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MELANOMA (KIM MARGOLIN, SECTION EDITOR)

Immunobiology of Merkel Cell Carcinoma: Implications for Immunotherapy of a Polyomavirus-Associated Cancer

Shailender Bhatia · Olga Afanasiev · Paul Nghiem

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Abstract Merkel cell carcinoma (MCC) is an aggressive skin malignancy with a high mortality rate and an increasing incidence. The recent discovery of Merkel cell polyomavirus has revolutionized our understanding of MCC pathogenesis. Viral oncoproteins appear to play a critical role in tumor progression and are expressed in the majority of MCC tumors. Virus-specific humoral and cellular immune responses are detectable in MCC patients and are linked to the natural history of the disease. Despite persistent expression of immunogenic viral proteins, however, MCC tumors are able to evade the immune system. Understanding of the mechanisms of immune evasion employed by MCC tumors is rapidly increasing and offers opportunities for development of rational immune therapies to improve patient outcomes. Here we review recent discoveries in MCC with a special focus on the pathogenic role of Merkel cell polyomavirus and the immunobiology of this virus-associated disease.

Keywords Merkel cell carcinoma · Immunotherapy · Merkel cell polyomavirus · MCV · MCPyV · Cancer virus · Viral cancer · Immune evasion · Immune escape · MHC · Tumor immunology · Tumor infiltrating lymphocytes · TILs · Viral oncoproteins · T-antigen · Immune suppression

S. Bhatia (✉)
Departments of Medicine/Medical Oncology,
University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance,
825 Eastlake Avenue E, G4830, Seattle, WA 98109, USA
e-mail: sbhatia@uw.edu

O. Afanasiev
Departments of Medicine/Dermatology, Pathology,
University of Washington,
815 Mercer Street,
Seattle, WA 98109, USA
e-mail: olga54@uw.edu

P. Nghiem
Departments of Medicine/Dermatology, Pathology,
University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance,
815 Mercer Street,
Seattle, WA 98109, USA
e-mail: pnghiem@uw.edu

Introduction

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer with a disease-associated mortality three times that of malignant melanoma (46% vs 15%, respectively) [1•]. MCC is an uncommon cancer with an estimated 1,600 cases/year in the US [2, 3]. The reported incidence has more than tripled over the past 20 years [3, 4], and the health impact of MCC is growing rapidly with the proportional increase in the aging population [2, 3]. This increasing incidence is in part due to improved detection following availability of a specific immunohistochemical marker, cytokeratin-20 [5], but is also likely due to the higher prevalence of known risk factors for MCC: T-cell immune suppression and Caucasians over 50 years of age with extensive prior sun exposure [6]. MCC now kills more patients than cutaneous T-cell lymphoma and a similar number as chronic myelogenous leukemia, both well-known and frequently studied cancers [2, 7, 8].

MCC is an aggressive cancer with prognosis dependent on the stage at presentation. Stages I and II represent low-risk and high-risk primary disease, respectively, while stages III and IV represent the presence of nodal and distant metastases, respectively. The reported 5-year relative survival for patients with local, nodal, and metastatic disease is 64%, 39% and

18%, respectively [1•]. Although surgery and/or radiation therapy (RT) may be curative for patients with locoregional MCC without distant metastases, relapses are common and often incurable. There is no established adjuvant therapy after definitive management. For patients with distant metastatic disease, systemic chemotherapy is considered. The objective response rate (ORR) with platinum-based chemotherapy regimens is around 60% [9]; however, responses are usually short-lived and the impact on survival is unclear. Also, the chemotherapy regimens are associated with significant toxicity and may not be suitable for many MCC patients who usually tend to be older with multiple comorbidities. There are no established second-line treatments for patients who have progressed on initial systemic chemotherapy regimens. There is therefore a strong and unmet need for novel, biology-driven therapies in this disease.

Fortunately, rapid strides are being made in our understanding of the biology of MCC that have opened up new avenues for investigation of rational therapies in this aggressive disease. We review the recent discoveries in MCC, with a special focus on the emerging importance of immune mechanisms in the pathogenesis of this disease.

Link with Immune Suppression Leads to Discovery of Merkel Cell Polyomavirus

Epidemiologic data suggest a strong link between MCC and the immune system. Individuals with T-cell dysfunction (solid organ transplant recipients [10, 11], HIV-infected patients [12], or chronic lymphocytic leukemia patients [6]) are at fivefold to 50-fold increased risk of developing MCC. MCC tumors sometimes regress following improvement in immune function [13, 14], underscoring the importance of immune surveillance in the development of MCC. Additionally, there are several reported cases of complete spontaneous regression in the MCC literature (a far greater number than expected for its rarity) that suggest a sudden recognition by the immune system leading to the clearance of MCC [15–20]. These epidemiologic data raised the possibility of an infectious etiology for MCC. Indeed, the recent discovery of the Merkel cell polyomavirus (MCV or MCPyV) has provided the missing link between MCC and its association with immune suppression [21••].

The Merkel cell polyomavirus was discovered in 2008 [21••]. Yuan Chang, Patrick Moore, and their colleagues created cDNA libraries from MCC tumor mRNA and used the Digital Transcriptome Subtraction method to identify a novel transcript with high homology to the African green monkey lymphotropic polyomavirus (AGM LPyV). The circular genome of MCPyV (~5,200 base pairs) has an early gene expression region containing the oncoprotein tumor (T) antigen locus with large T (LT) and small T (ST) open reading frames. A late gene region contains the viral structural proteins that encode capsid proteins. MCpyV was found to have the highest homology with the murine polyomavirus subgroup (includes AGM LPyV) and lesser homology to the known human polyomaviruses (BK or JC viruses) or to simian virus 40 (SV40). PCR-Southern hybridization revealed MCPyV sequences to be present in 8 of 10 (80%) MCC tumors, but uncommon in non-MCC tissues (8%) and normal skin or non-MCC skin tumor tissues (16%), suggesting strong association between MCPyV infection and MCC. The monoclonal pattern of integration of the viral genome into the tumor genome was suggestive of MCPyV infection and genomic integration prior to or very early in tumorigenesis. Since the original description of the virus in 2008, several groups around the world have independently verified the association between MCPyV and MCC [22–26•, 27, 28].

Epidemiology of MCPyV Infection

Similar to the other known human polyomaviruses (BK, JC, KI, and WU viruses) [29], exposure to MCPyV as measured by serum antibodies to viral capsid proteins appears to be widely prevalent among healthy subjects [30–32]. In one study, the prevalence of MCPyV seropositivity was 0% in infants, 43% among children aged 2–5 years old, and increased to 80% among adults older than 50 years [30]. A similar trend of increasing seroprevalence with age was seen in another study, suggesting that primary exposure to MCPyV occurs during childhood [29]. Consistent with the serologic data, MCPyV DNA was detected in cutaneous swabs from clinically healthy subjects with a prevalence of 40%–100% in three independent studies [33–35]; it appears that the virus is being shed chronically from clinically normal skin in the form of assembled virions [33]. Besides the skin, viral DNA has been detected in lower frequencies among respiratory secretions, on oral and anogenital mucosa, and in the digestive tract [36–41]. The exact mode of transmission remains to be elucidated and could involve cutaneous, fecal-oral, mucosal, or respiratory routes. Importantly, although widely prevalent, active MCPyV infection appears to be asymptomatic and with the exception of MCC, this virus has not yet been convincingly associated with any other human disease.

Role of MCPyV in Pathogenesis of MCC

Cancer-associated viruses may contribute to carcinogenesis directly via expression of viral oncogenes that promote cell transformation or indirectly via chronic infection and