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Microbial Metabolites as Potential Modulators of Tumor Microenvironment in Breast Cancer

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Abstract **Review Article**

The tumor microenvironment (TME) plays a pivotal role in the initiation, progression, and metastasis of breast cancer. Recent advances in microbiome research have unveiled the intricate interactions between microbial communities and host physiology, suggesting that microbial-derived metabolites can significantly influence cancer biology. These small molecules, including short-chain fatty acids (SCFAs), secondary bile acids, polyamines, and tryptophan-derived indoles, serve as biochemical messengers that modulate inflammation, immune responses, angiogenesis, and epithelial-mesenchymal transition (EMT) within the TME. Accumulating evidence indicates that specific microbial signatures are associated with distinct breast cancer subtypes, and their metabolic outputs may either promote or suppress tumorigenesis.

Keywords: Microbial Metabolites, Tumor Microenvironment, Breast Cancer, Immune Modulation, Cancer Immunotherapy.

1. INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer among women worldwide and a leading cause of cancer-related mortality [1]. While considerable advancements have been made in early detection, targeted therapy, and personalized medicine, the complexity of the tumor microenvironment (TME) continues to present significant challenges in effective treatment and long-term remission. The TME is not merely a passive backdrop for tumor growth but an active participant composed of immune cells, fibroblasts, endothelial cells, extracellular matrix components, and various soluble factors, all of which interact intricately with cancer cells to influence disease progression [2]. In recent years, attention has turned toward the human microbiome—a dynamic and diverse community of microorganisms that inhabit various niches of the human body—as a critical regulator of health and disease, including cancer [3]. Beyond the gastrointestinal tract, microbiota have been detected in breast tissue, suggesting a localized microbial influence in breast carcinogenesis [4]. Importantly, microbial metabolites—bioactive small molecules produced as a result of microbial metabolism—have emerged as key mediators of host-microbiota communication and are increasingly recognized for their capacity to modulate the TME [5]. These metabolites can impact several hallmarks of cancer, including immune evasion, angiogenesis, metabolic reprogramming, and epigenetic regulation [6]. Depending on the context, they may exert either pro-tumorigenic or anti-tumorigenic effects, thereby shaping the course of cancer development and response to therapy. For instance, short-chain fatty acids (SCFAs) such as butyrate have been shown to induce anti-inflammatory and anti-proliferative effects, whereas secondary bile acids and polyamines may promote tumorigenesis by enhancing DNA damage, oxidative stress, and chronic inflammation [7]. Given the growing recognition of microbial metabolites as functional components in the tumor ecosystem, understanding their mechanisms of action within the breast TME holds substantial promise for novel therapeutic strategies. This

review aims to provide a comprehensive overview of the types of microbial metabolites involved in breast cancer, their modulatory roles in the TME, and the potential clinical applications of microbiome-based interventions.

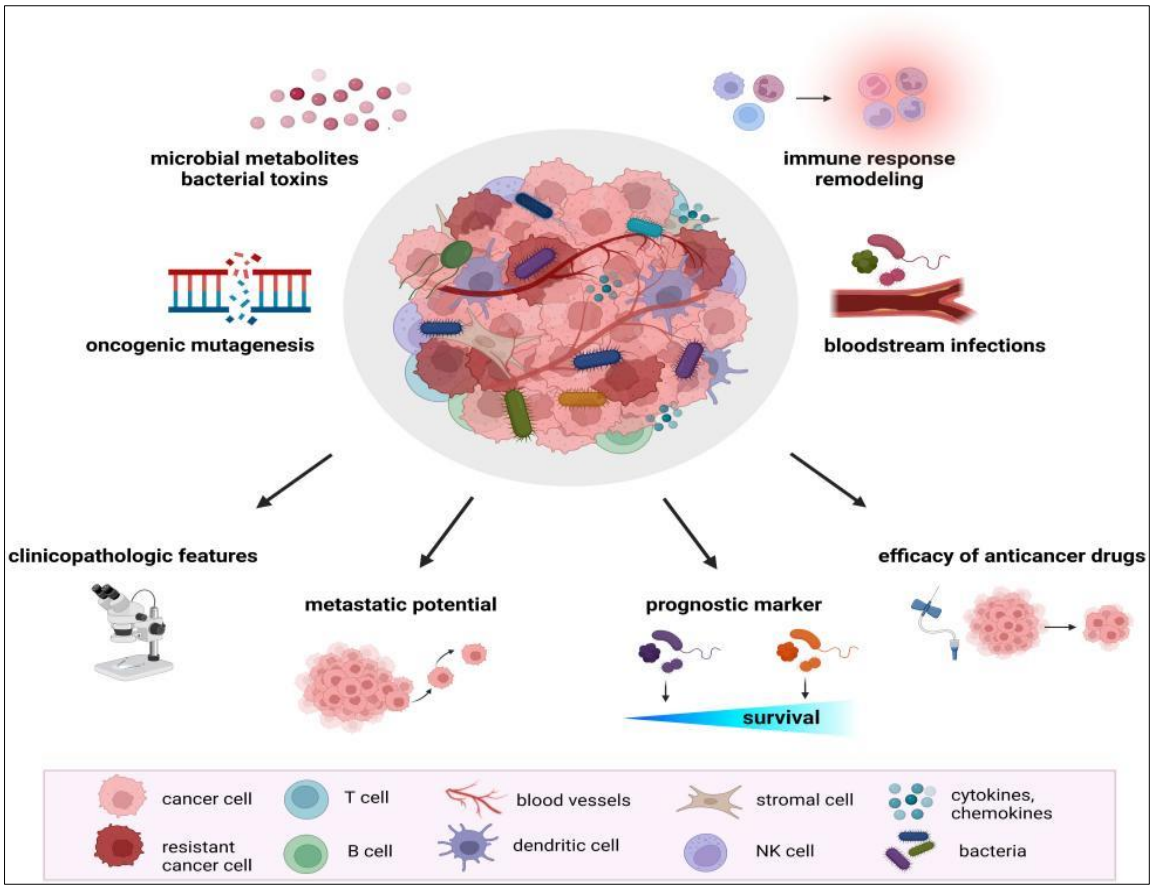

Fig. 1: The role of tumor microbiome in cancer development and treatment [7]

2. Breast Cancer and the Tumor Micro-Environment (TME)

2.1 Components of the TME

The tumor microenvironment (TME) is a highly dynamic and heterogeneous ecosystem composed of various cellular and acellular components that coexist and coevolve with cancer cells. In breast cancer, the TME includes immune cells (e.g., T lymphocytes, macrophages, dendritic cells, natural killer cells), cancer-associated fibroblasts (CAFs), endothelial cells, adipocytes, pericytes, and the extracellular matrix (ECM) [8]. These elements are not merely bystanders but active players that influence tumorigenesis through paracrine signaling, metabolic interactions, and immunomodulation. Immune cells within the TME often adopt immunosuppressive phenotypes. For instance, tumor-associated macrophages (TAMs), particularly the M2-like subtype, promote angiogenesis, tissue remodeling, and metastasis [9]. Similarly, regulatory T cells (Tregs) suppress anti-tumor immune responses, facilitating immune evasion by cancer cells [10]. Cancer-associated fibroblasts secrete cytokines, chemokines, and ECM-modifying enzymes that support tumor cell proliferation and invasion [11].

2.2 TME Dynamics in Breast Cancer

In breast cancer, the TME is particularly complex due to the hormonal sensitivity of breast tissue and its exposure to systemic and local metabolic signals. The interactions between estrogen signaling, immune infiltration, and stromal remodeling further complicate the TME landscape [12]. Notably, different subtypes of breast cancer—such as hormone receptor-positive (HR+), HER2-enriched, and triple-negative breast cancer (TNBC)—exhibit distinct TME profiles, which influence their response to immunotherapy and chemotherapy [13]. Triple-negative breast cancers, for example, often have a more immunologically "cold" TME characterized by reduced T-cell infiltration and high levels of immunosuppressive cells, making them less responsive to immune checkpoint inhibitors [14]. On the other hand, HER2-enriched tumors may show higher immune cell infiltration but are also accompanied by a pro-inflammatory milieu that can foster resistance mechanisms. Understanding the crosstalk between breast cancer cells and the surrounding microenvironment is essential for identifying new therapeutic targets. Emerging evidence suggests that microbial-derived metabolites may represent an additional layer of regulation within the TME, influencing everything from immune surveillance to metastatic potential.

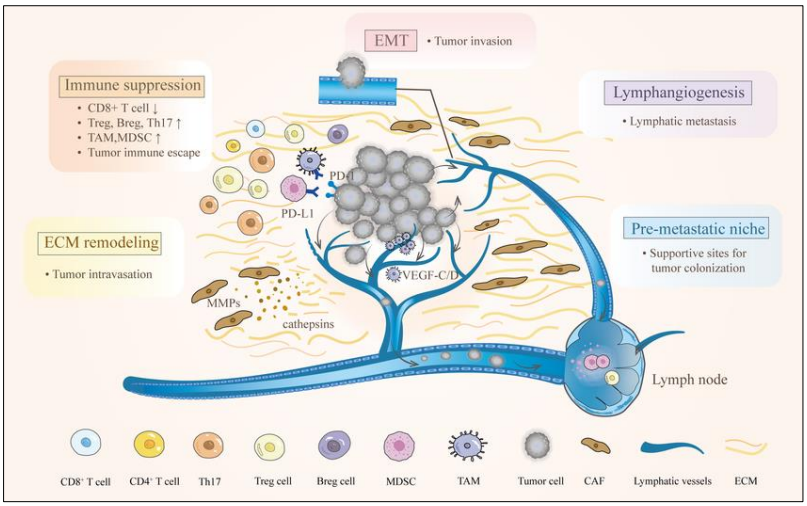

Fig. 2: TME Dynamics in Breast Cancer [15]

3. The Human Microbiome and Its Role in Cancer

3.1 Microbiota-Host Crosstalk

The human microbiome encompasses trillions of microorganisms, including bacteria, viruses, fungi, and archaea, residing on mucosal surfaces and within various body compartments. While traditionally associated with the gastrointestinal (GI) tract, recent studies have revealed the presence of microbiota in sterile tissues, including the breast [16]. These microbial communities engage in continuous crosstalk with host cells, influencing immunity, metabolism, and epithelial integrity through the secretion of metabolites, enzymes, and signaling molecules [17].

Microbial-host interactions occur via both direct contact with host tissues and the systemic distribution of microbial metabolites and components such as lipopolysaccharides (LPS), peptidoglycans, and extracellular vesicles [18]. These signals can influence gene expression, immune activation, and inflammatory responses. Importantly, microbial metabolites can function as ligands for host receptors, including G-protein coupled receptors (GPCRs), Toll-like receptors (TLRs), and nuclear receptors such as the aryl hydrocarbon receptor (AhR) and peroxisome proliferator-activated receptors (PPARs) [19].

In the context of cancer, this crosstalk can have dichotomous effects: while some microbial metabolites enhance immune surveillance and inhibit tumor progression, others may promote chronic inflammation, immune suppression, and genetic instability, thereby contributing to carcinogenesis.

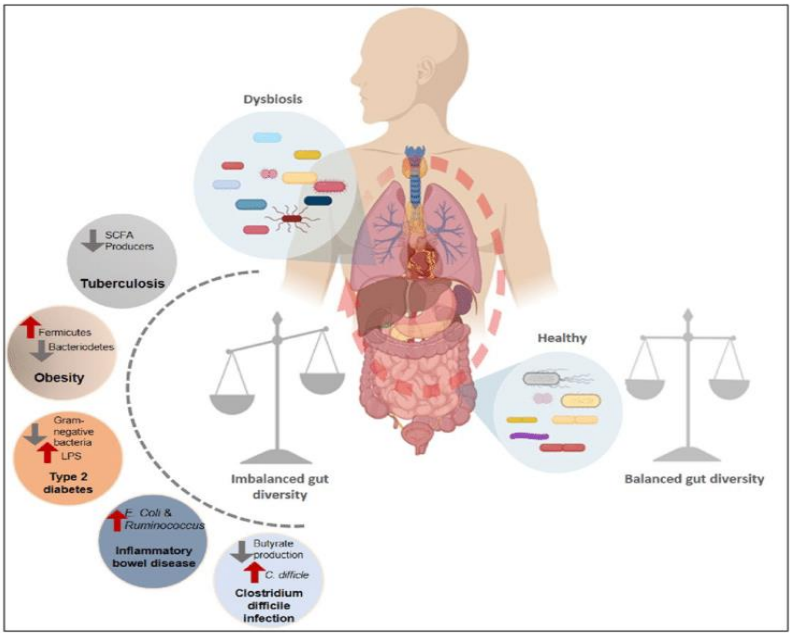

Fig. 3: A schematic illustration the cross talk between human microbiome and diseases. Shown in left demonstrates significant alterations of the gut bacterial diversity in various diseases [20]

3.2 Microbiome Signatures in Breast Cancer

Emerging evidence suggests that breast tissue harbors a distinct microbiome that differs between healthy individuals and breast cancer patients [21]. In breast tumors, alterations in microbial diversity and composition—termed dysbiosis—have been observed. Studies have identified increased abundance of certain bacterial taxa such as *Escherichia coli*, *Staphylococcus epidermidis*, and *Methylobacterium radiotolerans* in breast cancer tissues, while beneficial commensals like *Lactobacillus* and *Bifidobacterium* are often depleted [22].

These microbial shifts may affect the local TME via multiple mechanisms:

Induction of DNA damage: Some pathogenic bacteria produce genotoxins such as colibactin and cytolethal distending toxin (CDT), which can cause DNA strand breaks in host cells [23].

Modulation of immune responses: Dysbiotic microbiota can skew immune profiles toward immunosuppressive or pro-inflammatory states, promoting tumor progression [24].

Production of pro-tumorigenic metabolites: An altered microbiome may produce increased levels of carcinogenic bile acids, polyamines, and reactive oxygen species (ROS) [25].

Notably, differences in microbiome composition are also observed between various breast cancer subtypes, and between racial and geographic populations, suggesting the potential of microbiota as both diagnostic biomarkers and therapeutic targets.

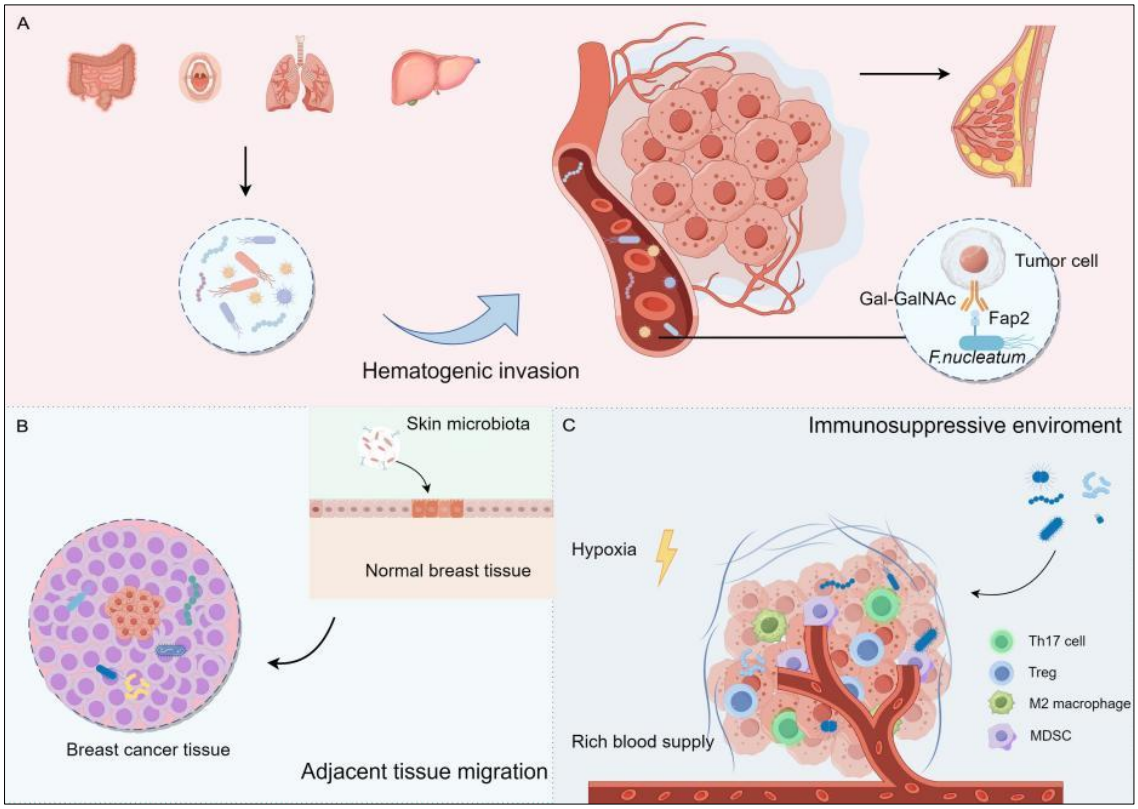

Fig 4: Interactions between the tumor microbiota and breast cancer [26]

4. Microbial Metabolites: Classification and Functions

Microbial metabolites are bioactive small molecules produced during microbial metabolism that serve as crucial mediators of host-microbe interactions. They can circulate systemically, accumulate in tissues, and influence various biological processes such as immunity, metabolism, and cell proliferation. In the context of breast cancer, these metabolites can profoundly modulate the tumor microenvironment (TME), either promoting or inhibiting tumor progression [27].

4.1 Short-Chain Fatty Acids (SCFAs)

SCFAs, primarily acetate, propionate, and butyrate, are produced by gut microbiota through the fermentation of dietary fibers. These molecules serve as energy sources for colonocytes and also act as signaling molecules that influence immune function, gene expression, and epigenetic modifications [28].

Butyrate, in particular, is a histone deacetylase (HDAC) inhibitor, which allows it to modulate gene transcription and induce cell cycle arrest or apoptosis in cancer cells [29]. SCFAs also bind to G-protein coupled receptors (GPCRs) such as GPR41 and GPR43, affecting immune cell recruitment and differentiation [30]. In

breast cancer models, butyrate has demonstrated anti-proliferative effects and may reverse epithelial-to-mesenchymal transition (EMT) [31].

4.2 Secondary Bile Acids

Secondary bile acids are produced by gut bacteria from primary bile acids secreted by the liver. Deoxycholic acid (DCA) and lithocholic acid (LCA) are the most studied secondary bile acids with established roles in cancer development [32]. DCA induces DNA damage, oxidative stress, and inflammation, all of which contribute to carcinogenesis [33]. These bile acids can activate signaling pathways such as NF-κB and MAPK, promoting tumor growth and survival [34]. Elevated levels of DCA have been detected in breast cancer patients and are associated with poor prognosis [35].

4.3 Tryptophan Metabolites

Tryptophan is an essential amino acid metabolized via multiple pathways by both host and microbial enzymes. Microbial metabolism yields several indole derivatives, including indole-3-acetic acid (IAA), indole-3-aldehyde, and tryptamine [36].

These indoles activate the aryl hydrocarbon receptor (AhR), which can modulate immune tolerance, inflammation, and barrier integrity [37].

Activation of AhR in the TME may either suppress or enhance tumor immunity depending on context and ligand specificity [38].

Dysregulation of tryptophan metabolism is increasingly recognized in aggressive breast cancer subtypes [39].

4.4 Polyamines

Polyamines such as putrescine, spermidine, and spermine are polycationic molecules involved in cellular proliferation, differentiation, and apoptosis. Microbial-derived polyamines contribute to local and systemic polyamine pools [40]. Elevated polyamine levels are associated with tumor progression and immune suppression in breast cancer [41]. They support tumor growth by stabilizing DNA structure, enhancing protein synthesis, and modulating ion channels [42]. Inhibiting polyamine synthesis or uptake has shown promise in preclinical cancer models [43].

4.5 Other Notable Metabolites

Lipopolysaccharides (LPS): Components of gram-negative bacterial membranes that activate TLR4 signaling and trigger pro-inflammatory responses in the TME [44].

Peptidoglycans and Muramyl Dipeptides: Modulate innate immunity via NOD receptors, potentially influencing anti-tumor immunity [45].

Extracellular Vesicles (EVs): Bacteria-derived EVs carry nucleic acids, proteins, and metabolites that can reprogram host cells and contribute to cancer progression [46].

5. Microbial Metabolites and Their Impact on the Breast Tumor Microenvironment

The tumor microenvironment (TME) is a dynamic ecosystem consisting of cancer cells, immune cells, stromal cells, blood vessels, extracellular matrix, and signaling molecules. In breast cancer, the TME not only supports tumor progression and metastasis but also determines the response to therapies [47]. Microbial metabolites can modulate various components of the TME through immunological, metabolic, and signaling pathways, thereby influencing cancer development, progression, and resistance to treatment.

5.1 Modulation of Immune Cell Functions

One of the most critical roles of microbial metabolites is their ability to shape immune responses in the TME. These metabolites influence the recruitment, differentiation, and effector functions of various immune cells:

SCFAs (e.g., butyrate and propionate) can promote the differentiation of regulatory T cells (Tregs) via epigenetic regulation and enhance the anti-inflammatory response, thereby dampening cytotoxic immunity in the TME [48]. However, they also induce apoptosis in certain breast cancer cells, highlighting context-dependent effects [49].

Tryptophan metabolites acting through AhR can suppress dendritic cell activation and induce Tregs, creating an immunosuppressive niche favorable for tumor growth [50].

Polyamines, at high levels in the TME, suppress T-cell activation, inhibit NK cell function, and reduce antigen presentation by dendritic cells, thereby impairing anti-tumor immunity [51].

5.2 Induction of Inflammation and Oxidative Stress

Chronic inflammation and oxidative stress are hallmarks of tumor-promoting environments, and microbial metabolites are key mediators of these processes:

Secondary bile acids, such as DCA, promote ROS generation and activate inflammatory pathways such as NF-κB and STAT3, contributing to DNA damage, cellular transformation, and tumor promotion [52].

LPS, derived from gram-negative bacteria, activates TLR4 on immune and epithelial cells, leading to the secretion of pro-inflammatory cytokines (e.g., IL-6, TNF-α), which further remodel the TME in favor of tumor progression [53]. Such inflammation-associated shifts can also enhance angiogenesis, epithelial-mesenchymal transition (EMT), and metastasis in breast cancer [54].

5.3 Epigenetic Reprogramming

Epigenetic modifications, such as histone acetylation, methylation, and DNA methylation, are central to tumor progression and therapy resistance. Several microbial metabolites act as epigenetic modulators:

Butyrate, by inhibiting HDACs, increases histone acetylation, leading to the reactivation of tumor suppressor genes and the suppression of oncogenes in breast cancer cells.

Indole derivatives, through AhR activation, modulate histone methyltransferases and chromatin remodelers, influencing gene expression patterns in tumor and immune cells.

Polyamines can alter chromatin structure and enhance DNA methylation, often leading to transcriptional silencing of tumor suppressor genes.

5.4 Angiogenesis and Metastasis

The ability of microbial metabolites to promote angiogenesis and metastasis significantly affects breast cancer progression and patient outcomes:

LPS and secondary bile acids upregulate VEGF and other angiogenic factors via TLR and GPCR-mediated signaling pathways, facilitating neovascularization required for tumor growth.

Polyamines support EMT by modulating the expression of transcription factors such as Snail and Twist, promoting a migratory and invasive phenotype in breast cancer cells.

Tryptophan metabolites have also been shown to increase vascular permeability and endothelial cell migration via AhR-dependent mechanisms.

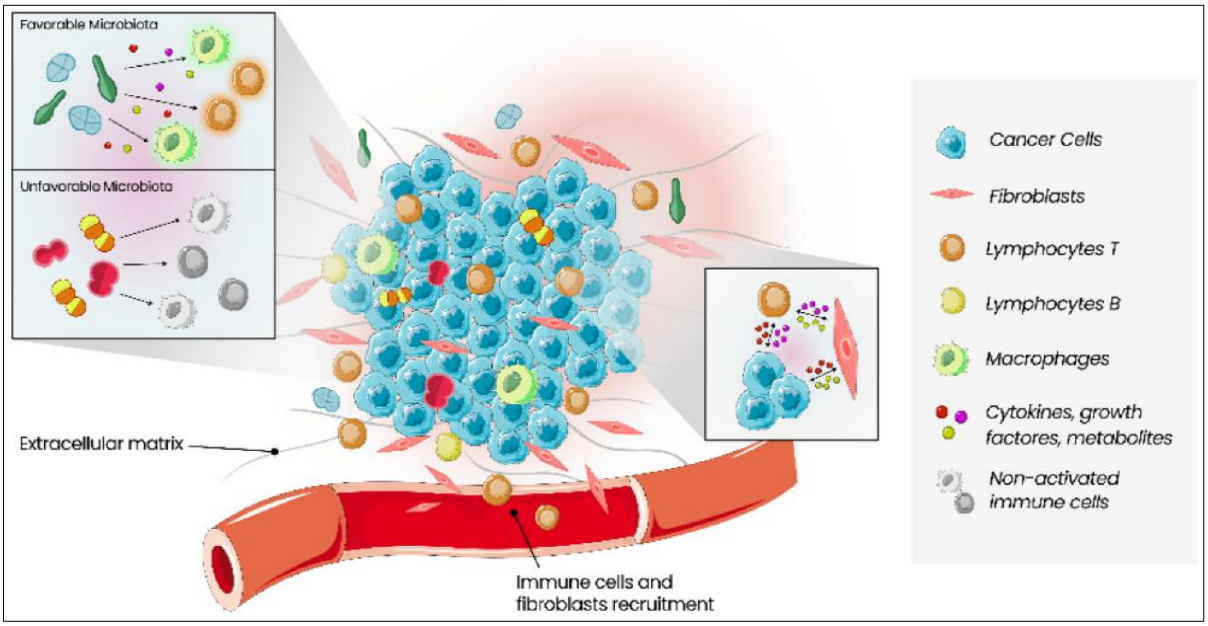

Fig. 5: Schematic of the main constituents of the tumour microenvironment

6. Therapeutic Implications: Targeting Microbial Metabolites in Breast Cancer

Understanding the role of microbial metabolites in modulating the breast tumor microenvironment (TME) offers promising therapeutic avenues. These bioactive compounds can be targeted or harnessed through various strategies, including microbial modulation, metabolite supplementation, and inhibition of specific metabolic pathways. As precision medicine advances, tailoring such interventions could improve treatment efficacy, reduce toxicity, and overcome resistance to conventional therapies.

6.1 Modulation of Gut Microbiota Composition

Altering the gut microbiome through diet, probiotics, prebiotics, and fecal microbiota transplantation (FMT) is a key strategy to influence metabolite profiles:

Probiotics, such as *Lactobacillus* and *Bifidobacterium* strains, can enhance the production of beneficial SCFAs like butyrate and suppress harmful metabolite-producing bacteria [55].

Prebiotics, including inulin and resistant starches, selectively promote beneficial bacteria that generate anti-cancer metabolites [56].

FMT, though still under investigation in oncology, has shown promise in restoring microbiome diversity and increasing responsiveness to immune checkpoint inhibitors (ICIs) [57].

6.2 Metabolite Supplementation or Inhibition

Direct manipulation of metabolite levels offers a more targeted therapeutic approach:

SCFA supplementation, particularly butyrate, has shown anti-tumor activity in preclinical breast cancer models by inducing apoptosis and epigenetic reprogramming [58].

Tryptophan metabolism inhibitors, such as IDO1 inhibitors, are being explored to block immunosuppressive pathways activated by kynurenine and other downstream metabolites [59]. Clinical trials are ongoing to evaluate their synergistic potential with immunotherapies.

Polyamine depletion therapies using agents like difluoromethylornithine (DFMO) can suppress tumor growth and enhance immune surveillance in breast cancer [60].

6.3 Targeting Receptor Pathways

Because microbial metabolites often signal through specific receptors, targeting these pathways can modulate their effects:

AhR antagonists can block immunosuppressive signaling mediated by tryptophan-derived indoles, thereby restoring effective anti-tumor immunity.

TLR4 inhibitors can mitigate the pro-inflammatory and pro-angiogenic effects induced by LPS, offering another strategy to restrain tumor progression.

GPCR modulation (e.g., GPR43, GPR109A) through synthetic ligands may replicate the beneficial effects of SCFAs in the TME.

6.4 Combination Therapies with Conventional and Immune Therapies

Harnessing microbial metabolites can sensitize tumors to conventional therapies and immune-based treatments:

Microbial modulation may improve the efficacy of **chemotherapy and radiotherapy** by reshaping the TME to support immune activation and reduce resistance mechanisms.

Certain **microbial metabolite signatures** are being investigated as **biomarkers** for predicting response to ICIs and other immunotherapies.

Butyrate and **polyamine modulators** are being tested in combination with checkpoint inhibitors and anti-angiogenic agents for synergistic effects in resistant breast tumors.

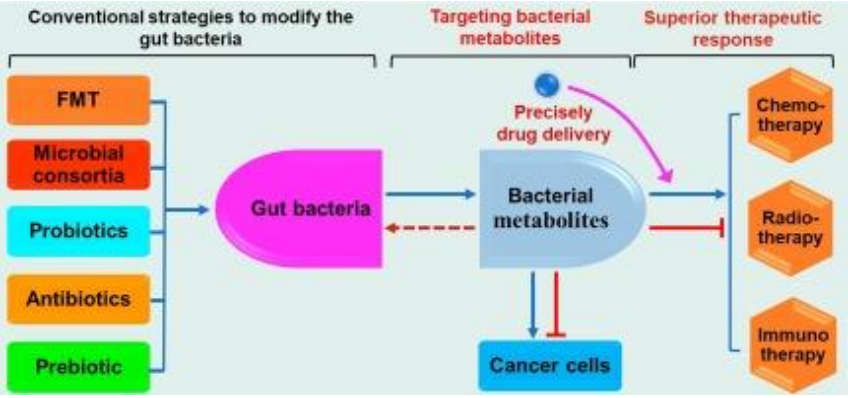

Fig. 6: Targeting bacterial metabolites in tumor for cancer therapy: An alternative approach for targeting tumor-associated bacteria

7. Challenges and Future Perspectives

Despite the promising role of microbial metabolites in modulating the breast tumor microenvironment (TME), several challenges limit their clinical translation. Understanding and addressing these hurdles will be essential for leveraging the full therapeutic potential of these microbial-derived compounds.

7.1 Complexity of Host-Microbiome Interactions

The dynamic interaction between the host, microbiota, and the tumor ecosystem is highly individualized and influenced by multiple factors such as genetics, diet, environment, medication, and disease state. This complexity makes it difficult to pinpoint specific microbial signatures or metabolites responsible for beneficial or deleterious effects in breast cancer patients. Furthermore, metabolites often exhibit pleiotropic effects, depending on their concentration, cellular context, and receptor engagement.

7.2 Lack of Standardized Methodologies

Variability in sampling techniques, sequencing platforms, and metabolomic analysis methods complicates comparisons across studies. A lack of standardized protocols for microbial profiling and metabolite quantification hampers reproducibility and limits the development of reliable biomarkers or therapeutic targets.

7.3 Safety and Efficacy of Microbiota-Based Therapies

Although prebiotics, probiotics, and fecal microbiota transplantation (FMT) hold therapeutic promise, concerns remain regarding their long-term safety, potential for horizontal gene transfer, and

unintended immunomodulation. Careful patient stratification and rigorous clinical trials are needed to determine their efficacy in breast cancer settings.

7.4 Personalized Medicine and Biomarker Discovery

The future of microbiome-based therapies lies in personalized medicine. Advances in artificial intelligence and systems biology are facilitating the development of predictive models that integrate multi-omics data (genomics, transcriptomics, metabolomics, and microbiomics) to tailor therapies based on an individual's unique microbial and metabolic landscape.

Emerging strategies such as synthetic biology**,** engineered probiotics**,** and microbial consortia are being developed to deliver targeted metabolites or modulate specific pathways within the TME. Additionally, identification of metabolite-based biomarkers could enhance early detection, prognosis, and therapeutic responsiveness in breast cancer.

8. CONCLUSION

The interplay between microbial metabolites and the breast tumor microenvironment is a rapidly evolving frontier in cancer biology. These small molecules influence immune responses, inflammation, epigenetic landscapes, angiogenesis, and therapeutic outcomes. Leveraging microbial metabolites for therapeutic modulation of the TME holds immense promise for improving breast cancer management. However, translating these findings into clinical applications requires overcoming several scientific, technical, and regulatory challenges.

A multidisciplinary approach integrating microbiology, oncology, immunology, and bioinformatics will be crucial for advancing this field. With continued research and innovation, microbial metabolites may soon become central players in the development of next-generation cancer therapeutics.

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