

Introducing a New Hypothesis in the Genesis of Breast Cancer: An Integrative Review

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Introduction: Breast cancer is the second most common cancer among women worldwide. Estrogen is currently identified as one of the main agents involved in the initiation of breast tumors; however, evidence indicates a greater risk when estrogen replacement is combined with progesterone, whereas its isolated use does not represent a significant risk. Inconsistencies in existing theories highlight the need for further detailed research on the relationship between hormone exposure and breast tumorigenesis, with particular emphasis on fibrinogen and its components in the context of this review.

Objective: Introduce a new theory into the medical literature concerning the genesis of breast cancer.

Methods: This is an integrative literature review based on a selection of relevant articles published between 2000 and 2025, in both Portuguese and English, and sourced from the following databases: Scielo, ScienceDirect, National Library of Medicine, PubMed, Cochrane, *Brazilian Journal of Development*, and ResearchGate.

Results: Fifty-six references were selected to support the development of the discussion components, which are subdivided into the following themes: physiology of estrogen and progesterone in the body, actions of hormonal therapies, both combined and isolated, in breast cancer, and fibrinolytic physiology.

Conclusion: After identifying contradictions in current theories about the influence of estrogen on tumor proliferation, which encouraged the search for new interpretations, it was demonstrated that free estrogen and its by-products, such as fibrinogen-related protein (fibrinogen-like protein 1 and 2), play a role in the immune system's failure to contain malignant cells, opening another field of therapeutic research for breast cancer.

Keywords: hormone replacement therapy, estrogen, FGL1, LAG-3, breast cancer, fibrinogen, oncogenesis, crosstalk

Introduction

Breast cancer represents a major global health burden, according to a study by the International Agency for Research on Cancer (IARC, 2025), an estimated 2.3 million new cases and 670,000 deaths occurred in 2022. The report further indicates that, by 2050, these numbers could rise to 3.2 million new cases and 1.1 million deaths per year, disproportionately affecting countries with a low Human Development Index.¹ Given the scale of this challenge, it is important to explore the pathogenesis of the disease, which may involve a complex interplay among genetic alterations, environmental exposures, and dysregulated immune responses, although much remains speculative. Genetic mutations (eg *TP53*, *BRCA1*, *BRCA2*), *HER2* amplification, and risk factors such as late menopause or family history are well-established contributors.² However, HRT and long-term hormonal exposure also represent modifiable elements implicated in breast tumor initiation.³

Estrogen is a well-established driver of breast tumorigenesis, exerting genotoxic and proliferative effects through the activation of ER α and β . Recent evidence further indicates that estrogen signaling can modulate immune evasion mechanisms. For example, estrogen signaling has been shown to regulate programmed death-ligand 1 and programmed cell death protein 1 expression in both tumour and immune cells. It also affects the recruitment and polarization of macrophages as well as regulatory T cells, thereby altering the tumour immune microenvironment.⁴

Immune checkpoint inhibitors have demonstrated benefit in early-stage triple-negative breast cancer and in programmed death-ligand 1–positive hormone receptor–positive and HER2–negative tumours when used as part of neoadjuvant therapy.⁵ These trials underscore the prognostic and therapeutic importance of immune checkpoints and highlight that the response to immunotherapy can be modulated by factors such as tumour infiltrating lymphocytes, mutational burden, and spatial distribution of immune cells in the tumour immune microenvironment.⁶

Another emerging pathway involves inflammation and its interplay with Fibrinogen (Fg). Beyond its classical role in coagulation and fibrinolysis, Fg also participates in inflammatory and immune processes, with a strong link to tumor progression, including angiogenesis and metastasis. Recent studies point to it as a useful biomarker in the prognosis and staging of various cancers, as high levels are associated with shorter survival and a higher risk of recurrence.⁷ Similar mechanisms have been reported in other malignancies, such as glioblastoma multiforme (GBM) and hepatocellular carcinoma (HCC), where Fg and FREPs promote immune evasion, tumour growth, and recruitment of immunosuppressive macrophages.^{8,9} Given the scarcity of large-scale in vivo studies on fibrinogen-related immune modulation in breast cancer, further investigation is critical to validate this hypothesis, which, although gaining traction, still requires assessment of its translational potential.

This manuscript proposes a hypothesis that integrates hormonal dysregulation, immune checkpoint biology, and fibrinogen-associated inflammation in the pathogenesis of breast cancer. By exploring these intersecting pathways, we aim to elucidate novel mechanisms of tumour initiation and progression, identify potential biomarkers, and suggest targets for therapeutic intervention.

Methods

Search Strategy and Selection Criteria

This review, “A new theory in the genesis of breast cancer: an integrative review”, combines existing knowledge to compare theory and evidence, offering a clear overview of complex concepts and theories.¹⁰ The study was guided by the following guiding questions, structured according to the PICO framework: “What is the physiology and metabolism of estrogen and progesterone in non-pathological cells?”, “Regarding HRT, what is the role of isolated estrogen and its association with progestogen in the pathogenesis of breast cancer?”, “How does Fg contribute to breast cancer development through its physiological and pathophysiological roles?”.

An electronic search of relevant bibliographic production was conducted using the following databases: Scielo, Science Direct, National Library of Medicine, PubMed, Cochrane, *Brazilian Journal of Development* and ResearchGate. The period of analysis was from 2000 to 2025, including studies published in Portuguese and English. Using the PRISMA method as a structural reference (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to ensure methodological transparency.

The following descriptors and their Boolean combinations were used: “Estrogen biosynthesis”; “Estrogen receptors”; “Estrogen and thrombosis”; “Progesterone receptor”; “Cross-talk steroid hormone receptors”; “Menopausal hormone therapy”; “Breast cancer and postmenopausal women”; “Estrogen-alone therapy”; “Hormonal therapy and breast cancer”; “Estrogen plus progestin and breast cancer”; “Progesterone and breast cancer”; “Fibrinogen metabolism and structure”; “Fibrinogen and breast cancer”; “Fibrinogen and estrogen”; “LAG-3”; “MCF-7 and breast cancer”.

Although the study selection and organization was guided by the PRISMA framework, the total number of records initially retrieved from the databases could not be precisely determined, as the searches were conducted manually and without the use of a reference management system. Therefore, only the studies effectively screened and analyzed in full text were counted and reported, as summarized in [Figure 1](#). The scope of this review was deliberately restricted in order to prioritize conceptual depth over exhaustive coverage consistent with the integrative nature of this review.

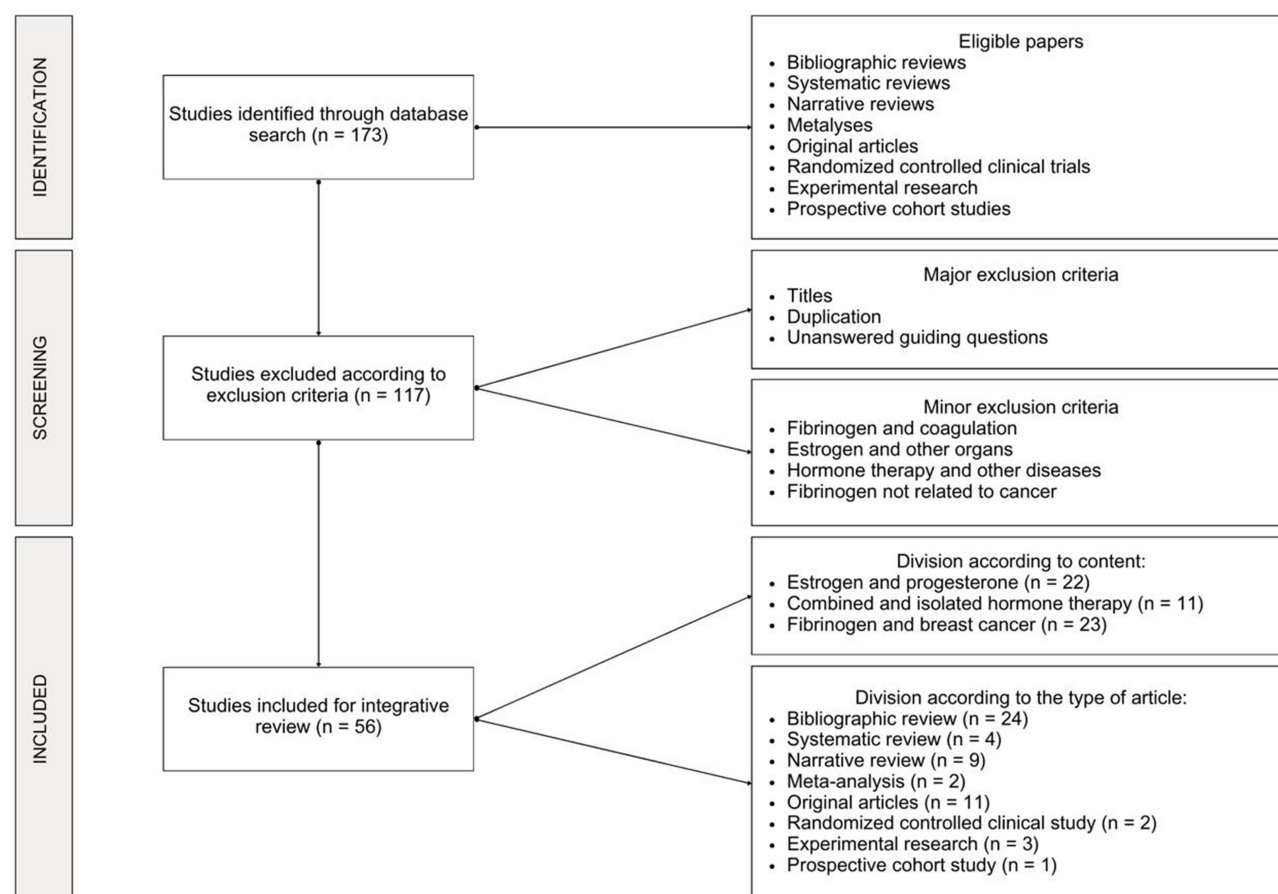


Figure 1 Flowchart of the results obtained.

Results

Initially, 173 articles were identified. After screening for relevance and suitability to the topic, 117 articles were excluded. The exclusion criteria included articles with irrelevant titles or duplicates, as well as studies focused on unrelated topics, such as the relationship between Fg and coagulation alone, the correlation between estrogen and non-reproductive organs, the relationship between HRT and other diseases, or those lacking a connection between Fg and cancer development.

The remaining studies met the inclusion criteria: type of article (randomized clinical trials, systematic reviews, meta-analyses, narrative reviews, and review articles), full-text availability, and relevance to the study topic, specifically addressing the physiology of estrogen and progesterone, analyses of hormonal therapies in postmenopausal women, and the physiology of Fg and related proteins, all evaluated using the guiding research questions as a reference.

Of the 56 articles analyzed, 22 focused on the physiology of estrogen and progesterone, 11 on the effects of combined or isolated hormone therapies, and 23 on fibrinolytic physiology and its potential relationship with breast cancer. This sample included 24 literature reviews, 4 systematic reviews, 9 narrative reviews, 2 meta-analyses, 11 original articles, 2 randomized controlled clinical trials, 3 experimental research studies, and 1 prospective cohort study.

Given the aim of synthesizing and contrasting existing theories, review articles were prioritized due to the limited availability of original studies addressing the combined roles of estrogen metabolism, hormone therapy, and Fg in breast cancer. While this approach allows a coherent theoretical synthesis, it also introduces limitations, including potential

selection bias, methodological heterogeneity among sources, and the speculative nature of the proposed associations, which require further experimental and clinical validation.

Discussion

The Relevance of Estrogen

Estrogen, produced by the ovaries, adrenal glands, and adipose tissue, regulates the female reproductive system through its receptors, promoting granulosa-cell differentiation, follicle and oocyte development, and ovulation.¹¹ Beyond these functions, estrogen is linked to pathological processes that trigger several estrogen-dependent conditions, including endometriosis, infertility, polycystic ovary syndrome, and neoplasms.^{11,12}

Estrogen biosynthesis occurs via steroidogenesis, with particularly low-density lipoprotein as its precursor. In the ovaries, cholesterol is converted into pregnenolone by P450 side-chain cleavage, then into androstenedione by cytochrome P450 17A1 and 3 β -hydroxysteroid dehydrogenase. Androstenedione is converted into testosterone or moves to granulosa cells, where it is aromatized into estrone, then converted into estradiol (E2) by 17 β -hydroxysteroid dehydrogenase. E2 is secreted by granulosa cells of the ovarian follicles and corpus luteum.^{13,14}

Estrogen cell receptors include G protein-coupled receptor and nuclear ER α /ER β , which primarily mediate estrogen's action by regulating gene expression through three mechanisms.¹⁵ The first is the classic direct binding to DNA, where estrogen binds to ER, located in the intracellular environment, and generates a change in the DNA structure allowing the binding of transcription factors. In the second, ER will bind to transcription factors that are already bound to DNA, regulating the direct expression of transcription factors. On the other hand, in the third mechanism, ERs are able to regulate estrogenic action without needing to be linked to the hormone, through the activation of growth factors without ligands using the phosphorylation process of serine residues present in the receptors themselves.¹⁶ These receptors act differently depending on the tissue and ligand, potentially working synergistically or antagonistically, with variations in their final action.^{11,17}

There is ongoing debate about estrogen's role in blood hemostasis, particularly in the coagulation cascade. Females, due to hormonal activity, experience a hypercoagulable state with faster clot formation.¹⁸ Although the exact molecular effect of estrogen on coagulation is unclear, it is known to lower factor V and anticoagulant protein levels, while increasing von Willebrand factor (vWF) and factors II, VII, VIII, X, and Fg. This rise occurs through the direct stimulation and replication of endothelial cells that have ERs. On the other hand, estrogen has been shown to be associated with increased fibrinolysis due to the decrease in the levels of fibrinolysis inhibitors. Plasminogen activator type 1 not having a sufficient effect to balance the increase in coagulation, thus resulting in a prothrombotic state.¹⁹ In addition to the increase in vWF, a study demonstrated, based on proteomic analysis, that estrogen appears to increase the formation of the β and γ chains of Fg, as it suggests a potential link to the formation of Fg and its related proteins, which may be associated with the prothrombotic state in females.^{20,21}

Progesterone and the Crosstalk Between ER and PR

Progesterone is a steroid hormone produced by the corpus luteum during the luteal phase of the menstrual cycle, and by the placenta during pregnancy.²² Progesterone exerts its function by binding to progesterone receptor (PR) A and B, responsible for activating the transcription of specific genes, which, when under the influence of estrogen, transform the endometrium from the proliferative phase to the secretory phase.^{23,24} Therefore, some progesterone functions depend on estrogen.^{24,25}

Elevated estrogen and progesterone promote breast DNA mutations through proliferative and pro-survival transcription, increasing breast cancer risk.^{17,26} Furthermore, E2 can be transformed into metabolites such as 4-OH-estradiol and 3,4-estradiol-quinone, which can bind to purine DNA bases, undergoing a process called depurination, thereby increasing the chance of making errors in DNA and consequently the development of cancer.^{17,27}

ER and PR do not act in isolation, but communicate and modulate each other, affecting the cellular response to their hormones.^{23,28} This functional interaction, called crosstalk, directly impacts gene expression and cell behavior, promoting pathologies like breast cancer.²⁹

According to Thomas and Gustafsson (2015), it is known that, in the absence of active PR, ER α activated by estrogen binds directly to DNA in chromatin regions containing estrogen-responsive elements, promoting cell proliferation.²⁹ However, when PR is activated by progesterone, it interacts with ER α , redirecting it to chromatin regions containing progesterone-responsive elements, where it acts as a coactivator of this complex.^{29,30} This mechanism indirectly inhibits ER α activity, preventing its binding to estrogen and thus leaving more estrogen unbound in circulation.^{28,29}

Hormone Replacement Therapy and Breast Cancer

Menopause, marked by 12 months of amenorrhea due to ovarian follicle loss, often causes symptoms like hot flashes, night sweats, vulvovaginal atrophy, sleep disturbances, and sexual dysfunction. HRT, the most effective treatment, is available as isolated estrogen or combined estrogen-progestogen therapy.^{31–33} The need for other drug options arose because, in the 1980s, it was found that the use of estrogen alone, which had been prescribed in excess in the previous decade, had increased the incidence of endometrial hyperplasia and cancer. Thus, in order to reduce the effects of estrogen on the endometrium, the association of these compounds with progestogen was encouraged. Therefore, women with an intact uterus or with residues of the endometrial cavity should receive combined HRT, while women who have undergone hysterectomy use HRT with estrogen alone.^{31,32}

Isolated therapy consists only of estrogen replacement therapy and is indicated for hysterectomized patients, since there is no longer a risk of developing endometrial cancer. Currently, there are a variety of synthetic estrogen-based medications, composed of drugs such as E2 and estrone, both derived from the ovaries, with ethinylestradiol being a widely known example. However, for hormone therapy, natural estrogen is the most widely used, with emphasis on conjugated estrogen and E2 in its transdermal or percutaneous forms.^{34,35}

Combined HRT associates progesterone with estrogen to counter estrogen's proliferative effects on the endometrium. Synthetic progesterone, the progestogens, are synthesized from components structurally similar to progesterone or testosterone. Among those related to progesterone, medroxyprogesterone acetate (MPA) stands out as a key derivative of 17-hydroxyprogesterone. Progestogens, despite having structural similarities and components that mimic some of the effects of progesterone, generate different effects on their receptors due to their different potencies and pharmacokinetics. In other words, their physiological effects depend not only on their properties, but also on their action on the receptor. In addition, they have varying affinities for other steroid receptors, such as glucocorticoids, mineralocorticoids and androgens.^{36,37}

There are some divergences in the literature regarding the relationship between HRT and breast cancer. In 1998, with the aim of evaluating the negative effects of HRT, such as cardiovascular diseases, cancer and osteoporosis, the randomized Women's Health Initiative study recruited postmenopausal women aged 50–79 years in 40 clinical centers in the United States of America and divided them into two large groups, women with a uterus (16,608 participants) who used therapy with conjugated equine estrogens (CEE) associated with MPA, and women without a uterus (10,739 participants) who received only conjugated equine estrogen or a placebo. In 2002, after a mean follow-up period of 5.6 years, the CEE+MPA trial was prematurely stopped due to an increased risk of breast cancer in women with an intact uterus and an unfavorable risk-benefit ratio. The study in hysterectomized women who received estrogen or placebo alone was stopped in 2004, after a mean of 7.2 years, due to increased rates of stroke. When analyzing the intervention phase, the hazard ratio for breast cancer with CEE+MPA was 1.24 (1.01–1.53), while for CEE-alone it was 0.79 (0.61–1.02). In the post-intervention and cumulative follow-up phase, the hazard ratio for breast cancer with CEE+MPA remained statistically significantly elevated, while for CEE the risk reduction became significant during cumulative follow-up. It was found that combined therapy increased the incidence of breast cancer, pointing to a determining influence of progestin on the mammary epithelium.^{38,39} Since then, new studies and trials have been conducted with the aim of elucidating the impact of HRT on breast safety, with particular emphasis on the pathogenic role of progestogen. A relevant example is the study carried out by Tian et al (2018), which investigated the effects of estrogen and progestogen administration on cell proliferation in MCF-7 breast cancer cells, which are sensitive to estrogen and dependent on it to proliferate.⁴⁰ After treating these cells with E2, progestogen, or both, it was observed that the isolated hormones promoted cell proliferation in a dose-

dependent manner, and that the combination resulted in even greater proliferation. Furthermore, the combined treatment increased the expression of cyclin G1, a negative regulator of the *TP53* tumor-suppressor gene and tumor growth promoter. In cells depleted of cyclin G1, proliferation was reduced, indicating that by depleting cyclin expression, E2 and progestogen-mediated cell proliferation was also limited. Thus, it is inferred that progestogen and estrogen have a synergistic role in promoting tumor growth in MCF-7 cells.⁴¹

The Role of Fibrinogen and Fibrinogen-Related Proteins

Fg is a heterogeneous molecule, predominantly of hepatic origin, but which can also have extrahepatic origin.^{42,43} It plays a crucial role as an inflammatory mediator, through its conversion and aggregation into fibrin. Under certain conditions, it can even influence leukocyte functions. However, knowledge about all the possible actions of Fg in the organism is still limited.^{43–45}

The Fg molecule is composed of three interconnected genes (FGA, FGB and FGG), which encode the three polypeptide chains that form Fg: the α , β and γ chains. These chains are connected by disulfide bonds and associated with a central node that contains the N-terminus. In the structure of the molecule, the β and γ chains form a globular domain, which is recognized as a similarity factor in other proteins, known as the Fg-like globular domain. These proteins are grouped into the family of FREPs.^{42,43,46,47}

Fg assembly occurs in the endoplasmic reticulum. The translation of its three genes results in the formation of half-molecules, each composed of three chains: α , β , and γ . Two half-molecules then join at the N-termini to form a hexamer.⁴⁸ The chains that make up Fg may eventually remain free if not used in the assembly. In human HCC cells, the presence of free α , β and γ chains has been observed, which can be degraded or remain free.⁴⁹ Furthermore, knowledge about the extrahepatic pathways in Fg synthesis is still limited. However, Fg synthesis and accumulation have been observed in breast cancer tumor cells, with high concentrations of Fg intermediate complexes and polypeptides from the α , β , and γ chains.⁵⁰

Among the FREPs, the most prominent are fibrinogen-like protein 1 (FGL1 or hepassokin) and fibrinogen-like protein 2 (FGL2 or fibroleukin). FGL1, also known as hepatocyte-derived fibrinogen-like protein 1, was initially cloned from human HCC.^{42,47} Current literature on the metabolic origin of these compounds is limited, but it is believed that their synthesis is supported by the accumulation of fibrinogen-forming subunits.

FGL1 has a carboxyl-terminal domain related to Fg, containing the β and γ subunits. However, this domain does not include platelet-binding sites, cross-linking regions or the thrombin-sensitive site, nor the coil-coil domain, unlike Fg. Originating from the liver, FGL1 is secreted in high amounts in response to hyperglycemia, hyperlipidemia and hormonal stimuli, playing roles in metabolism and liver regeneration. In addition, it can act in muscle and adipose tissues, mediating inflammatory processes and establishing connections between the liver and other tissues. However, FGL1 is frequently overexpressed in certain tumors, such as breast tumors.^{42,51,52}

It is important to note that FGL1 production does not originate only from the liver. It has been observed that increased interleukin-6 expression, generally associated with inflammatory conditions, also contributes to the induction of FGL1 expression, suggesting that FGL1 is involved in acute responses of the organism.⁵²

Additionally, FGL1, in its Fg-related domain, is one of the main proteins that promotes functional binding to the lymphocyte-activation gene 3 (LAG-3), an immune checkpoint, inhibiting the activation of specific T cells. The interaction between FGL1 and LAG-3 is highly specific.⁵³

LAG-3 is expressed on the surface of T lymphocytes and negatively regulates CD8⁺ and CD4⁺ T cells, mediating their interaction with the major histocompatibility complex class II (MHC-II), galectin-3, liver sinusoidal endothelial cell lectin, and FGL1. LAG-3 is also constitutively expressed on a subset of regulatory T cells, contributing to their suppressive function. The interaction of FGL1 with LAG-3 establishes an immune checkpoint pathway, resulting in the reduction of T cells and allowing the study of how tumor cells evade immune surveillance. Currently, monoclonal antibodies that block the interaction between LAG-3 and its canonical ligand, MHC-II, are being evaluated in clinical trials to determine their antitumor efficacy.^{47,51,53,54}

Current evidence suggests that the normal function of FGL1 may be altered by solid tumors, which could upregulate its expression to potentially suppress the antitumor immune response. In these cases, FGL1 has been proposed to

facilitate immune evasion by interacting with LAG-3 on tumor-infiltrating T cells. Studies in mice show that blocking the FGL1/LAG-3 interaction activates the T cell immune response in the tumor microenvironment, with minimal impact on systemic immunosuppression, indicating that FGL1 plays a crucial role in tumor immunosuppression. Although this mechanism remains to be confirmed in large-scale studies.^{47,53}

Therefore, experimental research indicates that inhibition of the FGL1/LAG-3 interaction can stimulate T cells and restore the immune response against tumors by promoting the T cell receptor–CD28 signaling pathway. Reducing FGL1 expression accelerates the immune response of CD8+ and CD4+ T cells against tumor growth and, in addition, FGL1 can increase the efficacy of anti-LAG-3 immunotherapy when mediated by oxysophocarpine.⁴²

FGL2, predominantly expressed by cells of the immune system, such as T cells, macrophages, and natural killer cells, can be found in two forms: membrane-associated FGL2 and soluble FGL2, with 36% homology to the β and γ chains of Fg. The membrane-associated form is involved in coagulation while the soluble one is predominantly expressed by regulatory T cells and can suppress their functions.^{49,55}

FGL2 has been shown to be involved in tumor growth, being overexpressed in CD57+, CD68+, CD8+ T cells and vascular endothelial cells, promoting breast cancer progression, facilitating tumor angiogenesis or inducing epithelial-mesenchymal transition.^{56,57} Specifically, soluble FGL2 can suppress the proliferation of alloreactive T cells and the maturation of bone-marrow dendritic cells, with functions distinct from membrane-associated FGL2, which is more associated with prothrombotic activities.^{42,58–60}

Furthermore, a study conducted in a gene expression system in mouse glioma cells identified that FGL2 plays a crucial role in tumor-mediated immune suppression in GBM multiforme, regulating the expression of immune checkpoints and contributing to the alteration of the tumor microenvironment.⁶¹

New Perspectives on the Origin of Breast Cancer

Currently, there is still great debate and conflicting opinions regarding the safety, efficacy and appropriate use of hormone replacement therapies. It is of utmost importance to highlight the Women's Health Initiative study, which, when analyzing the biological response of women undergoing combined HRT, revealed a higher incidence of breast cancer in this population, compared to women using estrogen alone. This publication, which has received harsh criticism regarding its outcomes, challenged the previously accepted notion that estrogen would be the sole and major factor responsible for the development of breast cancer, raising important discussions about the role of progesterone in this process.^{38,39} Furthermore, the trial by Tian et al (2018) confirmed a synergistic effect of estrogen and progesterone in the proliferation of MCF-7 breast cancer cells, suggesting that both hormones act in concert.⁴¹ Hormone-receptor interaction is a key mediator of this process, as activation of ERs leads to their binding to estrogen-responsive elements in DNA, regulating gene transcription. This has been proposed as one of several mechanisms contributing to proliferative signaling.²⁹

According to the current theory, it is believed that progesterone, when binding to its receptor, indirectly inhibits ERs, resulting in lower proliferative activity of this hormone, and consequently, lower risk of cancer.^{29,30} However, this premise conflicts with the results observed in the studies. That said, the question arises: why do women on combined HRT have a higher incidence of breast cancer if progesterone should, according to the original hypothesis, deactivate ERs, reducing the proliferative action of estrogen and therefore, decreasing the risk of tumor development?

Thus, this work seeks to add a new theory according to which, even in the absence of estrogen bound to its receptor, this hormone free in the body might still potentially stimulate cell growth and could contribute to breast tumor development. The importance of several compounds is also highlighted, particularly Fg and its related proteins, which may play a crucial role in understanding breast cancer, as evidenced by articles that address the physiology of estrogen and its action in the body. Yet, the proposed estrogen–FREPs–immune evasion axis should be interpreted as an emerging model rather than an established pathway.

It is known that, in the absence of binding to its receptors, estrogen remains available for metabolism, producing remnants of the β and γ subunits, components of the Fg structure.²⁰ An increase in these subunits could lead to a greater Fg production and, consequently, elevated levels of FREPs. This state of hyperfibrinogenemia has been suggested to play

a role in tumor progression by creating a microenvironment favorable to tumor cell proliferation and by potentially protecting them from the immune system response. Furthermore, literature indicates that estrogen metabolism generates several products. Evidence suggests that oral administration of estrogen, through first-pass hepatic metabolism, induces changes in procoagulant factors and antithrombotic mechanisms, thereby increasing the fibrinolytic potential in post-menopausal women. Therefore, the interaction between estrogen, its metabolism, and FREPs appears biologically relevant for breast cancer progression, although its capacity to drive cancer development in patients has not been conclusively demonstrated.^{20,62}

Aiming to better clarify this interaction, a study conducted by Rybarczyk and Simpson-Haidaris (2000) showed that Fg in breast carcinoma stroma is not solely from plasma exudation but is endogenously synthesized by tumor cells. Using MCF-7 cells, they found these cells produce and secrete Fg polypeptides, mainly the intact γ chain and degraded A α and B β chains. The absence of the intact B β chain prevents complete Fg formation, causing secreted Fg to associate with the cell surface instead of forming mature extracellular matrix fibrils. This supports the idea that tumor-derived Fg and its degradation products may influence cancer progression by adding adhesion sites and modulating tumor–extracellular matrix interactions.⁵⁰

From an immunological perspective, checkpoints on the surface of immune cells, including T lymphocytes and tumor cells, function as switches that generate signals to regulate T cell overactivation. In cancer, T cell dysfunction occurs due to continuous exposure to antigens, which is associated with the overexpression of multiple inhibitory receptors, decreasing both the proliferation capacity and functionality of the lymphocytes and facilitating tumor evasion.⁶³

In this context, FREPs have been proposed as potential mediators of immune escape. Among them, FGL1, has emerged as a candidate of interest, since it exerts an inhibitory function in the antitumor immune response. Its specific interaction with LAG-3, present on the surface of T lymphocytes, might negatively regulate CD8⁺ and CD4⁺ T cells, resulting in lower lymphocyte activity. Thus, therapies blocking the FGL1/LAG-3 interaction or using anti-FGL1 show potential in restoring the antitumor immune response and combating early cancer proliferation.⁵⁴ Additionally, FGL2, predominantly expressed in cells of the immune system, such as T cells, macrophages and natural killer cells, have been implicated in inhibiting lymphocyte activity, regulating the expression of immune checkpoints and altering the tumor microenvironment, promoting, for example, tumor neovascularization.^{49,61}

On the other hand, in most cancers, tissue factor, which converts prothrombin into thrombin, can promote tumor growth, cell migration and angiogenesis, through the activation of protease-activated receptor 2. Thrombin, in turn, favors tumor growth, angiogenesis, and metastasis by acting on protease-activated receptor 1 and generating fibrin, which could enhance Fg degradation and consequently a greater amount of FREPs, thereby protecting tumor cells from immune surveillance.⁶⁴

Based on the theories presented, a hypothetical link can be drawn between FREPs, immune regulation, and tumor progression, as showed in Figure 2. In this context, it becomes necessary to reconsider the possible interplay between estrogen signaling and breast cancer pathogenesis. Nevertheless, this association remains speculative, and further large-scale studies are required to clarify whether modulating this pathway could ultimately allow the safe use of hormonal therapies, without depriving patients of treatments that improve quality of life and well-being.

Created with BioRender. 1. Effect of combined hormone therapy on estrogen receptor α (ER α) inhibition, hepatocyte metabolism, and subsequent regulation of fibrinogen subunits (β and γ) and fibrinogen-related proteins (FGL1 and FGL2); 2. Breast cancer cells (MCF-7) secrete fibrinogen-subunits, which, together with plasma-derived fibrinogen (Fg), may interact with the tumor stroma; 3. Proposed role of Fg, FGL1 and FGL2, in the tumor microenvironment (TME). These proteins may modulate the extracellular matrix, increasing adhesion, and contribute to immune evasion through the FGL1/LAG-3 interaction, which suppresses lymphocyte activity. Together, these mechanisms are suggested to promote tumor growth and proliferation.

Estrogen & FREPs in Breast Cancer Progression: A New Hypothesis

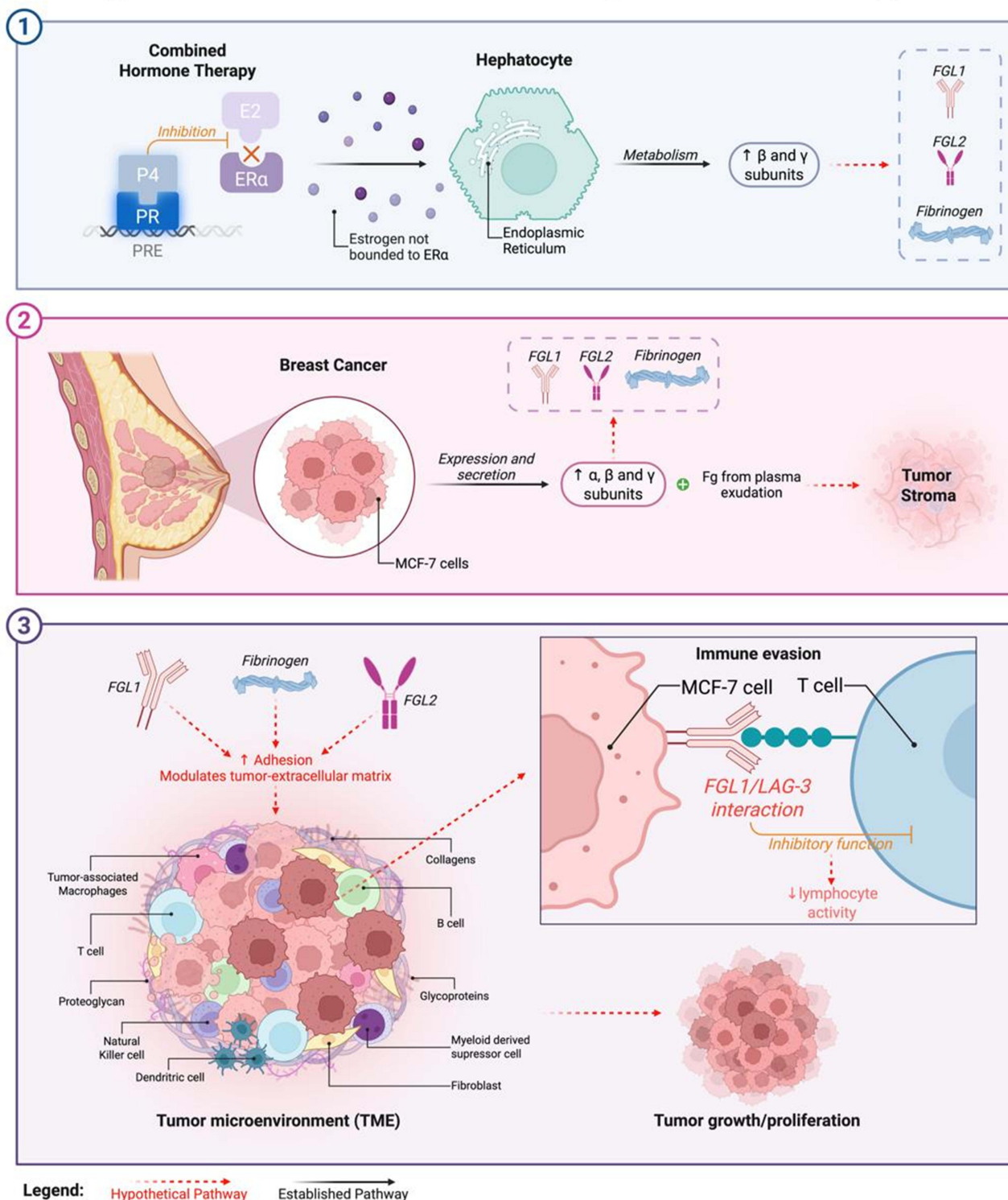


Figure 2 Estrogen & FREPs in Breast Cancer Progression: A New Hypothesis.

Conclusion

Fibrinogenic activity is associated with cancer progression, but its role in the early stages of breast cancer remains underexplored. This review highlights free estrogen metabolism and its byproducts, particularly FREPs such as FGL1

and FGL2, as potential contributors to immune evasion and tumor initiation. We propose this link as a core hypothesis in breast cancer pathogenesis. Future large-scale in vivo studies are essential to validate this mechanism, which may open new perspectives for understanding disease genesis and developing innovative preventive and therapeutic strategies.

Abbreviations

BRCA1, Breast Cancer Gene 1; BRCA2, Breast Cancer Gene 2; CEE, Conjugated Equine Estrogens; E2, Estradiol; ER, Estrogen Receptor; ER α , Estrogen Receptor Alpha; ER β , Estrogen Receptor Beta; FGL1, Fibrinogen-like Protein 1; FGL2, Fibrinogen-like Protein 2; Fg, Fibrinogen; FREPs, Fibrinogen-Related Proteins; GBM, Glioblastoma Multiforme; HCC, Hepatocellular Carcinoma; HER2/neu, Human Epidermal; GFR2, Growth Factor Receptor-type 2; HRT, Hormone Replacement Therapy; LAG-3, Lymphocyte Activation Gene 3; MHC II, Major Histocompatibility Complex II; MPA, Medroxyprogesterone Acetate; PR, Progesterone Receptor; vWF, Von Willebrand Factors.

Acknowledgments

We would like to express our sincere appreciation to Positivo University for providing us with an inspiring learning environment, valuable knowledge, and academic support that made this work possible. The university's commitment to academic excellence, state-of-the-art facilities, and support from faculty and staff played a fundamental role in the successful completion of this study. We are deeply grateful for the opportunities and support that Positivo University has provided throughout our academic journey.

Disclosure

The authors report no conflicts of interest in this work.

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