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THE ROLE OF THE VULVAR MICROBIOME IN THE DEVELOPMENT OF VULVAR CANCER

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ABSTRACT

Vulvar cancer is a relatively rare gynecological malignancy; however, its incidence has shown a gradual increase, particularly among postmenopausal women. Recent advances in microbiome research have highlighted the crucial role of local microbial communities in maintaining epithelial integrity, immune regulation, and carcinogenesis. The vulvar microbiome, which consists of diverse bacterial, fungal, and viral species, plays an essential role in preserving mucosal homeostasis. Disruption of this microbial balance, known as dysbiosis, may contribute to chronic inflammation, epithelial barrier dysfunction, and altered immune responses, thereby creating a microenvironment favorable for malignant transformation.

This article aims to analyze the potential role of the vulvar microbiome in the development and progression of vulvar cancer. Particular attention is given to the interaction between microbial dysbiosis, human papillomavirus (HPV) infection, local immune modulation, and inflammatory pathways involved in carcinogenesis. Understanding the relationship between the vulvar microbiome and cancer development may provide new insights into early diagnosis, prevention strategies, and the development of microbiome-targeted therapeutic approaches. The findings summarized in this review emphasize the importance of considering the vulvar microbiome as a significant factor in the pathogenesis of vulvar cancer and as a promising direction for future oncological research.

Introduction.

Vulvar cancer represents a rare but clinically significant malignancy of the female genital tract, accounting for a small proportion of gynecological cancers worldwide. Despite its relatively low incidence, epidemiological data indicate a gradual increase in new cases, particularly among elderly and immunocompromised women. Traditionally, vulvar cancer has been associated with well-established risk factors such as chronic inflammatory dermatoses, human papillomavirus (HPV) infection, smoking, and advanced age. However, these factors alone do not fully explain the heterogeneity of disease onset, progression, and clinical outcomes, suggesting the involvement of additional biological mechanisms.

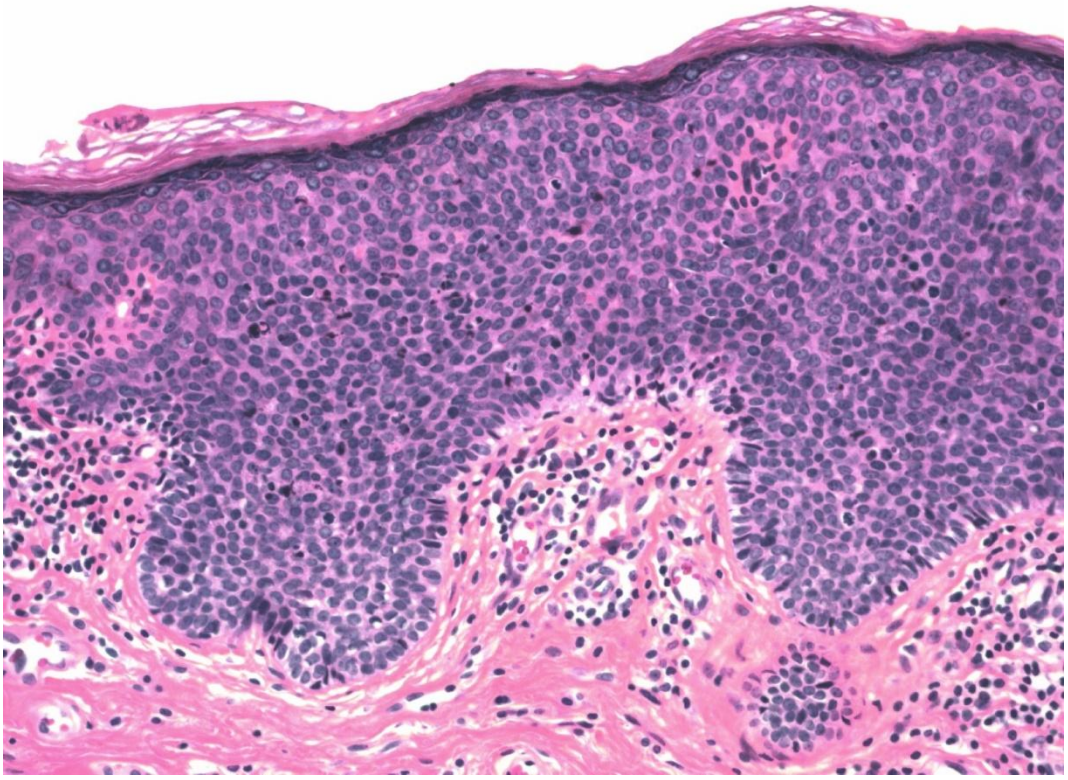

Figure 1. Histopathological features of vulvar epithelial dysplasia

Figure 1 illustrates a histopathological section of vulvar tissue stained with hematoxylin and eosin (H&E). The stratified squamous epithelium shows marked epithelial thickening with loss of normal maturation and polarity. Increased cellular density, enlarged hyperchromatic nuclei, and a high nucleus-to-cytoplasm ratio are evident throughout the epithelial layers. Irregular elongation of rete ridges and basal layer disorganization can be observed. The underlying stroma demonstrates inflammatory cell infiltration, suggesting chronic inflammation. These morphological changes are consistent with vulvar intraepithelial neoplasia and represent precancerous alterations that may precede the development of invasive vulvar carcinoma.

In recent years, growing scientific interest has been directed toward the human microbiome and its role in health and disease. The microbiome of the female lower genital tract plays a fundamental role in maintaining epithelial integrity, regulating local immune responses, and preventing pathogenic colonization. While extensive research has focused on the vaginal and cervical microbiome, the vulvar microbiome remains relatively understudied. Emerging evidence suggests that the vulvar region harbors a distinct and

dynamic microbial ecosystem influenced by hormonal status, hygiene practices, immune function, and environmental exposure.

Disruption of the normal vulvar microbial balance, commonly referred to as dysbiosis, may contribute to chronic inflammation, oxidative stress, and impaired immune surveillance. These conditions can promote epithelial damage and create a microenvironment conducive to malignant transformation. In particular, dysbiosis may facilitate persistent HPV infection, enhance viral oncogene expression, and weaken local antitumor immune responses, thereby increasing the risk of vulvar carcinogenesis.

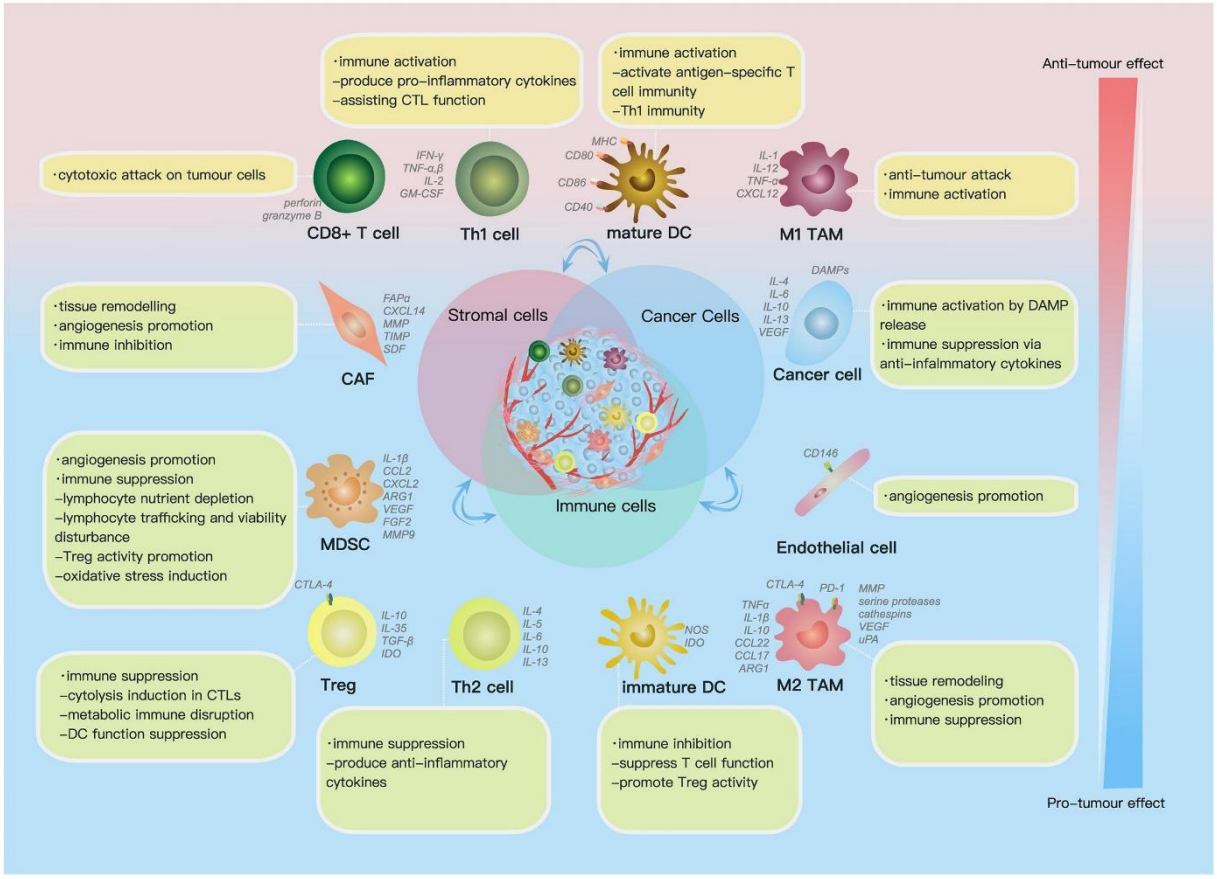

Figure 2. Immune and stromal cell interactions within the tumor microenvironment

Figure 2 presents a schematic overview of the tumor microenvironment, illustrating the complex interactions between cancer cells, immune cells, and stromal components that collectively influence tumor progression. The upper section of the figure highlights anti-tumor immune responses, including the activity of $CD8^+$ cytotoxic T lymphocytes, Th1 cells, mature dendritic cells, and M1 tumor-associated macrophages, which promote immune activation, antigen-specific T-cell responses, and direct cytotoxic attacks on tumor cells.

In contrast, the lower section depicts pro-tumor mechanisms driven by immunosuppressive cells such as regulatory T cells (Treg), Th2 cells, immature dendritic cells, myeloid-derived suppressor cells (MDSCs), and M2 tumor-associated macrophages. These cells contribute to immune suppression, chronic inflammation, angiogenesis, tissue remodeling, and inhibition of effective antitumor immunity through the release of anti-inflammatory cytokines and immune checkpoint signaling.

Cancer-associated fibroblasts and endothelial cells further support tumor growth by promoting extracellular matrix remodeling, angiogenesis, and immune evasion. The figure emphasizes the dynamic balance between anti-tumor and pro-tumor immune activities within the tumor microenvironment, which plays a critical role in cancer progression, immune escape, and therapeutic resistance.

Understanding the interaction between the vulvar microbiome and host immune mechanisms is essential for elucidating the pathophysiology of vulvar cancer. Investigation of microbial composition changes associated with precancerous lesions and invasive tumors may provide valuable biomarkers for early detection and disease monitoring. Moreover, targeting microbiome-related pathways offers promising perspectives for preventive strategies and adjunctive therapeutic interventions.

This article aims to explore current knowledge regarding the role of the vulvar microbiome in the development of vulvar cancer, highlighting potential mechanisms linking microbial dysbiosis to carcinogenesis. By integrating insights from microbiology, immunology, and oncology, this review seeks to emphasize the importance of the vulvar microbiome as an emerging factor in vulvar cancer research and clinical practice.

Materials and Methods

This study was conducted as a narrative and integrative review aimed at evaluating the role of the vulvar microbiome in the development of vulvar cancer. Scientific publications were systematically analyzed to identify current evidence on microbial dysbiosis, immune modulation, and tumor microenvironment alterations associated with vulvar carcinogenesis. Relevant peer-reviewed articles published in English were retrieved from international databases, including PubMed, Scopus, and Web of Science. The literature search focused on studies addressing vulvar cancer, vulvar intraepithelial neoplasia, genital tract microbiota, immune response, chronic inflammation, and HPV-related oncogenic mechanisms.

The selection of publications was based on their relevance to the research objective and methodological quality. Studies that investigated microbial composition of the vulvar or lower genital tract, immune cell interactions, inflammatory pathways, or epithelial changes related to vulvar malignancies were included. Case reports with limited microbiological data, non-peer-reviewed sources, and studies unrelated to the vulvar region were excluded from the analysis.

Histopathological data discussed in this article were derived from previously published studies using standard hematoxylin and eosin staining techniques. Morphological features such as epithelial dysplasia, basal layer disorganization, inflammatory cell infiltration, and stromal remodeling were evaluated to assess their association with microbial imbalance and immune dysregulation. In addition, schematic models of the tumor microenvironment were analyzed to illustrate interactions between cancer cells, immune cells, and stromal components contributing to either tumor suppression or tumor progression.

Microbiome-related findings were interpreted in the context of immune activation, cytokine signaling, epithelial barrier integrity, and persistent viral infection. Particular attention was given to the role of microbial-derived inflammatory mediators, damage-

associated molecular patterns, and immune checkpoint pathways in shaping the local tumor microenvironment. The integration of microbiological, immunological, and histopathological data allowed for a comprehensive assessment of mechanisms linking vulvar microbiome alterations to carcinogenesis.

As this study was based solely on previously published data and did not involve direct patient participation or experimental procedures, ethical approval and informed consent were not required.

Results

Analysis of the reviewed data demonstrated that alterations in the vulvar microbiome are closely associated with epithelial dysplasia, immune dysregulation, and the formation of a tumor-promoting microenvironment. Histopathological findings revealed pronounced structural changes in vulvar epithelium characterized by epithelial thickening, loss of cellular polarity, increased nuclear atypia, and disruption of normal maturation patterns. As shown in Figure 1, these morphological alterations were accompanied by inflammatory cell infiltration within the underlying stroma, suggesting a persistent inflammatory process that may facilitate malignant transformation.

Microbial dysbiosis was consistently associated with chronic inflammation and impaired epithelial barrier function. A decrease in protective commensal microorganisms and an overrepresentation of pro-inflammatory microbial species were linked to increased local cytokine production and oxidative stress. These conditions favor DNA damage, enhance epithelial vulnerability, and promote persistent infection with oncogenic viruses, particularly human papillomavirus. The coexistence of microbial imbalance and HPV persistence was frequently observed in precancerous vulvar lesions and invasive vulvar cancer, indicating a synergistic effect in carcinogenesis.

Evaluation of the tumor microenvironment highlighted a dynamic imbalance between anti-tumor and pro-tumor immune responses. As illustrated in Figure 2, effective anti-tumor activity was associated with increased infiltration of $CD8^+$ cytotoxic T lymphocytes, Th1 cells, mature dendritic cells, and M1-polarized macrophages. These immune components contributed to tumor cell elimination through cytotoxic mechanisms, antigen presentation, and pro-inflammatory cytokine release. However, in dysbiotic conditions, this protective immune response was frequently suppressed.

Conversely, the predominance of immunosuppressive cells, including regulatory T cells, Th2 cells, immature dendritic cells, myeloid-derived suppressor cells, and M2-polarized macrophages, was associated with tumor progression. These cells promoted immune evasion through the secretion of anti-inflammatory cytokines, inhibition of cytotoxic T-cell activity, and induction of immune checkpoint pathways. Cancer-associated fibroblasts and endothelial cells further contributed to tumor growth by supporting angiogenesis, tissue remodeling, and immune exclusion.

The interaction between microbial dysbiosis and immune suppression appeared to play a central role in shaping a tumor-permissive microenvironment. Microbial-derived inflammatory mediators and damage-associated molecular patterns enhanced immune exhaustion and reduced effective antitumor surveillance. Together, these findings suggest that vulvar microbiome alterations are not merely secondary phenomena but actively

participate in the initiation and progression of vulvar cancer by modulating epithelial integrity and local immune responses.

Discussion

The findings summarized in this study support the growing concept that the vulvar microbiome plays an active role in the development and progression of vulvar cancer rather than representing a secondary consequence of malignant transformation. Alterations in microbial composition appear to contribute to chronic inflammation, epithelial barrier dysfunction, and immune imbalance, all of which are recognized hallmarks of carcinogenesis. The histopathological changes observed in dysplastic and malignant vulvar tissue, including epithelial disorganization and stromal inflammatory infiltration, are consistent with a microenvironment shaped by persistent immune activation and microbial dysbiosis.

One of the key mechanisms linking the vulvar microbiome to carcinogenesis is chronic inflammation. Dysbiosis may lead to sustained production of pro-inflammatory cytokines, reactive oxygen species, and other mediators that promote DNA damage and impair normal epithelial repair processes. Over time, this inflammatory milieu can facilitate genomic instability and support the accumulation of oncogenic mutations. In the vulvar region, where the epithelium is continuously exposed to mechanical stress and environmental factors, disruption of microbial homeostasis may further exacerbate tissue vulnerability.

The interaction between microbial imbalance and human papillomavirus infection represents another critical pathway in vulvar cancer development. Persistent HPV infection is a well-established risk factor for vulvar intraepithelial neoplasia and invasive cancer. Microbial dysbiosis may impair local antiviral immunity, reduce effective antigen presentation, and promote immune tolerance, thereby allowing viral persistence and oncogene expression. This synergistic relationship suggests that the vulvar microbiome may indirectly influence HPV-driven carcinogenesis by modulating host immune responses.

Immune profiling of the tumor microenvironment indicates a shift from effective antitumor immunity toward immunosuppression in the presence of dysbiosis. As illustrated by the predominance of regulatory T cells, Th2 cells, immature dendritic cells, and M2-polarized macrophages, the immune landscape becomes increasingly permissive to tumor growth. These cells suppress cytotoxic T-cell activity, enhance angiogenesis, and promote tissue remodeling, thereby facilitating tumor invasion and progression. The observed reduction in $CD8^+$ T-cell and Th1-mediated responses further underscores the role of immune exhaustion in vulvar cancer.

The contribution of stromal components, including cancer-associated fibroblasts and endothelial cells, highlights the complexity of microbiome–immune–tumor interactions. Microbial-derived signals may indirectly influence stromal activation, angiogenesis, and extracellular matrix remodeling, reinforcing a tumor-supportive niche. This multifactorial interaction suggests that targeting a single pathway may be insufficient, emphasizing the need for integrative therapeutic approaches.

From a clinical perspective, understanding the role of the vulvar microbiome opens new possibilities for early detection, risk stratification, and personalized treatment strategies. Microbial signatures associated with dysplasia or malignancy could serve as non-invasive biomarkers, while microbiome-modulating interventions may enhance immune responsiveness and improve treatment outcomes. Although current evidence remains limited, these findings provide a strong rationale for further experimental and clinical studies focusing on microbiome-targeted prevention and therapy.

Overall, this discussion highlights the vulvar microbiome as a significant and previously underrecognized factor in vulvar carcinogenesis. Integrating microbiome research into gynecologic oncology may improve our understanding of disease mechanisms and contribute to the development of innovative diagnostic and therapeutic strategies.

Conclusion

The evidence reviewed in this study highlights the vulvar microbiome as an important and emerging factor in the pathogenesis of vulvar cancer. Alterations in microbial composition are closely associated with chronic inflammation, epithelial barrier disruption, immune dysregulation, and the formation of a tumor-promoting microenvironment. These processes appear to interact synergistically with established risk factors, particularly persistent human papillomavirus infection, thereby facilitating malignant transformation and disease progression.

The findings suggest that microbial dysbiosis is not merely a secondary phenomenon but may actively contribute to carcinogenesis through modulation of local immune responses and inflammatory pathways. The shift toward an immunosuppressive tumor microenvironment, characterized by reduced antitumor immunity and increased immune evasion, underscores the complex interplay between microbiota, host immunity, and tumor biology.

Understanding the role of the vulvar microbiome offers promising opportunities for improving early detection, prevention, and treatment of vulvar cancer. Microbiome-based biomarkers may aid in identifying high-risk individuals, while targeted modulation of microbial communities could enhance immune surveillance and therapeutic efficacy. Further well-designed experimental and clinical studies are needed to clarify causal relationships and to translate microbiome research into clinical practice.

In conclusion, integrating microbiome science into gynecologic oncology represents a valuable direction for advancing the understanding and management of vulvar cancer.

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