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# Emerging Mechanisms Linking High-Fat Diet and Endometrial Cancer: Insights into the Role of Gut Microbiota and Metabolic Dysregulation

Kana Wang[1,a,b], Kunang Liu[1,c], Lin Li[1,a,b], Dongxia Ge[2] and Zongbing You[1,2,3,4,5,6*]

[1]Department of Structural & Cellular Biology, Tulane University, New Orleans, Louisiana, USA; [2]Department of Orthopaedic Surgery, Tulane University, New Orleans, Louisiana, USA; [3]Tulane Cancer Center and Louisiana Cancer Research Consortium, Tulane University, New Orleans, Louisiana, USA; [4]Tulane Center for Stem Cell Research and Regenerative Medicine, Tulane University, New Orleans, Louisiana, USA; [5]Tulane Center for Aging, Tulane University, New Orleans, Louisiana, USA; [6]Tulane Center of Excellence in Sex-Based Biology & Medicine, Tulane University, New Orleans, Louisiana, USA.

[a]Present address: Department of Obstetrics and Gynecology, West China Second University Hospital, Chengdu, Sichuan Province 610041, China; [b]Present address: Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Chengdu, Sichuan Province 610041, China; [c]Present address: Institute of Biology, Hebei Academy of Sciences, Shijiazhuang, Hebei Province 050081, China.
*Correspondence: zyou@tulane.edu; Tel.: +1-504-988-0467.

## ABSTRACT

High-fat diet (HFD) consumption has been recognized as a significant risk factor for the development of endometrial carcinoma (EC). Emerging research highlights gut microbiota as crucial mediators of HFD-induced systemic effects, which not only promote metabolic disorders such as obesity, insulin resistance, and systemic inflammation but also lead to profound alterations in gut microbiota composition. These changes subsequently influence estrogen metabolism, inflammatory signaling pathways, and endometrial remodeling, thereby exacerbating cellular proliferation and atypical changes within the endometrium. The underlying mechanisms may involve dysbiotic shifts in intestinal flora that contribute to increased endotoxemia, compromised intestinal barrier function, and chronic low-grade inflammation. This review synthesizes current findings on how HFD-induced gut microbiota dysbiosis and metabolic dysregulation contribute to the pathogenesis of EC while highlighting potential preventive and therapeutic strategies.

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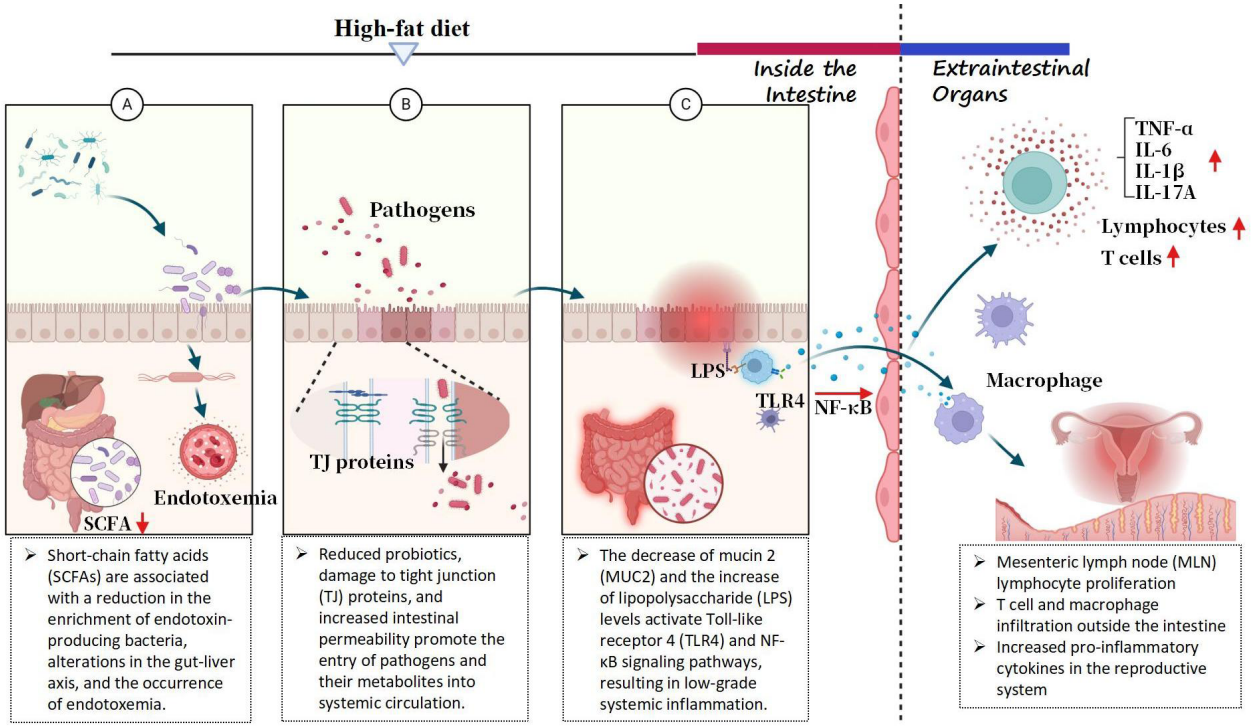
## 1. Background

Endometrial carcinoma (EC) represents the most prevalent gynecological malignancy, with a notably elevated risk observed in obese women. The global incidence of EC is on the rise, with 417,000 new cases reported worldwide in 2020 [1]. In clinical practice, EC can be classified into two types: Type I and Type II. Type I is estrogen-sensitive, accounting for approximately 80% of cases, and is more prevalent in perimenopausal women. In contrast, Type II is characterized as non-estrogen-sensitive. The primary molecular events associated with Type I EC include inactivation of phosphatase and tensin homolog (PTEN) gene and microsatellite instability, whereas Type II is linked to mutations in the p53 gene and human epidermal growth factor receptor 2 (HER2) [2]. The rising incidence has been linked to obesity and diet-related metabolic disturbances. Among various dietary factors, high-fat diet (HFD) has emerged as a significant modulator of endometrial physiology [3]. HFD contributes to increased adiposity and metabolic imbalance, which can disrupt systemic hormone levels, trigger chronic inflammation, and alter immune homeostasis [4]. Recent findings indicate that gut microbiota play a crucial role in the pathogenesis of endometrial cancer. HFD disrupts the composition and function of gut microbial communities by promoting pro-inflammatory taxa while diminishing beneficial bacteria [5-7]. These alterations influence host estrogen levels through estrobolome and stimulate both local and systemic inflammatory responses. Therefore, gut microbiota may serve as an

**Figure 1.** A high-fat diet induces gut microbiota imbalance and impaired barrier function, activating the TLR4/NF-κB pathway, which leads to systemic chronic inflammation and immune cell migration to peripheral tissues (this figure was created using BioRender).




essential link between dietary habits and endometrial health [4,7-8]. Understanding these pathways is critical for developing effective prevention and treatment strategies.

## 2. Intestinal Microbiota and Extraintestinal Diseases

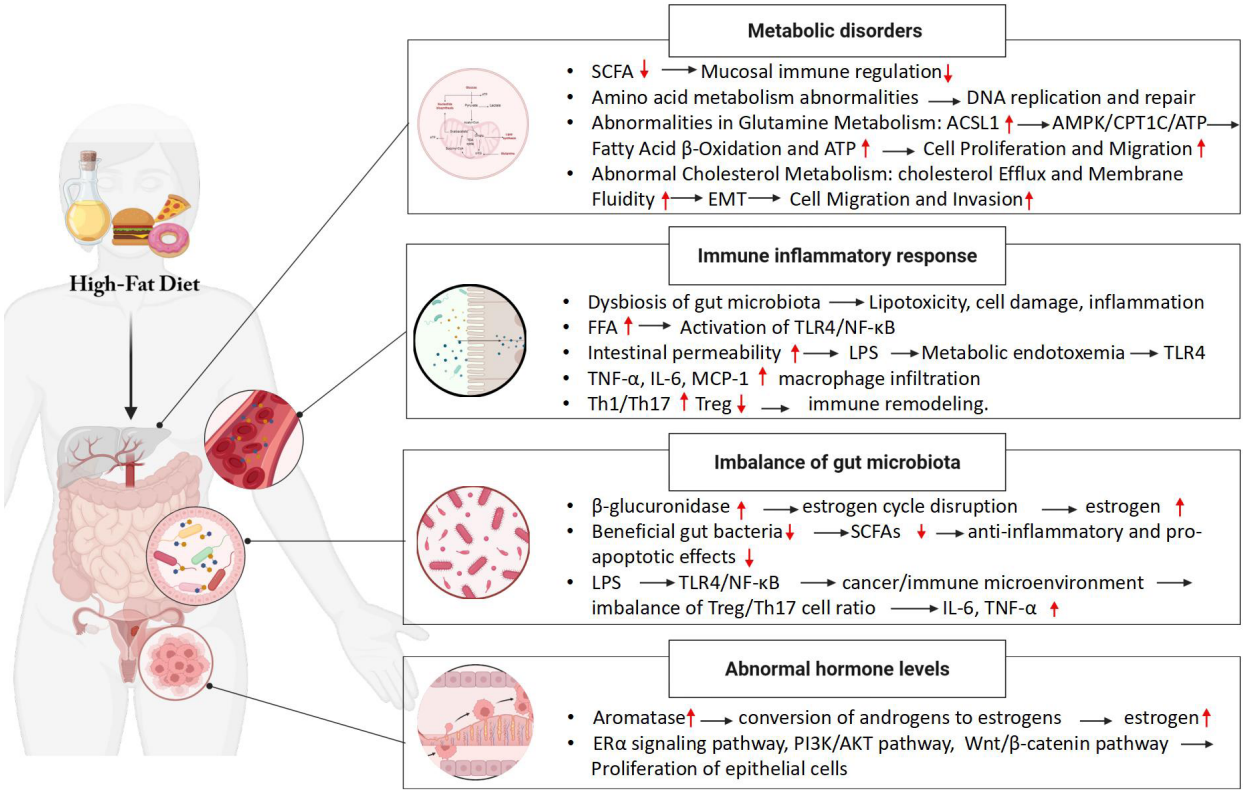
The human gut hosts a diverse array of microorganisms that play a critical role in maintaining homeostasis across various bodily systems and producing metabolic byproducts that influence health. In recent years, research on the gut microbiome has expanded beyond the gastrointestinal tract to include numerous studies related to extraintestinal diseases, such as cardiovascular disorders, neurological conditions, and tumors [9,10]. Previous studies have demonstrated that gut microbiota can influence immune homeostasis in both intestinal and extra-intestinal organs by modulating the balance between T helper (Th17) and regulatory T (Treg) cells. Th17 and Treg cells regulated by the gut microbiota are derived not only from the intestine and extra-intestinal organs but also from peripheral blood and the spleen [11].

Gut microbiome is involved in a variety of physiological functions and exerts beneficial effects on the host by enhancing intestinal barrier integrity, resisting pathogen invasion, and modulating host immunity. However, dysregulation of these processes can lead to physiological disorders; toxic metabolites produced by microorganisms may contribute to inflammation and activate pathways associated with tumorigenesis. This dysregulation can subsequently impact the body's absorption metabolism and tumor progression and deterioration [10,12].

## 3. HFD-Induced Gut Microbiota Dysbiosis

Consumption of HFD has been linked to cognitive deficits and gastrointestinal dysfunction in humans, with the gut microbiota emerging as a critical mediator of these diet-related pathologies [13]. Recent studies have demonstrated that HFD can lead to a reduction in gut microbiota diversity, particularly affecting species responsible for production of short-chain fatty acids (SCFAs), while simultaneously enriching endotoxin-producing bacteria. Dysbiosis within the gut microbiome is often accompanied by impaired intestinal barrier function, endotoxemia, alterations in the gut-liver axis, and subsequent overexpression of inflammatory genes [13-15]. When dysbiosis occurs in the gut, there is a decrease in certain microbial populations including Lactobacillus, Bacte-

**Figure 2.** HFD exerts multifaceted effects on the promotion of endometrial carcinogenesis through various mechanisms, including metabolic dysregulation, immune-inflammatory responses, gut microbiota imbalance, and hormonal level abnormalities (this figure was created using BioRender).




roides, and Bifidobacterium. This decline contributes to damage to tight junction (TJ) proteins and changes in intestinal permeability, facilitating the entry of pathogens and their metabolites into systemic circulation and subsequently activating pro-inflammatory pathways. Mice on an HFD with polystyrene microspheres (microplastics) showed decreased mucin 2 (MUC2) expression and increased serum levels of lipopolysaccharide (LPS) and inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1β, and IL-17A [16]. Increased levels of LPS activate signaling pathways mediated by Toll-like receptor 4 (TLR4) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby promoting low-grade systemic inflammation [14] (Figure 1). Prebiotics may play a regulatory role within the gut-brain axis; dietary supplementation with prebiotics has been shown to alleviate HFD-related behavioral disorders by modifying interactions between gut microbiota and colonic cells [15].

A more critical aspect is that high-fat diet may be associated with the modulation of immune functions by gut microbiota. HFD can lead to dysbiosis of gut microbiota, increased intestinal permeability, and enhanced systemic inflammation. Pre-existing immune-related diseases in these mice, such as multiple sclerosis and systemic lupus erythematosus, are exacerbated [17-19]. The dysbiosis induced by HFD promotes a significant proliferation of intestinal lymphocytes within the mesenteric lymph nodes (MLN), facilitating their migration from MLN to peripheral tissues and enhancing T cell accumulation [20]. In addition to the infiltration of T cells and macrophages into the intestine, there is a notable increase in pro-inflammatory cytokines within the reproductive system. Research by Ding et al. has demonstrated that in mice with HFD-induced microbial dysbiosis, severe inflammatory responses occur in epididymal tissue, which are closely linked to defects in spermatogenesis [21].

## 4. High-Fat Diet and Its Role in Endometrial Hyperplasia and Carcinogenesis

EC is closely associated with various factors, including menstrual history, reproductive history, metabolic syndrome, insulin resistance, obesity, and estrogen levels. Patients diagnosed with EC frequently present with comorbidities such as hypertension,

diabetes, and obesity. However, the specific molecular mechanisms underlying the occurrence and development of EC remain unclear. In a $Pten^{+/-}$ mouse model, feeding with a high-fat diet significantly increased the incidence of endometrial gland hyperplasia accompanied by atypia and malignant lesions [22]. Furthermore, this dietary intervention notably promoted tumor growth and elevated the protein expression levels of estrogen receptor α (ERα) in tumor tissues [23]. HFD is associated with risk factors related to EC and may contribute to the occurrence and progression of EC through the following mechanisms (summarized in Figure 2).

### 4.1. Imbalance of Gut Microbiota

Increasing evidence indicates that HFD disrupts the intricate balance of gut microbiota, leading to dysbiosis - a condition characterized by diminished microbial diversity, overgrowth of pathogenic bacteria, and a reduction in beneficial commensals. This state of dysbiosis not only contributes to metabolic disorders and chronic inflammation but is also increasingly implicated in the development and progression of various cancers, including EC. Recent Mendelian randomization studies have reinforced the causal relationship between gut microbiota imbalance and EC risk. For example, one study demonstrated that specific bacterial genera such as Prevotella and Clostridium species were associated with heightened susceptibility to EC, potentially through mechanisms involving immune modulation and interference with estrogen metabolism [24]. Moreover, emerging data suggest that the composition of the gut microbiome may differ according to the histopathological subtype of EC. A case–control metagenomic study identified distinct microbial signatures between type I and type II EC, indicating that gut microbiota profiles could serve not only as biomarkers for diagnosis and classification but also as modulators influencing tumor behavior [25].

The potential mechanisms may include the following: First, gut microbiota regulate estrogen reabsorption through β-glucuronidase; dysbiosis can lead to abnormal estrogen circulation and prolonged exposure to estrogen. Second, a reduction in beneficial bacteria (such as butyrate-producing enterorhabdus and lactobacillus bacteria) and their bacterial metabolites results in decreased SCFAs, thereby weakening anti-inflammatory and pro-apoptotic effects. Third, an increase in pathogenic bacteria promotes the production of inflammatory molecules such as LPS, activating signaling pathways like TLR4/NF-κB and creating a pro-cancer microenvironment. Additionally, high-fat diets can disrupt the intestinal epithelial barrier, and the damage to this barrier allows microbial components to enter the circulatory system, leading to endotoxemia that triggers systemic chronic inflammation and alters the immune environment of the endometrium. Furthermore, gut microbiota modulates the ratio of Treg/Th17 cells and influences the release of various inflammatory factors (e.g., IL-6, TNF-α), indirectly regulating both immune tolerance and proliferative status within the endometrium [14-15, 24-26].

### 4.2. Immune Inflammatory Response

Excessive intake of HFD not only leads to metabolic disorders but also activates the immune system through various mechanisms, resulting in low-grade chronic inflammation. HFD induces dysbiosis of gut microbiota, hypertrophy of adipose tissue, and excessive lipid deposition in non-adipose tissues. This accumulation of triglycerides and their metabolites in non-adipose tissues causes lipotoxicity, cellular damage, and inflammation. Moreover, elevated levels of free fatty acids (FFAs) in the bloodstream can activate the TLR4/NF-κB pathway and enhance the expression of pro-inflammatory cytokines [27-29].

Additionally, HFD may compromise intestinal barrier integrity, leading to increased intestinal permeability and enhanced transport of microbial products into circulation. Bacterial components such as LPS enter the bloodstream, inducing metabolic endotoxemia that activates TLR4 and other receptors while triggering systemic inflammation [27,30]. The oxidative stress and inflammatory responses within the body further contribute to local hypoxia in tissues such as the endometrium and ovaries. This environment enhances pro-inflammatory cytokine production, such as TNF-α, IL-6, and monocyte chemoattractant protein-1(MCP-1), along with macrophage infiltration [28]. Macrophages transition from an anti-inflammatory phenotype (M2) to a pro-inflammatory phenotype (M1) [29]. Concurrently, there is an increase in T helper cells (Th1/Th17) a decrease in Treg cells, resulting in heightened inflammatory responses and tissue immune remodeling. Such a localized inflammatory milieu can lead to abnormal endometrial hyperplasia and may adversely affect ovarian function by causing ovulation disorders or abnormal hormone levels [31-33].

### 4.3. Metabolic Disorders

HFD is associated with dysregulation of lipid metabolism, characterized by elevated levels of plasma free fatty acids and triglycerides. Fatty acids belong to a family of lipids whose structure consists of two main components: a straight chain of carbon atoms and a carboxyl group. The length of the straight chain can range from 2 to 36 carbon atoms. SCFAs, which are beneficial microbial products, tend to decrease under HFD conditions, thereby impairing mucosal immune regulation [34].

Current perspectives suggest that metabolic reprogramming, including remodeling of glucose, amino acids, and lipids, serves as a hallmark for tumors. The development and progression of endometrial cancer may be linked to alterations in fatty acid metabolism and composition; DNA replication and repair could represent critical points connecting glutamine metabolism, amino acid metabolism, and the advancement of endometrial cancer [35, 36]. Razghonova et al. analyzed the fatty acid (FA) profiles at different stages of endometrial carcinoma (EC), revealing lower levels of saturated FAs and branched-chain FAs in EC tissues while showing higher concentrations of very long-chain FAs, n-3 polyunsaturated FAs (PUFAs), and monounsaturated FAs. Acyl-CoA synthetase long chain family member 1 (ACSL1) is one key enzyme involved in glutamine metabolism; its overexpression may activate adenosine monophosphate- activated protein kinase (AMPK)/carnitine palmitoyltransferase 1C (CPT1C)/ATP pathway, enhancing β-oxidation of fatty acids within EC cells along with ATP production. This process subsequently promotes cell proliferation and migration [36]. Additionally, research indicates that nicotinamide N-methyltransferase (NNMT), which participates in cholesterol metabolism, is also overexpressed in EC cases where patients exhibit reduced survival rates post-chemotherapy. NNMT enhances cholesterol efflux through activation of ATP binding cassette subfamily A member 1 (ABCA1), leading to increased membrane fluidity while decreasing cholesterol levels within both cytoplasm and cell membranes; this enhancement facilitates epithelial-mesenchymal transition (EMT) in EC cells, thereby promoting their migratory and invasive capabilities [37].

### 4.4. Abnormal Hormone Levels

Gut microbiota play a crucial role in regulating the systemic immune inflammatory response and modulating estrogen circulation, thereby influencing estrogen metabolism and serving as a risk factor associated with elevated estrogen levels [38]. Conversely, HFD can enhance aromatase activity within adipose tissue, facilitating conversion of androgens to estrogens. This process results in increased estrogen levels, which may lead to insulin resistance and hyperinsulinemia. These metabolic alterations activate key signaling pathways, including the estrogen receptor alpha (ERα) signaling pathway, phosphoinositide 3-kinase (PI3K)/AKT pathway, and Wingless and Int-1(Wnt)/β-catenin pathways, ultimately promoting epithelial cell proliferation [23, 32, 39]. Shen et al. established an estrogen receptor-positive patient-derived orthotopic xenograft (PDOX) tumor mouse model. Their findings indicated that HFD significantly accelerated tumor growth while increasing ERα protein expression levels in tumor tissues. This suggests that HFD may facilitate the development of endometrial cancer by activating the estrogen signaling pathway [23]. Furthermore, gene expression patterns can be modified through alterations in the transcriptome of endometrial epithelial cells and stromal cells, further contributing to the emergence of endometrial lesions [32].

Elevated ERα signaling plays a pivotal role in the initiation and progression of hormone-dependent endometrial cancer. Prolonged exposure to HFD in rat models leads to histopathological alterations that mirror those observed in humans, including glandular crowding, epithelial stratification, and nuclear atypia [40,41]. Research has demonstrated that both estrogen-related receptor alpha (ERRα) and transcription factor EB (TFEB) are significantly overexpressed in patients with EC. The TFEB-ERRα axis facilitates lipid reprogramming, thereby promoting EC progression; concurrently, TFEB enhances EC cell migration through EMT in an ERRα-dependent manner [42]. Furthermore, hypoxia-inducible factor-1 alpha (HIF-1α), a key regulatory element of tumor cell metabolic reprogramming, is closely associated with ERRα and may also play a role in the metabolic reprogramming of EC [43].

## 5. Potential Preventive and Therapeutic Strategies

### 5.1. Dietary Habit Intervention

Obesity, high-fat diet, and sedentary lifestyles are well-established risk factors for endometrial cancer. Implementing a fat-controlled diet or increasing the intake of n-3 polyunsaturated fatty acids (such as

those found in fish oil) can enhance the lipid profile of endometrial tissues and potentially reduce the risk of developing endometrial cancer. Oleic acid, one of the most significant monounsaturated fatty acids presenting in the human body, exhibits both pro-tumor and anti-tumor activities across various preclinical models [44]. Yammine et al. conducted a follow-up study over 8.8 years involving 1,886 new cases of endometrial cancer alongside 297,432 non-cases. Their findings suggest that higher consumption of plant-based gamma-linolenic acid and alpha-linoleic acid may be linked to a decreased risk of endometrial cancer [45]. Furthermore, compounds with antioxidant properties and metabolic regulatory effects, such as omega-3 fatty acids, resveratrol, and metformin, may also contribute to cancer prevention. Carnovale et al. reported structural alterations in the endometrium within a mouse model induced by HFD-related metabolic syndrome; these changes included cellular proliferation abnormalities that compromised reproductive function. Notably, metformin was shown to restore normal endometrial structure by inhibiting cell proliferation [46].

### 5.2. Regulating Gut Microbiota

Currently, although research on endometrial microbiota is limited, it has been demonstrated that the relationship between EC and local immune regulation is associated with harmful metabolites from gut microbiota. Modulating the gut microbiome may provide a promising avenue for the prevention and treatment of EC. Dietary interventions aimed at reducing fat intake while increasing fiber consumption can help restore gut microbial balance. Additionally, supplementation with probiotics can enhance intestinal barrier function and modulate immune responses [38, 46-47]. Probiotics, prebiotics, fecal microbiota transplantation (FMT), and personalized therapies based on microbial composition have been explored as clinical interventions for managing EC [46]. Research shows that Lactobacillus acidophilus can reduce weight gain, fat accumulation, inflammation, and insulin resistance in mice on HFD while activating brown adipose tissue (BAT). This results in improved energy expenditure and glucose and lipid metabolism; it also helps maintain the integrity of the intestinal barrier and reduces metabolic endotoxemia. The ratio of Firmicutes to Bacteroidetes in the intestines of these mice decreases alongside levels of Gram-negative bacteria carrying endotoxins. The reversal of HFD-induced dysbiosis by Lactobacillus acidophilus may be linked to its mechanism involving inhibition of the TLR4/NF-κB signaling pathway [47]. Furthermore, another study found that sodium butyrate (NaB), a metabolite produced by gut microbiota, could restore mucosal damage induced by HFD. Following NaB intervention, there was a significant downregulation of endotoxin-related genes such as TLR4 and myeloid differentiation primary response 88 (Myd88) in liver or epididymal fat tissues along with pro-inflammatory genes including MCP-1, TNF-α, IL-1β, IL-2, IL-6, and IFN-γ [48].

### 5.3. Metabolic Targeting and Immunotherapy

Metabolic reprogramming plays a crucial role in tumorigenesis and progression. Metabolic-targeted therapy provides precise treatment options with relatively low side effects for endometrial cancer. Key alterations, such as enhanced glycolysis (Warburg effect), increased fatty acid synthesis, glutamine dependence, and abnormal one-carbon metabolism, present various strategies for targeted therapy [44,48-50]. Several metabolic targets, including glucose transporter type 1 (GLUT1), fatty acid synthase (FASN), glutaminase (GLS), serine hydroxymethyltransferase 2 (SHMT2), and mechanistic target of rapamycin (mTOR), have been identified for new drug development [44,49-53]. Inhibitors like CB-839 (a GLS inhibitor) and TVB-2640 (a FASN inhibitor) are being investigated for their anti-tumor effects [54, 55]. Studies indicate that inhibiting key enzymes in lipid metabolism, such as FASN, acyl-CoA synthetase long-chain family member 1 (ACSL1), and stearoyl-CoA desaturase 1 (SCD1), can reduce lipid supply and suppress tumor proliferation [56]. Another important enzyme is phosphoglycerate dehydrogenase (PHGDH), the first rate-limiting enzyme in the serine synthesis pathway linking serine to glutamine metabolism, which when inhibited may disrupt interconnected metabolic processes and hinder cancer cell growth [57]. Kong et al. used Tirzepatide, a dual glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) receptor agonist, in the endometrial cancer mouse model; it reduced body weight and tumor growth by affecting the metabolic and immune pathways of obese mice [58].

Additionally, combining glutamine metabolism inhibition with mTOR or DNA repair mechanisms significantly enhances anti-tumor effects. Synthetic lethality strategies selectively target cancer cells' unique metabolic dependencies or genetic defects for effective killing, which represents a precision treatment approach against endometrial cancer's metabolic reprogramming [59-63]. For instance,

DNA repair-deficient tumor cells rely on one-carbon metabolism; inhibiting serine hydroxymethyltransferase 2 (SHMT2) or methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) induces replication stress and cell death [60, 61]. Loss of SHMT2 triggers ROS-dependent, mitochondrial-mediated apoptosis [62]. Additionally, mutations in AT-rich interaction domain 1A (ARID1A) combined with inhibition of enhancer of zeste homolog 2 (EZH2, a histone methyltransferase) show promising results in synthetic lethality approaches [63]. These strategies offer novel therapeutic targets in endometrial cancer, potentially enhancing personalized treatment and overcoming drug resistance.

## 6. Conclusion and Future Directions

In conclusion, HFD plays a significant role in the development and progression of EC through mechanisms such as dysbiosis of gut microbiota, metabolic disturbances, and hormonal imbalances. Evidence indicates that alterations in the gut microbiome can influence systemic inflammation, immune responses, and estrogen metabolism, ultimately leading to endometrial hyperplasia and malignant transformation. As research advances in the future, multi-omics approaches may be utilized to elucidate these mechanisms further, develop personalized dietary interventions, and explore the therapeutic potential of probiotics and fecal microbiota transplantation. Strategies targeting the microbiome may be combined with hormonal or immunotherapeutic treatments to yield synergistic effects for novel prevention and treatment options. This underscores the importance of the "diet-microbiome-cancer" axis in the precise prevention and management of endometrial cancer.

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