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Viral Etiology of Merkel Cell Carcinoma:Implications in Diagnosis, Prognosis, Therapy and Prevention

Editorial

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Merkel cell carcinoma (MCC) is a rare and a highly aggressive skin cancer of neuroendocrine origin that is frequently associated with a poor prognosis, a clonal integration of a polyomavirus (MCPyV), and a high propensy for recurrence and metastasis; its incidence increases with age, immunodeficiency and sun exposure [2, 4, 5, 6, 8]. Importantly, cytokeratin 20 (CK20) is expressed in approximately 95% of MCC cases, MCPyV in about 80% of cases, and MCPyV is less common in CK20-negative MCC [6]. The disease progression could be evaluated by means of high numbers of mitoses, proliferation and survival of tumour cells as marked by Ki-67- and Bcl-2-staining, and infiltration of lymphatic vessels [12]. Moreover, a recent meta-analysis using random effects model revealed that there is an increased risk for second malignancies due to MCC (e.g. malignant melanoma) [9]. In fact, the origin of MCC is rather controversial, its pathogenesis (e.g. the molecular mechanisms underlying MCC development after MCPyV infection) remains unclear, and MCC seems to be a heterogenous entity with distinct subtypes [2, 3]. Indeed, while the presence of neurosecretory granules and expression of specific biomarkers (i.e. PGP 9.5, chromogranin A and several neuropeptides) has suggested that MCCs originate from one of the neurocrest derivatives, most probably Merkel cells, zurHausen et al. hypothesized that they could originate from early B cells since they commonly express. Terminal deoxynucleotidyl Transferase (TdT) and Paired Box Protein-5 (PAX5), which are restricted to pro/pre-B cells and pre-B cells when co-expressed under certain physiologic circumstances [3].

Interestingly, Merkel cell polyomavirus (MCPyV), identified in 2008 as a clear first causal agent underlying a human cancer, suggests that healthy human skin harbors resident or transient MCPyV critically capable of neoplastic transformation [7, 8]. In this context, MCPyV was recently classified as a 2A carcinogen based on a consensus staging system for MCCs adopted worldwide in 2010, which replaced anyone of the five unique systems in active use [7, 8]. The consensus system that includes sub-stages that reflect prognostic differences based on whether nodal evaluation was performed by histopathology analysis or clinical assessment alone, has improved the ability to track and manage this malignancy [7]. MCPyV, and MCC tumor cells express putative polyomavirus on coprotein small T antigen (sTAg) with robust transforming activity *in-vivo* as well as a truncated large T antigen (lTAg) [11, 13]. In patients who produce antibodies to the viral T-antigen on coprotein, the titer increases and decreases with MCC disease burden and can be a clinically useful marker of recurrence [7]. Importantly, epithelial transformation strictly depends on a recently described MCPyVsTAg domain interaction with Fbxw7, the substrate-binding component of the Skp1/Cullin1/F-box (SCF) protein ubiquitin ligase complex [11]. Furtheremore, using a proteomic quantitative approach, another recent study showed that MCPyVsTAg expression promotes microtubule destabilization, via the involvement of microtubule-associated protein stathmin and its association with cellular phosphatase catalytic subunit protein phosphatase 4C (PP4C), leading to a motile and migratory phenotype, suggesting eventually a molecular mechanism for the highly metastatic phenotype associated with MCC [4]. These findings highlight stathmin as a possible biomarker of MCC and as a target for novel anti-tumor therapies. In the other hand, phosphorylation at Ser-816 in the C-terminal domain of the lTAg is ATM kinase-dependent, which led to anti-tumorigenic properties induced by MCPyV [5]. This report shows that radiotherapy could be efficient to treat polyomavirus-positive MCC. The characterization of downstream targets of ATM, such as p53 and p21, as well as the possible involvement of crossing signaling pathways, could be an asset for the better understanding of the mechanistic molecular regulation of the polyomavirus-positive MCC pathogenesis. Eventually, the insignificant difference of protein expression (activation) in most Akt (Kinase involved in the cell survival)/mTOR (rapamycin)/4E-BP1 (4E-binding protein 1) pathway signals both in MCPyV-positive and MCPyV-negative MCCs, although these two types may differ in tumorigenesis, suggest that Akt/mTOR/4E-BP1 pathway signals could be novel therapeutic targets for MCC regardless of MCPyV infection status.

Recent years have brought an enhanced understanding of MCC biology, especially with regard to the MCPyV as the most representative causative agent. Differences between polyomavirus-positive and polyomavirus-negative MCCs in morphology, gene expression, signaling pathways, genomic and epigenetic alterations,

microRNA profiles, dysregulated immune surveillance, aberrant protein expression, post-translational modifications have been reported, which participate to the inter-individual prognosis variations. For instance, mutations, including TP53, retinoblastoma (RB) and PIK3CA, have been documented in subsets of patients [2]. Besides, it was found, by using microarray hybridization and qRT-PCR, that the miRNA named miR-34a was significantly under-expressed in MCPyV-negative tumors independently of tumor location or development of metastases [10]. To some extent, this study provides another possible molecular diagnosis marker of MCC. Also, the search of the best tumor cell line mimicking MCC has led to a recent whole transcriptome gene expression signatures study which allowed to characterize WaGa and Mkl-1 cell lines as the closest MCC model native tumors compared to some other MCC cell lines (i.e. UISO, MCC13, and MCC26) and fresh frozen MCC tumors [1]. Indeed, the characterization of cell lines similar to native MCC tumors is quite important in order to perform more reliable ex-vivo studies and easier unravel certain molecular mechanisms (e.g. molecular interactions studies, dissecting signaling pathways). Unfortunately, established cell types or tumor-derived cell lines have also its own limitations since they cannot fully mimic a particular tumor or cancer due to the lack of complex micro-environmental 3D tissue architecture.

Eventually, what we clearly know up-to-date is that Merkel cell polyomavirus (MCV) is frequently detectable in Merkel cell carcinoma (MCC) tumors, but the significance of MCV infection is not yet totally understood. Several translational research insights that will lead to improved staging, prognostic accuracy, optimizing the medical and surgical treatment, radiotherapy, follow-up, and surveillance procedures for this often-lethal skin cancer should result, at least partially, from: (i) updated knowledge about risk of second malignancies; (ii) studies linking CD8-positive T-cell function with outcomes, which could serve as the rational basis for ongoing trials of therapies to augment cellular immunity; (iii) possible involvement of MCC stem cells (aka initiating/propagating cancer cells); (iv) strategies targeting overexpressed oncogenes; (v) better definition of molecular prognostic signatures (implicated in majority of cases); (vi) Relative importance of adjuvant (radio or chemo-) therapy in polyomavirus-positive and polyomavirus-negative MCCs; (vii) better understanding of the significance between CK20 and MCPyV.

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