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Uncovering the role of cutaneous microbiota in the immunopathogenesis and therapeutic resistance of merkel cell carcinoma: a precision oncology perspective

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare but highly aggressive cutaneous neuroendocrine malignancy predominantly affecting immunocompromised and elderly individuals. Driven by Merkel cell polyomavirus (MCPyV) in over 80% of Western cases and by ultraviolet (UV)-induced mutagenesis in the remainder, MCC presents significant clinical challenges due to propensity for rapid metastasis and resistance to conventional therapies. The cutaneous microbiota has recently emerged as a critical modulator of tumour immune microenvironment composition, antitumour surveillance, and responsiveness to immune checkpoint inhibitors (ICIs). This review synthesises current evidence on MCC epidemiology, viral oncogenesis, tumour microenvironment (TME) biology, and ICI therapy with evolving insights into host-microbiome interactions. We explore how microbial dysbiosis may potentiate immunopathogenesis and attenuate ICI efficacy, and we highlight translational opportunities including fecal microbiota transplantation (FMT), defined bacterial isolates, and bacterial consortia as microbiome-targeted adjuncts within a precision oncology framework.

Keywords: Cutaneous microbiota; Immune checkpoint inhibitors; Merkel cell carcinoma; Merkel cell polyomavirus; microRNA biomarkers; precision oncology.

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INTRODUCTION

Merkel Cell Carcinoma (MCC) is a rare and highly aggressive cutaneous neuroendocrine carcinoma that predominantly affects elderly individuals with significant exposure to ultraviolet (UV) radiation. First described as trabecular carcinoma by Cyril Toker in 1972, its neuroendocrine origin was later confirmed through electron microscopy, leading to its reclassification as MCC due to its resemblance to Merkel cells-specialized mechanoreceptors located in the skin [1,2]. A major advancement in understanding MCC occurred with the discovery of Merkel cell polyomavirus in 2008, which is associated with approximately 80% of cases in Western populations [3,4]. Clinically, MCC typically presents as a rapidly growing, painless, reddish-purple cutaneous nodule. The incidence of MCC has been steadily increasing, likely due to factors such as an aging population, increased UV exposure, immunosuppression, and improved diagnostic techniques including immuno histochemistry[5–7]. MCC is characterized by an aggressive clinical course with a high propensity for local recurrence and metastasis. At the time of diagnosis, approximately 50–65% of patients present with localized disease, 25–50% with regional nodal involvement, and around 10% with distant metastases [8,9].

Overview of Merkel Cell Carcinoma (MCC)

Epidemiology and pathogenesis: Merkel Cell Carcinoma (MCC) is a rare malignancy with a global incidence ranging from 0.1 to 1.6 cases per 100,000 individuals, with the highest rates reported in

Australia [10]. In the United States, MCC incidence increased by approximately 95% between 2000 and 2013, exceeding the growth rate of melanoma, likely due to improved diagnostics, aging populations, and enhanced cancer registries [6]. MCC predominantly affects fair-skinned, elderly individuals, particularly males with prolonged sun exposure, while advanced age and immunosuppression such as in organ transplant recipients or patients with chronic lymphocytic leukemia are significant risk factors [11] .

A major etiological factor is Merkel cell polyomavirus, identified in approximately 80% of MCC cases, with viral DNA clonally integrated into tumor genomes, indicating a pathogenic role [3]. The virus expresses oncogenic large T (LT) and small T (ST) antigens; truncated LT protein disrupts the retinoblastoma (Rb) pathway, while ST indirectly suppresses p53 function, promoting tumorigenesis [12]. In MCPyV-negative MCC, carcinogenesis is primarily driven by ultraviolet (UV)-induced mutations, particularly in TP53 and RB1 genes, which similarly impair tumor suppressor pathways [13].

The cellular origin of MCC remains under investigation, with proposed sources including pro-B/pre-B lymphocytes, fibroblasts, dermal stem cells, and epithelial cells. Evidence such as B-cell marker expression and responses to B-cell–targeted therapies like idelalisib supports a possible lymphoid origin in MCPyV-positive tumors [14] .

In contrast, MCPyV-negative tumors are thought to arise from keratinocytes through UV-induced malignant transformation, sometimes showing features overlapping with squamous cell carcinoma.

Etiology, pathology, and tumor biology: Merkel Cell Carcinoma (MCC) is histologically characterized as a monomorphic “small round blue cell tumor” composed of cells with scant cytoplasm, round to oval nuclei, finely granular chromatin, and high mitotic activity. Due to its resemblance to other small cell malignancies such as lymphoma, melanoma, and small-cell lung carcinoma, immunohistochemistry is essential for diagnosis. MCC typically expresses neuroendocrine markers including chromogranin A, synaptophysin, CD56, cytokeratin 20 (dot-like pattern), neurofilament, and Merkel cell polyomavirus large T antigen, while being negative for leukocyte common antigen (LCA), S-100, and thyroid transcription factor-1 (TTF-1) [15].

The exact cell of origin remains controversial, although MCC shares features with normal Merkel cells. MCPyV-positive and MCPyV-negative tumors likely arise from different cellular origins, with virus-positive tumors possibly deriving from dermal or precursor cells, whereas virus-negative tumors are associated with ultraviolet (UV)-induced transformation of epidermal keratinocytes [16]. MCPyV is a small double-stranded DNA virus (~5.4 kb) encoding early (large T and small T antigens) and late (capsid proteins VP1, VP2, VP3) regions . Oncogenesis requires clonal viral integration and truncation of the large T antigen, leading to inhibition of tumor suppressor pathways such as Rb and p53 and promoting cell cycle progression [12,16].

MCPyV-positive MCCs generally exhibit a low mutational burden, whereas virus-negative tumors demonstrate high UV-induced mutational signatures [15]. Prognostically, virus-negative MCC may have a higher mortality risk, although not always statistically significant [17]. Increased infiltration of CD8+ T cells in MCPyV-positive tumors suggests an active antitumor immune response [15,18]. Rare cases of spontaneous tumor regression, particularly following biopsy, further support the role of immune-mediated tumor control [19].

Role of cutaneous microbiota in skin immunity

Controlling local immune responses and maintaining skin homeostasis depend on the cutaneous microbiota, a community of microorganisms that reside on the skin's surface. The bacteria, fungi, viruses, and mites are among the microorganisms that interact with host cells to alter both innate and adaptive immunity, thereby influencing skin health and disease.

Barrier function and immune education

Commensal microbes stimulate keratinocytes to produce antimicrobial peptides such as cathelicidins and defensins, thereby strengthening the epithelial barrier and preventing pathogen invasion [20]. They also contribute to immune education by modulating Langerhans cells and dermal dendritic cells, ensuring effective immune surveillance.

Modulation of inflammation: Certain commensals such as Staphylococcus epidermidis produce lipoteichoic acid, which modulates Toll-like receptor signaling and reduces excessive skin inflammation[21]. Additionally, commensal microbiota promote regulatory T cell (Treg) activation, maintaining immune tolerance and preventing chronic inflammatory or autoimmune responses[22].

Pathogen defense: Skin microbiota compete with pathogens for nutrients and space and produce antimicrobial substances such as bacteriocins. For instance, phenol-soluble modulins produced by S. epidermidis inhibit the growth of Staphylococcus aureus [23].

Barrier Function and Immune Education

In order to maintain the integrity of the epithelial barrier and help defend against harmful pathogens, commensal microbes stimulate keratinocytes to produce antimicrobial peptides (AMPs), such as cathelicidins and defensins [24] .Furthermore, the microbiome educates immune cells such as Langerhans cells and cutaneous dendritic cells, which provide a balanced immune surveillance system.

Modulation of Inflammation

Staphylococcus epidermidis and other commensal bacteria create lipoteichoic acid, which can reduce inflammation of the skin by altering Toll-like receptor (TLR) signaling[25] .Commensals have the ability to activate regulatory T cells (Tregs) in order to maintain immunological tolerance and prevent overactivation, which could lead to persistent inflammation or autoimmune skin problems [26].

Pathogen Defense

Commensal microbes can produce bacteriocins, which stop the growth of harmful species, in addition to competing with pathogens for food and space[27].

For example, the phenol-soluble modulins (PSMs) released by S. epidermidis can kill the common skin pathogen S. aureus.

Adaptive Immune Shaping

The skin microbiota influences adaptive immunity by promoting T cells that generate IL-17A and IL-22, which are essential for epithelial defense and repair[28].

Microbial antigen exposure may impact the ratio of Th1, Th2, and Th17 responses in T cells in skin-draining lymph nodes.

Key microbial taxa and immune regulation: The skin cancer known as Merkel cell carcinoma (MCC) is extremely aggressive and has a significant immunological component. Among the many different components of the tumor microenvironment are CD8 T cells, which are essential for launching a successful immune response[29,30]. One important immunosuppressive characteristic of MCC is the high expression of CD200, an immunoregulatory ligand that is known to stimulate the growth of regulatory T cells and M2 macrophages, hence reducing anti-tumor immunity[31-32] .In spite of this, MCC can still advance when immune monitoring is active, suggesting that immune evasion tactics are involved [32].Targeting immunological checkpoints, specifically PD-1/PD-L1 and possibly CD200, immunotherapies have demonstrated promise in boosting anti-tumor immunity and improved patient outcomes. In order to advance immunotherapeutic methods in MCC, a better knowledge of the interactions among MCPyV status, immunological dynamics, and clinical behavior is necessary.

Dysbiosis and its potential oncogenic influence: An imbalance in the microbial population, known as dysbiosis, has been linked to the emergence of several malignancies, including Merkel cell carcinoma (MCC) and head and neck squamous cell carcinoma (HNSCC). Oral dysbiosis in HNSCC promotes carcinogenesis via genotoxic effects, immunological modulation, and chronic inflammation [33]. Despite the lack of evidence linking dysbiosis to MCC, epigenetic dysregulation is recognized to be a key factor in Merkel cell polyomavirus-driven carcinogenesis [34].The preservation of systemic immunological homeostasis depends on the gut microbiota, which contains between 60 and 80 percent of the body's immune cells. Nonetheless, intestinal dysbiosis can result in immunological dysregulation, persistent inflammation, and the encouragement of carcinogenesis [35]. Numerous cancer forms, including as colorectal, stomach, and breast malignancies, have been linked to these microbial imbalances[36]. In order to clarify the function of the microbiome in the development of cancer and to direct future treatment approaches, it is essential to comprehend the complex interactions among dysbiosis, host immunological responses, and inflammation[36,37].

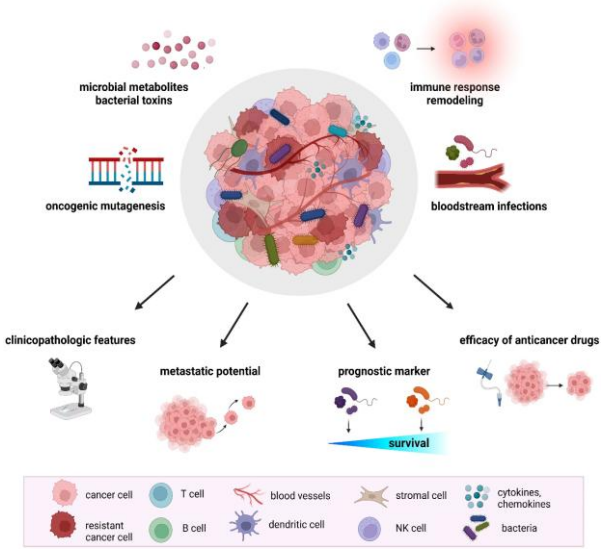

Figure 1: Tumour microbiome in cancer development and treatment.

Tumor microenvironment in MCC: The tumor microenvironment (TME) of Merkel Cell Carcinoma (MCC) comprises malignant cells, immune infiltrates (macrophages, lymphocytes, NK cells, dendritic cells, and myeloid-derived suppressor cells), cancer-associated fibroblasts (CAFs), endothelial cells, and extracellular matrix (ECM) components such as collagen, fibronectin, elastin, and laminin [37,38]. The ECM can constitute up to 60% of tumor mass, where CAF-mediated remodeling promotes therapeutic resistance and suppresses CD8+ T cell–mediated antitumor immunity [39,40] .

MCC tumor vasculature is typically abnormal, characterized by disorganized and poorly structured vessels, leading to hypoxic tumor cores that impair immune cell infiltration and drug delivery. This process is largely driven by dysregulated VEGF-A signaling [41,42]. Additionally, TME interactions are regulated by cytokines, chemokines, growth factors, and extracellular vesicles such as exosomal microRNAs [43,44]. The gut microbiome further influences the TME by releasing metabolites into

systemic circulation, thereby modulating tumor progression and immune responses [45] .

The role of the tumour microbiome in cancer development and treatment. The tumour microbiome influences tumorigenesis and cancer progression through microbial metabolites and bacterial toxins, oncogenic mutagenesis, immune response remodelling, and facilitation of bloodstream infections. These interactions shape clinicopathologic features, metastatic potential, prognostic markers, patient survival, and the efficacy of anticancer drugs. TME constituents shown include cancer cells, resistant cancer cells, T cells, B cells, dendritic cells, stromal cells, NK cells, bacteria, blood vessels, and cytokines/chemokines.

Micrornas as biomarkers and therapeutic targets

MicroRNAs (miRNAs) are small non-coding RNAs with cancer-specific expression patterns, making them promising biomarkers. Circulating and exosomal miRNAs detected in plasma, urine, and saliva provide minimally invasive alternatives to tissue biopsy [46]. In Merkel Cell Carcinoma (MCC), miR-30a, miR-34, and miR-375 have been identified, with miR-375 showing a potential association with Merkel cell polyomavirus-positive tumors [47,48]. Elevated miR-150 levels have been linked to poor prognosis, indicating their role in prognostic stratification [48].

Quantification of circulating miRNAs using real-time PCR may serve as a non-invasive diagnostic and monitoring tool, potentially replacing MCPyV-specific assays. Furthermore, miRNA-based therapeutics, including miRNA mimics and inhibitors (e.g., miR-34), represent an emerging strategy in cancer treatment, though large-scale validation studies are required for clinical translation [46].

Microbiome-targeted therapeutic strategies

Fecal Microbiota Transplantation (FMT): Fecal microbiota transplantation (FMT) involves the transfer of processed stool from a healthy donor to a recipient via colonoscopy, nasogastric tube, or oral capsules. It is an established therapy for recurrent Clostridioides difficile infection and is increasingly being explored as an adjunct in cancer immunotherapy [49] .

Preclinical studies have shown that germ-free mice receiving FMT from anti-PD-1 therapy responders exhibit reduced tumor growth and enhanced immune responses. Specific microbial species such as Akkermansia muciniphila and Faecalibacterium play key roles in modulating antitumor immunity [49]. Early-phase clinical trials in melanoma have demonstrated safety and preliminary efficacy, including increased immune infiltration and tumor regression in some patients [49].

Bacterial Isolates: Targeted supplementation with specific immunomodulatory bacteria represents a controlled microbiome-based therapeutic strategy. Administration of Bifidobacterium species has been shown to enhance the efficacy of PD-L1 inhibitors in murine melanoma models by promoting dendritic cell activation and increasing tumor-specific CD8+ T cell responses [50]. In clinical settings, higher abundance of Bifidobacterium longum has been associated with improved responses to PD-1 inhibitors in melanoma patients. Additionally, Akkermansia muciniphila and Enterococcus hirae have been linked to favorable outcomes in non-small cell lung cancer and renal cell carcinoma [50]. These findings highlight the therapeutic potential of defined bacterial isolates in enhancing cancer immunotherapy responses.

Bacterial Consortia and Probiotics

Bacterial consortia represent a standardized and controlled alternative to fecal microbiota transplantation. A defined consortium of commensal bacteria has been shown to enhance antitumor immunity by increasing interferon-γ (IFN-γ)-producing CD8+ T cells and improving the efficacy of anti–PD-1 therapy in tumor-bearing models, with combined strains demonstrating superior effects compared to individual species [51]. These findings highlight the importance of cooperative microbial interactions, and live biotherapeutic products (LBPs) based on such consortia are currently under clinical development. However, clinical observations indicate that non-prescribed probiotic use may negatively impact immune checkpoint inhibitor (ICI) responsiveness in cancer patients, suggesting that microbiome-based therapies require careful standardization and clinical validation [52]. *Clostridium difficile* infection (CDI) remains a leading cause of antibiotic-associated diarrhea and pseudomembranous colitis, especially within healthcare environments. The growing frequency of recurrent and antibiotic-resistant CDI presents a considerable challenge to treatment efforts. Faecal microbiota transplantation (FMT) has gained recognition as a highly effective treatment for recurrent or treatment-resistant CDI by reestablishing a healthy gut microbiota [53] .

DISCUSSION

The convergence of tumour virology, cutaneous microbiology, and immuno-oncology in MCC pathobiology opens a richly complex research frontier. The MCPyV-positive/negative dichotomy-with distinct mutational landscapes, immune infiltration profiles, and prognostic trajectories-necessitates subtype-stratified microbiome analyses, as differential UV exposure and immunosuppressive backgrounds likely correlate with distinct microbial ecosystems. The gut–skin axis merits particular attention: gut microbiota-derived short-chain fatty acids and other metabolites access systemic circulation and modulate TME composition, suggesting that intestinal dysbiosis may exert distal

Table 1: Comparison of MCPyV-Positive and MCPyV-Negative Merkel Cell Carcinoma

Sl.No.	Feature	MCPyV-Positive	MCPyV-Negative
1	Geographic prevalence	United States & Europe (predominant)	Australia (predominant)
2	Morphology	Pure pattern	Pure and combined pattern
3	Prognosis	Favourable3. Etiology, Pathology, and Tumour Biology	Unfavourable
4	Tumour-infiltrating lymphocytes (TILs)	Brisk (+++)	Sparse (+)
5	Immunohistochemistry	Rb(+++) p53(+) p63(+)	Rb(+) p53(+++) p63(+++)
6	Genetics	TMB low; no RB1/TP53 mutations; no UV mutational signature	TMB high; RB1/TP53 mutations; UV mutational signature

Table 2: FDA-Approved Immune Checkpoint Inhibitors and Indications

Sl.No.	Drug	Target	Approval	FDA-Approved Indication
1	Nivolumab	PD-1	Mar 2015	Stage III-B or IV Squamous NSCLC
2	Pembrolizumab	PD-1	Oct 2016	Stage IV nonsquamous/squamous NSCLC
3	Atezolizumab	PD-L1	Oct 2016	Stage III-B or IV nonsquamous/squamous NSCLC
4	Cemiplimab	PD-1	Sep 2018	Metastatic cutaneous squamous cell carcinoma
5	Ipilimumab	CTLA-4	Aug 2010	Stage 3–4 malignant melanoma
6	Avelumab	PD-L1	Mar 2017	Metastatic Merkel cell carcinoma (first-line)
7	Durvalumab	PD-L1	Feb 2016	Stage III non-small-cell lung cancer
8	Pembrolizumab + cis/carboplatin + pemetrexed	—	Aug 2018	Stage III NSCLC (combination)
9	Pembrolizumab + paclitaxel/ nab-paclitaxel + carboplatin	—	Oct 2018	Stage IV Squamous NSCLC
10	Atezolizumab + carboplatin + paclitaxel + bevacizumab	—	Dec 2018	Stage IV NSCLC

Table 3: Cancer Clinical Trials Investigating Fecal Microbiota Transplantation (FMT)

Sl.No.	Trial No.	Phase	Cancer Type	Intervention
1	NCT03341143	II	Melanoma	FMT (colonoscopy) + immune checkpoint inhibitors
2	NCT03353402	I	Melanoma	FMT (colonoscopy + stool capsules) + immune checkpoint inhibitors
3	NCT03772899	I	Melanoma	FMT + immune checkpoint inhibitors
4	NCT04577729	—	Melanoma	Autologous or allogeneic FMT + immune checkpoint inhibitors
5	NCT04521075	I/II	Melanoma/NSCLC	FMT (stool capsules) + immune checkpoint inhibitors
6	NCT04056026	I	Mesothelioma	FMT (colonoscopy) + immune checkpoint inhibitors
7	NCT04116775	II	Prostate	FMT (endoscopy) + ICI + enzalutamide
8	NCT04130763	I	Gastrointestinal	FMT (stool capsules) + immune checkpoint inhibitors

Table 4: Clinical Trials Investigating Defined Bacterial Isolates in Cancer Immunotherapy

Sl.No.	Trial No.	Phase	Cancer Type	Intervention
1	NCT03775850	I/II	Solid tumours	EDP1503 (Bifidobacterium capsule) + pembrolizumab
2	NCT03595683	II	Melanoma	EDP1503 (Bifidobacterium capsule) + pembrolizumab
3	NCT03829111	I	Renal cell carcinoma	CBM588 (Clostridium butyricum probiotic) + nivolumab + ipilimumab
4	NCT03637803	I/II	Solid tumours	MRx0518 (Enterococcus gallinarum capsule) + immune checkpoint inhibitors

Table 5: Intervention of Previous Trials done

Sl.No.	*Trial No.*	*Phase*	*Cancer Type*	*Intervention*
1	NCT03686202	I	Solid tumours	MET-4 (defined bacterial consortia) + immune checkpoint inhibitors
2	NCT03817125	Ib	Melanoma	SER-401 (defined bacterial consortia) + immune checkpoint inhibitors
3	NCT01895530	—	Colorectal	Probiotic Saccharomyces boulardii supplementation
4	NCT03072641	—	Colorectal	ProBion Clinica (Bifidobacterium lactis, Lactobacillus acidophilus, inulin)
5	NCT03782428	—	Colorectal	Probiotic with six Lactobacillus spp. and Bifidobacterium spp.
6	NCT03358511	—	Breast	Over-the-counter probiotic with 13 bacterial species

effects on cutaneous tumour immunogenicity. Pre-treatment microbiome profiling-incorporating both cutaneous and gut communities via shotgun metagenomics and 16S rRNA sequencing-may yield predictive signatures for ICI responsiveness. The therapeutic promise of microbiome modulation is

tempered by significant challenges: interindividual microbiome variability, lack of standardised microbial fingerprints, and the failure of germ-free preclinical models to fully recapitulate the complexity of the human microbiome-immune axis. Standardising therapeutic microbial compositions and establishing whether strain combinations outperform monocultures in enhancing ICI efficacy are priorities for the next generation of microbiome-oncology trials.

CONCLUSION

MCC is a virally- and UV-driven cutaneous malignancy in which the cutaneous microbiota emerges as a critical and previously underappreciated regulator of immune homeostasis, TME composition, and therapeutic responsiveness. Dysbiosis-mediated immune evasion, modulation of ICI efficacy, and the potential for microbiome-targeted interventions represent compelling translational opportunities within a precision oncology paradigm. Integration of microbiome profiling with MCPyV status, tumour stage, and immune biomarkers into prospective MCC clinical trials is essential to develop validated predictive signatures and realise the full potential of individualised, microbiome-informed immunotherapy, ultimately translating mechanistic insights into improved patient outcomes for this rare but lethal malignancy.

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Informed Consent: Informed consent was not applicable, as no individual patient data were collected or analyzed in this study.

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