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Immunobiology of Merkel cell carcinoma: implications for immunotherapy of a polyomavirus-associated cancer

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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

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].

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MCC is an uncommon cancer with an estimated 1600 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 Caucasian 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 loco-regional 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 percent [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 co-morbidities. 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 5- 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 (∼5200 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 [22-28].

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 3 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 inflammation, which may predispose host cells to acquire carcinogenic mutations [42]. Polyomaviruses are a genus of non-enveloped viruses with a circular double-stranded DNA genome of approximately 5000 base pairs. The ability of certain polyomaviruses to transform mammalian cells is well known. The best studied example is the SV40 polyomavirus that was originally discovered in the primary monkey kidney cells used to

prepare polio vaccines. Alarmingly, SV40 was found to induce multiple tumors in newborn hamsters [43]). Fortunately, despite their prevalence, the known polyomaviruses other than MCPyV have not been associated with formation of any human tumors. Typically, human polyomavirus infection is asymptomatic except in immunosuppressed individuals who can develop nephropathy (BK virus) or progressive multifocal leukoencephalopathy (JC virus). In humans, MCPyV is the first polyomavirus with demonstrated integration into genomic DNA. Several significant observations suggest that MCPyV contributes to the pathogenesis of MCC (Figure 1): (1) it is present in a substantial portion of MCC tumors [21]; (2) monoclonality of MCPyV integration in MCC tumor cells suggests viral integration is an early event in tumorigenesis [21]; and (3) LT antigen transcript and protein is expressed in most MCC tumors, (4) the MCPyV LT antigen expressed in MCC tumors is truncated due to mutations that preserve critical cell-cycle progression functions, but eliminate cell-lethal virus-replication activities [44] and (5) persistent expression of these MCPyV proteins is required for continued growth of MCC cell lines in vitro [26]. These findings strongly suggest that MCPyV plays a key role in MCC carcinogenesis rather than merely being a passenger virus that secondarily infects tumor cells.

The MCPyV LT antigen appears to retain the major conserved features of other polyomavirus LT antigens, including the DnaJ motif (binds to heat-shock proteins) and the LxCxE motif (inactivates retinoblastoma family proteins), and the origin-binding and helicase/ATPase domains (promote viral replication) [44]. These various domains allow the polyomaviruses to use host cell machinery for viral genome replication, but can also target tumor suppressor proteins resulting in cellular transformation [45]. The LT antigen transcripts are commonly expressed in MCC tumors [44]. However, tumor-specific truncating mutations retain LT-antigen DnaJ and LxCxE motifs that promote cellular growth, but eliminate origin-binding and helicase domains that are essential for production of progeny virions [44]. This acquired inability of tumor-derived LT antigen to initiate constitutive viral genome replication protects virus-infected tumor cells from apoptosis triggered by DNA-damage response mechanisms.

The mechanisms by which MCPyV may contribute to MCC carcinogenesis continue to be elucidated. MCPyV T antigen appears to be essential for cell survival among tumors infected with the virus. In MCPyV-infected MCC cell lines and xenograft models, the expression of T-antigen appears to be essential for sustained proliferation; knockdown of this viral protein leads to growth arrest and/or cell death while restoration of T-antigen expression rescues cell growth [26, 46]. Furthermore, interaction with the retinoblastoma (Rb) tumor suppressor protein appears to be critical to the observed growth-promoting effects of LT antigen [46]. Immunohistochemistry (IHC) data from human MCC tumors shows strong positive association between tumor Rb expression and MCPyV LT-antigen expression with LT-antigen positive MCC tumors also expressing Rb and 87% of LT-antigen negative tumors being Rb-negative as well [47, 48]. Similar to the well-characterized interactions between SV40 LT-antigen and the Rb family of proteins (Rb, p107, p130), the MCPyV LT-antigen is likely to sequester hypophosphorylated Rb that usually binds to E2F transcription factors. This sequestration of Rb allows E2F-mediated transcription that leads to the entry of the cell into S-phase. The integrity of the DnaJ- and the LxCxE-motifs is required for this mechanism in SV40, and the retention of these

domains (with intact Rb-binding ability) in the truncated MCPyV LT-antigen is consistent with this mechanism being relevant to MCC pathogenesis.

The other putative mechanism by which polyomaviruses contribute to transformation is interference with the p53 tumor suppressor pathway. The usual functions of p53 are not conducive to viral replication as p53 transactivates genes that lead to cell cycle arrest, which could deprive the virus of essential replication factors. Additionally, active p53 could lead to cellular apoptosis in response to the presence of viral or cellular oncoproteins. In order to complete their normal infectious cycles, the polyomaviruses have developed the ability to block p53 function through several mechanisms. The bipartite domain of the SV40 LT-antigen can bind directly to the specific DNA binding domain of p53, hence interfering with p53-dependent gene transcription [49, 50] (this binding has also been shown to increase the half-life and steady-state levels of p53 in cells [51]. As the MCPyV LT-antigen seems to be prematurely truncated in the MCC tumor cells lacking the helicase domain and the supposed p53-binding sites [44], the significance of the p53 pathway in pathogenesis of MCPyV-associated MCC is unclear. However, even if the truncated T-antigen does not bind to p53, MCPyV may play a role in suppressing p53 function in MCC tumors via other mechanisms. For example, there is evidence that the binding of T-antigen to p53 in SV40 may not be sufficient to block p53 function and that other indirect mechanisms (involving small T-antigen and/or the J- and Rb-binding domains of the LT-antigen) are also important in functional suppression of p53 [52, 53]. Consistent with MCPyV somehow disabling p53 function in MCC tumors, inactivating mutations in TP53 gene and/or overexpression of p53 have been seen only in a small subset of MCC tumors [54, 55]. Moreover, recent studies have indicated an inverse relationship between p53 expression and MCPyV viral abundance in MCC tumors as well as p53 overexpression potentially being associated with poor outcome [56, 57].

In addition to the processes described above, there are likely additional mechanisms by which MCPyV contributes to the development/maintenance of MCC tumors. While some of these pathways may also be relevant to MCPyV-negative MCC tumors (albeit via non-viral mechanisms), the virus-associated MCC subgroup is likely to have important biological distinctions from the virus-negative subgroup. Understanding the molecular mechanisms that contribute to disease progression in various MCC subgroups will be crucial to the development of mechanism-based targeted therapies for this disease.

Immunology of Merkel Cell Cancer

The discovery of MCPyV and its role in MCC pathogenesis raise several interesting questions about interactions between the host immune system and MCC tumor cells. The sero-epidemiologic data (discussed above) suggests that exposure to MCPyV is widely prevalent and that viral capsid proteins are recognized by the human immune system in infected individuals [30, 31]. Also, as discussed above, MCC tumor cells commonly express the MCPyV LT antigen [44, 58] and the LT antigen is essential for continued growth of cells infected with the virus [26, 46]. Despite this persistent expression of viral proteins, however, MCC tumor cells are somehow able to evade the immune system. While this can be explained by the presence of generalized T-cell dysfunction in a small subset of MCC

patients with comorbidities such as HIV-infection, immunosuppressive medications or concurrent hematologic malignancies, the vast majority (>90%) of MCC patients have no clinically apparent immune dysfunction [6]. Our understanding of host-virus immune interactions in MCC pathogenesis is increasing rapidly with new insights into the humoral and cellular immunity in MCC patients (Figure 1).

Humoral immune response

Although the prevalence of antibodies to viral capsid proteins (VP) in the general population is high, all studies have found that IgG antibodies to MCPyV VP1 and VP2 are even more prevalent in MCC patients [27, 30, 31, 59]. Interestingly, the titer of antibodies to viral capsid proteins is typically higher in MCC patients than in control populations [30-32]. This finding is not attributable to increased viral capsid antigen production by tumor cells because MCC tumor cells do not express viral capsid proteins [31, 32]. One possible explanation for higher antibody titers in MCC patients could be exposure to a greater virus burden in MCC patients. Supporting this hypothesis, the MCPyV DNA levels in cutaneous swabs from MCC patients were found to be significantly higher than levels in control population [34] and another study reported a positive correlation between serum MCPyV antibody titers and MCpyV DNA levels in skin biopsies [59]). The apparently higher virus burden in MCC patients could possibly be a risk factor that predisposes to subsequent development of MCC in these patients; alternatively, the development of MCC could somehow have resulted in a MCPyV-specific immunodeficiency that leads to the higher virus levels on the skin of MCC patients (further discussed below). Interestingly, higher anti-MCPyV capsid antibody titers have also been associated with better progression-free survival in MCC patients [32]; whether this indicates the presence of a more robust host immune system remains unclear.

The limited serologic data from patients with MCPyV-negative MCC tumors suggests that the majority of these patients have been exposed to MCPyV [27], and in many patients, antibody titers can be very high, similar to patients with MCPyV-positive MCC [30]. This raises the fascinating possibility of MCPyV infection possibly playing a role in tumor initiation with subsequent selection for less immunogenic, MCPyV-negative MCC tumor subclones in these patients. Indeed, the heterogeneity of MCPyV DNA or T-antigen expression levels in MCC tumors supports immune selection within the tumors and is consistent with the ‘hit and run’ hypothesis for tumorigenesis in MCPyV-negative MCC tumors.

As compared to antibodies to viral capsid proteins, antibodies to MCPyV T-Ag oncoproteins are more specifically associated with MCC; these antibodies are rarely detected in the general population (<1%) but appear to be present in a substantial proportion (∼40%) of patients with active MCC [60]. Importantly, the titer of antibodies to T-antigen oncoproteins correlates strongly with the presence of MCPyV DNA and the expression of T-antigens in MCC tumor cells [60]. Moreover, the antibody titer to T-Ag oncoproteins can potentially serve as a biomarker of MCC disease burden; the antibody titer drops rapidly after successful treatment of MCC tumors and a rising titer in a previously treated patient has been shown to herald disease progression prior to development of symptoms [60]. This

apparent correlation between the humoral response to T-antigens and MCC disease burden is not completely unexpected because T antigen expression is selectively linked to MCC tumors. Specifically, in contrast to viral capsid proteins that are readily visible to the host humoral immune system, T-antigens are not present in viral particles, are only expressed after viral entry into host cells, are located in the nucleus [61], and are thus less likely to trigger an antibody response except in the setting of dying or diseased tissue (such as a tumor that persistently expresses T-antigens).

Cellular immune response

The presence of MCPyV T-antigen specific antibodies that appear to correlate with tumor burden in MCC patients [60] suggests ongoing expression of viral proteins in tumor cells and their recognition by the adaptive arm of the immune system. Histologic analyses have revealed the presence of variable numbers of tumor-infiltrating lymphocytes (TILs) in the MCC tumors with possible prognostic significance [62]. Our group has recently documented that intratumoral (but not peritumoral) infiltration of CD8+ lymphocytes is an independent predictor of improved survival among MCC patients. In this study, unbiased gene expression analyses revealed overexpression of immune response genes in tumors with favorable prognoses. These immune response genes included genes that encode components of cytotoxic granules (granzymes), chemokines (CCL19), lymphocyte-activation molecules and CD8 receptor molecules [63]. Importantly, in an independent cohort of 156 cases, patients with robust CD8+ intratumoral infiltration had 100% MCC-specific survival as compared to 60% survival among patients with sparse or no CD8+ intratumoral infiltration [63]. This evidence highlights the important role of cellular immune responses in the natural history of MCC and further explains the increased incidence of MCC in patients with cellular immune suppression. While the antigen specificity and differentiation phenotype of infiltrating CD8+ T cells in MCC tumors are yet to be defined, the MCPyV-specific T cell response could presumably be an excellent target for therapeutic manipulation in MCC patients.

Immune evasion mechanisms in MCC

Despite the expression of immunogenic virus-encoded oncoproteins in the majority of tumors [44, 60], MCCs that became clinically evident were significantly able to evade host immune responses. According to the cancer immunoediting hypothesis [64], development of tumors generally requires cancer cells to navigate successfully through three distinct (and usually sequential) phases of the interaction between the cancer and the host immune system: (1) *Elimination phase*, an immunosurveillance phase in which the innate and adaptive immune systems work together to detect the presence of nascently transformed cells and destroy them before a tumor becomes clinically apparent; (2) *Equilibrium phase*, a tumor dormancy phase in which the adaptive immune system restrains the outgrowth of tumors and sculpts the immunogenicity of the tumor cells; (3) *Escape phase*, a tumor progression phase in which the tumor cells are able to circumvent the host immune response manifesting as clinically progressing tumors. The lack of a good animal model for MCC pathogenesis and the inherent challenges of conducting longitudinal studies in at-risk individuals for a rare cancer render it difficult to study the precise events during the

elimination and equilibrium phases of MCC tumorigenesis. However, the potential mechanisms of immune escape by MCC tumors are becoming increasingly apparent (Figure 1).

The progression from equilibrium to the escape phase may occur due to changes in tumor cell population that may acquire new immune evasive characteristics or due to changes in the host immune system that may get suppressed either generally or more selectively toward the tumor cells. Both of these broad mechanistic categories appear relevant to MCC:

1. ***Tumor cell changes***: Under the pressures of immune selection, MCC tumor cells may acquire new features to become either “less visible” to the immune system or “more resistant” to the effects of the cytotoxic immune cells. The former may occur via loss of tumor antigen expression. Cell surface major histocompatibility complex class I (MHC-I) serves to present intracellular peptides to CD8+ T lymphocytes; specifically, viral oncoproteins expressed in MCC tumor cells would be presented to T cells via MHC-I. Indeed, multiple viruses (eg. adenovirus and HSV) and virus-associated cancers (e.g. Kaposi's sarcoma, cervical cancer) are known to directly or indirectly down-regulate the expression of MHC-I as a key mechanism of immune escape [65-70]. Besides MHC-I loss, dysregulation of other components of cellular antigen presenting machinery such as the transporter associated with antigen processing (TAP) [71] or downregulation of appropriate tissue-specific T cell homing signals may also preclude the presentation of persistently expressed tumor antigens to T cells and need to be investigated further in MCC. Indeed, our laboratory findings suggest that 46% of MCC tumors exhibit a 'stalled phenotype' of lymphocytic infiltration where CD8+ cells accumulated near the tumor-stroma border but were unable to infiltrate into the tumors [63]. Such ‘peritumoral’ T cells were not associated with significantly improved survival. These features together likely lead to poor visibility of the MCC tumor cells to the immune system and may explain the sparse infiltrates of T cells in most MCC tumors that are associated with poor outcomes [63]. Another important adaptation at the tumor cell level that can result in immune escape is increased resistance of the tumor cell to immune control mechanisms. Innate immune signaling networks and tumor suppressor pathways share some key proteins such as p53 [72] and cyclin-dependent kinase inhibitor p21 [73]. Due to this functional overlap, the targeting of tumor-suppressor pathways by MCC oncoproteins may also serve as an immune evasion mechanism for MCC. In addition, tumor cells may secrete proteins that interfere with the functioning of the immune cells (discussed below).
2. ***Immune system changes***: Immunosuppression resulting in T-cell dysfunction may predispose to the immune escape of transformed cancer cells; however, clinically evident systemic immunosuppression due to comorbidities such as post-transplant status, concurrent hematological malignancy, HIV infection etc. is present only in fewer than 10% of MCC patients. What may be of even greater relevance to the pathogenesis of MCC, a disease of the elderly population, could be the altered phenotype and functional incapacity of an aging immune system that allows the development and progression of the disease (Figure 1). This phenomenon of

immunosenescence, an erosion of the immune response with aging, is associated with phenotypic and functional changes in both innate and adaptive arms of the immune system, including a contracted repertoire of naïve and cytotoxic T-cells and impaired function of effector T cells [74]. Ultraviolet radiation (UVR), another risk factor for MCC, may not only promote critical LT-antigen mutations and ST-antigen upregulation [75], but may also play a key role in cutaneous immune system inhibition and tolerance [76]. Specifically, UVR has been implicated in recruitment of regulatory T cells and in inhibition of antigen presentation via direct damage to antigen presentation cells (APCs) or via functional inhibition of APCs by cytokines (interleukin 10, tumor necrosis factor-alpha) released by keratinocytes and mast cells [77, 78]. In addition to systemic immune dysfunction contributing to immune escape, it is likely that MCC tumor cells establish a local immune suppressive microenvironment in order to thrive. In this scenario, immunologically sculpted tumor cell subclones may overproduce immunosuppressive cytokines, such as TGF-β [79], Fas-L [80], IL-10 [81] or inhibitors of T cell responses such as galectin-1 [82] and indoleamine 2,3-dioxygenase (IDO) [83]. Tumors could also suppress proinflammatory danger signals through pathways involving activated STAT3, leading to impaired dendritic cell maturation [84] or could downregulate the NKG2D receptor on immune effector cells by secretion of soluble forms of the MIC NKG2D ligands thereby attenuating lymphocyte-mediated cytotoxicity [85]. Tumor cells may also facilitate the generation, activation, or function of immunosuppressive cells [86], such as CD4+CD25+ regulatory T cells (T-regs) [87] or myeloid-derived suppressor cells [88]. T-cell exhaustion, originally described in the context of chronic viral infection in mice [89, 90], is being found to be increasingly relevant to human cancers. In response to chronic antigen exposure, antigen-specific CD8+ T-cells often develop an exhausted phenotype with poor effector function, sustained expression of inhibitory receptors, and a transcriptional state distinct from that of functional effector or memory T cells. The final stage of exhaustion may involve physical deletion of antigen-specific T cells [89, 91]. In the context of viral infection, more severe CD8+ T cell exhaustion has been correlated with higher viral load. Moreover, in the setting of the same viral load, epitopes that were present in larger amounts led to more extreme exhaustion and/or deletion than epitopes present in smaller amounts [91]. This phenomenon may possibly be relevant in MCC as well and could explain the observed higher MCPyV viral load on the skin of MCC patients as compared to the general population (discussed above) if MCPyV-specific T cells are exhausted by chronic antigen exposure in the tumors and hence fail to suppress MCPyV colonization [34]. The interaction of programmed death (PD)-1 expressed on T-cells with its ligand B7H1 or PDL-1 is an important mechanism of T-cell exhaustion [92] that could be harnessed for therapeutic purposes.

Moving towards biology-driven immunotherapy

The discovery of the MCPyV and the increasing recognition of the importance of the immune system in MCC pathogenesis suggest several new targets for therapeutic exploration; rational immunotherapeutic approaches can possibly advance outcomes for this

aggressive disease. The critical role of viral oncoproteins in tumorigenesis of MCPyV-positive MCC tumors and the resultant cellular expression of viral peptides could not only be exploited to develop virus-targeting therapies interfering with the function of the oncoproteins, but also be harnessed to stimulate immune responses against virus-infected tumor cells. As an example, the T-antigen specific antibody response is confined to a 78 amino acid N-terminus domain shared by the small- and large- T-antigens [60], which could provide a suitable vaccine or adoptive T-cell therapy target. Similarly, other non-viral tumor associated-antigens such as survivin [93] or the oncoprotein HIP1 that interacts with c-KIT [94] may also be suitable immunotherapy targets. Immunostimulatory cytokines, such as Interferons, interleukin(IL)-2, IL-12, IL-15, or IL-21 could be delivered systemically or intratumorally to counteract immune evasion mechanisms employed by MCC tumors. A phase II trial using intratumoral delivery of IL-12 followed by in vivo electroporation of MCC tumors will be opening to accrual soon. Other therapeutic agents that look appealing to investigate for MCC treatment include CTLA-4 receptor blocking agents such as Ipilimumab (recently approved by FDA for metastatic melanoma), drugs targeting the PD-1/PDL-1 pathway to reverse immune exhaustion of infiltrating lymphocytes or drugs targeting the costimulatory 4-1BB pathways that could promote T cell infiltration, proliferation and cytokine production [95, 96].

Given the heterogeneity of MCC tumors and individual variations in host immune systems, it is unlikely that one single approach will be effective in all patients. Rather, a combination of various strategies and personalization to the unique biologic characteristics of MCC tumors in individual patients will be required. Nevertheless, it is an exciting time for investigation of novel targeted and/or immune therapies in this fascinating malignancy.

Conclusion

The discovery of Merkel cell polyomavirus has revolutionized our understanding of MCC pathogenesis. The immune system appears to be playing a major role in MCC biology with increasing evidence of virus-specific cellular and humoral immune responses that influence the prognosis of MCC patients. MCC tumors are able to evade the immune system by establishing a local immunosuppressive microenvironment. Understanding the mechanisms of immune evasion by MCC tumors will offer opportunities for development of biologically driven therapies to improve patient outcomes from this often-lethal virus-associated cancer.

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* Of importance

** Of outstanding importance

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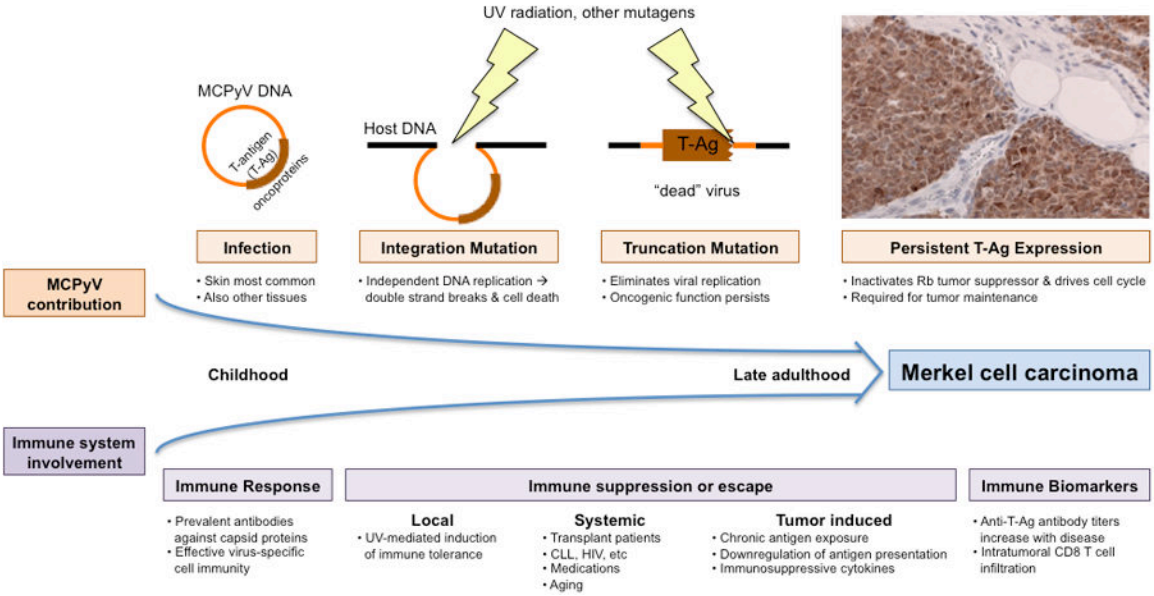

Figure 1. Although infection with MCPyV is common, a progression of several rare mutagenic events and escape from immune surveillance likely precede the development of Merkel cell carcinoma

Infection with MCPyV occurs early in childhood [30], is clinically asymptomatic and likely induces an appropriate humoral and cellular immune response. Ultraviolet (UV) radiation or other environmental mutagens may mediate virus integration into the host genome and Large T (LT)-antigen truncation mutations [44]. These sequential mutational events result in persistent T-Ag expression (brown stain with IHC anti-LT antibody, CM2B4) that plays a key role in MCC pathogenesis [26, 42, 46]. Importantly, in parallel, local, systemic or tumor induced loss of immune surveillance may allow for an unsupervised increase in both wild-type virus burden and T-Ag dependent MCC disease. Oftentimes, disease progression can be monitored via immune biomarkers such as anti-T-Ag antibody levels [60] and disease outcome can be predicted by levels of CD8 T cell infiltration [63].