wang F, Larabell CA, Briand P, Damsky C, et al. Reversion of the malignant phenotype of human breast cells in three-dimensional culture and in vivo by integrin blocking antibodies. J Cell Biol. 1997;137(1):231–245.
6. Kenny PA, Bissell MJ. Tumor reversion: Correction of malignant behavior by microenvironmental cues. Int J Cancer. 2003;107(5):688–695.
7. Soto AM, Sonnenschein C. The tissue organization field theory of cancer: A testable replacement for the somatic mutation theory. BioEssays. 2011;33(5):332–340.
8. Sonnenschein C, Soto AM. The Society of Cells: Cancer and Control of Cell Proliferation Revisited. Cham: Springer Nature; 2024.
9. Mardamshina M, Lee S, Wang Y, Müller S, Kwon Y, Kim J, et al. Integrated spatial proteomic analysis of breast cancer heterogeneity unravels cancer cell phenotypic plasticity. Nat Commun. 2025;16:10482.
10. Kotsifaki A, Papadaki MA, Karagiannis GS, Rupp C, Psarianos P, Stournaras C, et al. Emerging breast cancer subpopulations: Functional heterogeneity beyond the classical subtypes. Int J Mol Sci. 2025;26(23):11599.
11. Chen M, Liu S. Breast cancer stem cell heterogeneity, plasticity and treatment strategies. Cancer Heterog Plast. 2025;2(1):0004.
12. Duan Z, Liu X, Chen Y, Zhang J, Wang Y, Li H, et al. Mapping thirty years of tumour-microenvironment-driven drug resistance in breast cancer: A global bibliometric analysis. Discover Oncol. 2025;16:3324.
13. Valde K. From metaphysics to methods? Pluralism in cancer research. Acta Anal. 2025;40:601.
14. Nelson CM, Bissell MJ. Of extracellular matrix, scaffolds, and signaling: Tissue architecture regulates development and cancer. Annu Rev Cell Dev Biol. 2006;22:287–309.
15. Higgins KS, Turner MA, Davies EJ, Patel R, Chen L, O'Neill GM, et al. 3D in vitro models of breast cancer: Current challenges and future directions. Adv Biol. 2025;9:2400846.
16. Egeblad M, Nakasone ES, Werb Z. Tumors as organs: Complex tissues that interface with the entire organism. Dev Cell. 2010;18(6):884–901.
17. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423–1437.

18. Kalluri R. The biology and function of fibroblasts in cancer. Nat Rev Cancer. 2016;16(9):582–598.
19. Sahai E, Astsaturov I, Cukierman E, DeNardo DG, Egeblad M, Evans RM, et al. A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer. 2020;20(3):174–186.
20. Wu T, Dai Y. Tumor microenvironment and therapeutic response. Cancer Lett. 2017;387:61–68.
21. Polyak K. Heterogeneity in breast cancer. J Clin Invest. 2011;121(10):3786–3788.
22. Cassetta L, Pollard JW. Targeting macrophages: Therapeutic approaches in cancer. Nat Rev Drug Discov. 2018;17(12):887–904.
23. Vitale I, Manic G, Coussens LM, Kroemer G, Galluzzi L. Macrophages and metabolism in the tumor microenvironment. Cell Metab. 2019;30(1):36–50.
24. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer. 2009;9(4):239–252.
25. Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, et al. The indoleamine 2,3-dioxygenase (IDO) pathway in cancer. Nat Rev Cancer. 2011;11(10):685–694.
26. Prendergast GC, Mondal A, Dey S, Laury-Kleintop LD, Müller AJ. Discovery of IDO1 inhibitors: From bench to bedside. Cancer Res. 2018;78(12):3095–3102.
27. Wang D, DuBois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Endocr Rev. 2010;31(4):465–494.
28. Greenhough A, Smartt HJM, Moore AE, Roberts HR, Williams AC, Paraskeva C, et al. The COX-2/PGE2 pathway: Key roles in cancer. Carcinogenesis. 2009;30(3):377–386.
29. McAllister SS, Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. Nat Cell Biol. 2014;16(8):717–727.
30. Plaks V, Kong N, Werb Z. The cancer stem cell niche: How essential is the stroma? Cell Stem Cell. 2015;16(3):225–238.
31. Wu Q, Li B, Li Z, Li J, Sun S, Sun S. Cancer-associated adipocytes: Key players in breast cancer progression. J Hematol Oncol. 2019;12:95.
32. Lisanti MP, Martinez-Outschoorn UE, Pavlides S, Whitaker-Menezes D, Pestell RG, Howell A, et al. The reverse Warburg effect: Aerobic glycolysis in cancer-associated fibroblasts and the tumor stroma. Cell Cycle. 2010;9(17):3508–3516.
33. Martinez-Outschoorn UE, Pavlides S, Howell A, Pestell RG, Tanowitz HB, Sotgia F, et al. Energy transfer in cancer: A new paradigm in the Warburg effect. Nat Rev Clin Oncol. 2011;8(11):656–670.
34. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med. 2011;17(11):1498–1503.
35. Dirat B, Bochet L, Dabek M, Daviaud D, Dauvillier S, Majed B, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res. 2011;71(7):2455–2465.
36. Pattabiraman DR, Weinberg RA. Tackling the cancer stem cell hazard. Nat Rev Drug Discov. 2014;13(7):497–512.
37. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: Tumor microenvironment and inflammation. J Clin Oncol. 2016;34(35):4270–4276.
38. Lu P, Weaver VM, Werb Z. The extracellular matrix: A dynamic niche in cancer progression. J Cell Biol. 2012;196(4):395–406.
39. Pickup MW, Mouw JK, Weaver VM. The extracellular matrix modulates the hallmarks of cancer. EMBO Rep. 2014;15(12):1243–1253.
40. Jain RK. Normalizing tumor microenvironment to treat cancer: Bench to bedside to biomarkers. J Clin Oncol. 2013;31(17):2205–2218.
41. Munn LL, Jain RK. Vascular regulation of antitumor immunity. Science. 2019;365(6453):544–545.
42. Levental KR, Yu H, Kass L, Lakins JN, Egeblad M, Erler JT, et al. Matrix crosslinking forces tumor progression by enhancing integrin signaling. Cell. 2009;139(5):891–906.
43. Provenzano PP, Inman DR, Eliceiri KW, Knittel JG, Yan L, Rueden CT, et al. Collagen density promotes mammary tumor initiation and progression. BMC Med. 2006;4:11.
44. Paszek MJ, Zahir N, Johnson KR, Lakins JN, Rozenberg GI, Gefen A, et al. Tensional homeostasis and the malignant phenotype. Cancer Cell. 2005;8(3):241–254.
45. Butcher DT, Alliston T, Weaver VM. A tense situation: Forcing tumour progression. Nat Rev Cancer. 2009;9(2):108–122.
46. Schürch CM, Bhate SS, Barlow GL, Phillips DJ, Noti L, Zlobec I, et al. Coordinated cellular neighborhoods orchestrate antitumoral immunity at the localized tumor-immune microenvironment. Cell. 2020;182(5):1341–1359.
47. Wagner J, Rapsomaniki MA, Chevrier S, Anzeneder T, Langwieder C, Dykgers A, et al. A single-cell atlas of the tumor and immune ecosystem of human breast cancer. Cell. 2019;177(5):1330–1345.
48. Azizi E, Carr AJ, Plitas G, Cornish AE, Konopacki C, Prabhakaran S, et al. Single-cell map of diverse immune phenotypes in the breast tumor microenvironment. Cell. 2018;174(5):1293–1308.
49. Keren L, Bosse M, Thompson S, Risom T, Vijayaragavan K, McCaffrey E, et al. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. Cell. 2018;174(6):1373–1387.

50. Jackson HW, Fischer JR, Zanotelli VRT, Ali HR, Mechera R, Soysal SD, et al. The single-cell pathology landscape of breast cancer. Nature. 2020;578(7796):615–620.
51. Ali HR, Jackson HW, Zanotelli VRT, Danenberg E, Fischer JR, Bardwell H, et al. Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer. Nat Cancer. 2020;1(2):163–175.
52. Prat A, Perou CM. Deconstructing the molecular heterogeneity of breast cancer. Nat Rev Cancer. 2011;11(10):689–703.
53. Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, et al. Characterization of a naturally occurring claudin-low molecular phenotype in human breast cancer. Cancer Res. 2009;69(10):4116–4124.
54. Fougner C, Bergholtz H, Norum JH, Sørlie T. Re-evaluating the claudin-low subtype of breast cancer. Nat Commun. 2020;11:3640.
55. Pommier AJ, Sturny R, Keime C, Blache P. Unresolved issues in the claudin-low breast cancer subtype. Front Oncol. 2020;10:583.
56. Scheel C, Weinberg RA. Cancer stem cells and epithelial-mesenchymal transition: Concepts and molecular links. Semin Cancer Biol. 2012;22(5–6):396–403.
57. Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell. 2008;133(4):704–715.
58. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci U S A. 2003;100(7):3983–3988.
59. Gavrilova A, Chen X, Patel R, Singh P, Alvarez JV, Smith J, et al. Phenotypic plasticity and competition shape therapy resistance in breast cancer. bioRxiv. 2025:2025.12.27.696676.
60. Tiffon C. The role of the tumor microenvironment in cancer progression. Int J Mol Sci. 2018;19(10):3228.