Review

Reviewing the current evidence supporting early B-cells as the cellular origin of Merkel cell carcinoma

C.M. Sauer\textsuperscript{a, c, 1}, A.M. Haugg\textsuperscript{a, 1}, E. Chteinberg\textsuperscript{a}, D. Rennspiess\textsuperscript{a}, V. Winnepenninckx\textsuperscript{a}, E.-J. Speel\textsuperscript{a}, J.C. Becker\textsuperscript{b}, A.K. Kurz\textsuperscript{c}, A. zur Hansen\textsuperscript{a, *}

\textsuperscript{a} Department of Pathology, GROW-School for Oncology & Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands
\textsuperscript{b} Department for Translational Dermato-Oncoology (DKTK), Center for Medical Biotechnology (ZMB), University Hospital Essen, Essen, Germany
\textsuperscript{c} Department of Internal Medicine IV, University Hospital Aachen, Aachen, Germany

Contents

1. Introduction ..........................................................99
2. The "Out of Merkel Cell" hypothesis .................................100
3. The "Epidermal/Dermal Stem Cell" hypothesis ..................100
4. The "Pre/pro B-Cell" hypothesis ..................................101
5. Conclusion ............................................................103
Role of the funding source ............................................104
References ............................................................104

ARTICLE INFO

Article history:
Received 18 September 2016
Received in revised form 13 February 2017
Accepted 28 May 2017

Keywords:
Merkel cell carcinoma
Merkel cell polyoma virus
Cell of origin
B-cell differentiation
Lymphoma
Merkel cell
Stem cell
Oncogenesis
Pathogenesis
Cutaneous B-cell lymphoma

ABSTRACT

Merkel cell carcinoma (MCC) is a highly malignant skin cancer characterized by early metastases and poor survival. Although MCC is a rare malignancy, its incidence is rapidly increasing in the U.S. and Europe. The discovery of the Merkel cell polyomavirus (MCPyV) has enormously impacted our understanding of its etiopathogenesis and biology. MCCs are characterized by trilinear differentiation, comprising the expression of neuroendocrine, epithelial and B-lymphoid lineage markers. To date, it is generally accepted that the initial assumption of MCC originating from Merkel cells (MCs) is unlikely. This is owed to their post-mitotic character, absence of MCPyV in MCs and discrepant protein expression pattern in comparison to MCC. Evidence from mouse models suggests that epidermal/dermal stem cells might be of cellular origin in MCC. The recently formulated hypothesis of MCC originating from early B-cells is based on morphology, the consistent expression of early B-cell lineage markers and the finding of clonal immunoglobulin chain rearrangement in MCC cells. In this review we elaborate on the cellular ancestry of MCC, the identification of which could pave the way for novel and more effective therapeutic regimens.

© 2017 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Merkel cell carcinoma (MCC) has originally been described as "trabecular carcinoma of the skin" (Toke, 1972). MCC mainly occurs in elderly or immunosuppressed patients and is associated with poor clinical outcome (Mudigonda et al., 2013). Although the incidence of MCC is low, a steady rise has been observed throughout the last decades (Reichgelt and Visser, 2011). Histologically, MCC reveals distinctive subtypes, which are the intermediate (approx. 90%), the small cell and the trabecular type of which all reveal cytokeratin 20 (CK20), neural cell adhesion molecule (NCAM/CD56), chromogranin A and synaptophysin expression (Becker, 2010).
Based on this, MCC has been believed to be a neuroendocrine carcinoma deriving from Merkel cells.

The discovery of the Merkel cell polyomavirus (MCPyV) significantly contributed to the understanding of the etiopathogenesis of MCC (Feng et al., 2008). The clonal integration of the viral genome in MCC, tumor specific oncogenic mutations within the large T antigen (LTAg) of MCPyV, the dependence of MCC cells on the expression of LTAg and the presence of MCPyV-DNA in approximately 80% MCC cases (Feng et al., 2008), led to the classification of MCPyV as a class 2A carcinogen by the International Agency on Research of Cancer (Bouvard et al., 2012). Of note, MCPyV-negative MCCs have a different mutational landscape and are mostly caused by sun light exposure. (Goh et al., 2016)

The current treatment is surgical excision of the primary tumor and the involved lymph nodes in combination with adjuvant radiotherapy (Medina-Franco et al., 2001). Nevertheless, even aggressive local treatment results in a poor control of the disease, limiting the median survival rate of MCC to 29 months (Soult et al., 2012). For more elaborations on the epidemiology, prognosis and therapy of MCC we refer to another recent review (Schadendorf and Lübke, 2017).

Over decades, the favored theory was that MCC originates from MCs (Toker, 1972). Subsequent to the formulation of the epidermal/dermal stem cell hypotheses as possible cells of origin of MCCs the controversy has intensified (Lemasson et al., 2012). Based on the consistent expression of early B-cell antigens in MCCs, the hypothesis that MCCs derive from pre/pro B-cells was formulated (Zur Hausen et al., 2013). Hereinafter, the current hypotheses on the cellular origin of MCC, with a strong focus on the B-cell hypothesis, are comprehensively reviewed. The identification of the cellular ancestors of MCC will contribute to establish more effective treatment regimens.

2. The “Out of Merkel Cell” hypothesis

Based on clinical characteristics, histological studies and the ultra-structural proof of neuroendocrine granules, MCs were considered to be the source of MCC (Tang and Toker, 1978). This theory was supported by the immunohistochemical finding that MCs and MCCs share the expression of CK20 and CD56 (Gallego et al., 1995). The typical perinuclear dot-like expression pattern of CK20 in 82% of MCC is considered almost pathognomonic for MCC diagnosis. In addition, neurofilament expression in 90% of MCCs has also served as a distinctive marker for MCC (Shah et al., 1993).

The arrangement of filaments, such as CK20 and neurofilament, discloses important differences between MCCs and MCs. While the cytoskeleton is arranged diffusely in MCs, it is arranged in plaque-like aggregates in MCC (Tilling and Moll, 2012), which is of interest, since it suggests an alternative activation. Noteworthy, many genes commonly expressed in MCCs, including KIT, PAX-5, SCF and BCL-2, are absent in MCs, which opposes the “out of Merkel cell hypothesis”.

Reasonable concerns have been rising during the past years, doubting the hypothesis that MCC derive from MCs. Of importance, no proliferative activity is detected in MCs as tested either in fetal or adult skin, strongly indicating that MCs are post-mitotic (Moll et al., 1996). In addition, transgenic mice models revealed that MCC homeostasis is maintained by differentiating epidermal progenitors and not by proliferating differentiated MCs (Van Keymeulen et al., 2009). Considering that the restoration of the proliferative potential is critical for cells to become cells of origin of cancer, post-mitotic MCs are unlikely to give rise to MCC (Tilling and Moll, 2012; Visvader, 2011). Further evidence challenging MCs as the cell of origin of MCC relies on the localization of MCC: While MCs are located within the basal layer of the epidermis (Moll et al., 2005), MCCs are generally localized in the dermis or subcutis with spatial distance to the epidermis or to epithelial structures of skin appendages (Fig. 1). Only in about 3–8% of cases, MCCs reveal contact to the epidermis.

Moreover, the cytonuclear morphology of the different subtypes of MCC has to be taken into consideration. The intermediate type of MCCs is morphologically almost indistinguishable from blastic lymphoid malignancies and other small blue round cell tumors (Walsh, 2001). If one MCC subtype was considered to derive from MCs at all, it would be the trabecular type, which in contrast to the intermediate and small cell type of MCC, is a rather well differentiated skin tumor. It appears counterintuitive that fully differentiated cells, including MCs, give rise to three very divergent histomorphological phenotypes.

3. The “Epidermal/Dermal Stem Cell” hypothesis

Lately, research interest shifted to epidermal stem cells as potential cells of origin of MCC. According to this, MCC is considered to be the consequence of a malignant transformation of an epidermal stem cell. Since epidermal stem cells give rise to different lineages, this pathogenic process could explain the divergent histological phenotypes of MCCs.

Testing 13 cases of MCC, Lemasson et al. reported strong cytokeratin 14 (CK14)-positivity by IHC. Since CK14 derives from the
basal epidermal layer, which also contains epidermal stem cells, the authors reasoned that MCCs may arise from this layer. (Lemasson et al., 2012)

The frequent expression of neuronal cell markers such as neurofilament, synaptophysin and neuron-specific enolase (NSE) in MCC, renders the dermal stem cell an intriguing candidate for the cellular origin of MCC (Visscher et al., 1989). Oncogenic mutations of dermal stem cells, which originate from the embryonic neural crest (Zabierowski et al., 2011), could explain the expression of these neuronal cell markers. Furthermore, expression of the transcription factor SOX-2, a neural crest-derived stem cell factor (Clewes et al., 2011), was detected in all cases of a small series of MCCs (N = 9), with a majority (5/9) even showing a strong nuclear staining. On the contrary, SOX-2 has recently also been found to be expressed in epidermal progenitors of murine tongues (Okubo et al., 2009), thereby suggesting that SOX-2 expression may be more widespread than previously assumed.

Due to their dermal location and their broad differentiation, a third stem cell population, skin-derived precursors, can be considered to be a possible cell of origin of MCC (Zabierowski et al., 2011). Evidence from mouse models shows that MCPyV T-antigen expression results in neoplastic features, such as hyperplasia and increased proliferation (Verhaegen et al., 2015; Shuda et al., 2015). In another mouse model, Keratin 14-mediated Cre recombinase expression induced expression of MCPyV T antigens in stratified-squamous epithelial cells and Merkel cells of the skin epidermis. Again, features for neoplastic progression could be found, however no malignancy, including MCC, could be induced (Shuda et al., 2015; Spurgeon et al., 2015). To this date, MCPyV-DNA could neither be detected in (epi-)dermal stem cells nor skin-derived precursor cells.

Very recently, Liu et al. isolated human foreskin cells and in vitro separately infected the different cells with a MCPyV-GFP pseudovirus and control. Using this experimental approach, the authors identified human dermal fibroblasts – in which productive viral transcription and replication was observed – to be the major target of MCPyV-infection. Using a cell culture model, Liu et al. showed that MCPyV-infection is facilitated by matrix metalloproteinase and by the β-catenin/WNT pathway. This signaling cascade has previously been shown to be stimulated upon UV light exposure and by aging, which are two major risk factors for the development of MCC (Liu et al., 2016). Although MCPyV-DNA is normally not detected in human dermal fibroblasts adjacent to MCPyV-positive MCC by diverse molecular techniques, i.e. DNA-PCR and DNA FISH, these are very interesting findings possibly pointing to the mode of MCPyV-infection of the skin.

4. The “Pre/pro B-Cell” hypothesis

The frequent expression of B-lymphoid lineage markers in MCC and its sometimes difficult histological discrimination from lymphoid malignancies (Walsh, 2001) contributed to the formulation of the hypothesis that MCC could originate from pre/pro B-cells (Zur Hausen et al., 2013). According to this, the stage of early B-cell development in which a MCPyV infection occurs, could determine the phenotype and B-cell expression profile of the later MCC. The pre/pro B-cell as the cellular origin of MCC would explain why most MCCs are located within the dermis and subcutis (Calder and Smoller, 2010), without revealing contact to the epidermis, where MCs or epidermal stem cells reside (Fig. 1). To this end, the minority of histopathological grossly divergent, MCPyV-negative cases with epidermal dysplasia, such as those recently described by Martin et al. (Martin et al., 2013), would not be considered to derive from pre/pro B-cells, but represent a distinct subset of MCCs, possible deriving from epidermal or dermal stem cells. In the paragraphs below, an overview of the most decisive steps in early B-cell development is given.

B-cell development starts with pluripotent hematopoietic stem cells (HSC) that differentiate into a pre/pro B-cell (Fig. 2). These are irreversibly committed to the B-cell lineage by expression of early B-cell factor 1 (EBF-1) and E2A, both synergistically cross-regulating the paired-box gene 5 (PAV-5) (Tijchon et al., 2013). Notably, their absence results in a failure to develop mature B-lymphocytes (Zhuang et al., 1996).

Due to the critical role of PAV-5, also known as B-cell specific activator protein (BSAP), for B-cell commitment, it is considered to be the guardian of the B-cell lineage (Cobaleda et al., 2007). In hematopoiesis, PAV-5 expression is B-cell specific and critical for maintaining B-cell function through the whole process of maturation and hereafter (Cobaleda et al., 2007). On inactivation of PAV-5 in vivo, mature B-cells regain the possibility to undergo gene recombination and may even differentiate into macrophages. Interestingly, PAV-5 expression is commonly deregulated or mutated in B-cell malignancies such as B-cell acute lymphoblastic leukemia (B-ALL) (Mullighan et al., 2007), B-cell chronic lymphocytic leukemias (B-CLL), mantle cells lymphoma (MCL), or follicular lymphomas (FLs) (Krenacs et al., 1998). C-KIT, also known as CD117 is another critical factor in early B-cell development. Binding of the C-KIT ligand Stem Cell Factor (SCF) results in the activation of this tyrosine kinase, ultimately promoting survival and proliferation through the RAS/MEK/ERK-signaling pathway (Edling, 2007).

For a cutaneous malignancy, it is very remarkable that MCCs commonly expresses early B-cell markers. A meta-analysis shows high frequencies with more than 60% for the TdT and KIT expression and more than 80% for PAV-5 expression in MCC. In three studies, the KIT ligand SCF was detected in 25.0% of cases. In addition, immunoglobulin expression and rearrangement in MCPyV-positive MCCs has been described. Here, we briefly summarize the previous reports on expression of terminal deoxynucleotidyl transferase (TdT), PAV-5, KIT, BCL-2, IgM, IgA and IgG, as well as the Ig lambda and kappa light chain in MCCs (Table 1).

PAV-5 expression is a frequent finding in MCCs. In 89.9% (24/27) of cases it was recently detected by Kolhe et al. (Kolhe et al., 2013). This was confirmed by Mhawech-Fauceglia et al. (70.6%, 24/34) (Mhawech-Fauceglia et al., 2007). We found PAV-5 expression in all (N = 21) tested MCCs (Zur Hausen et al., 2013), which is in concordance with another recent study (100%, 30/30) (Murakami et al., 2014). Overall PAV-5 is detected in 89.5% (128/143) of MCCs by immunohistochemistry (Table 1).

TdT expression has been identified as a potential diagnostic pitfall in the discrimination between MCC and lymphoblastic hematological malignancies (Buresh et al., 2008; Sur et al., 2007). Sur et al. detected TdT in 8 out of 15 MCCs (Sur et al., 2007), while in two other studies a prevalence of 73% and 78% (Kolhe et al., 2013; Buresh et al., 2008) was reported. In a larger analysis, 70% (28/40) of the analyzed MCCs were found to be TdT positive (Sidiropoulos et al., 2011). We observed TdT expression in 76.2% (16/21) of MCCs (Zur Hausen et al., 2013). Interestingly, TdT expression is significantly correlated with the presence of MCPyV (Bhatia et al., 2010). A meta-analysis (Table 1) establishes that TdT is expressed in 65% (122/187) of all MCCs.

Published data on the expression of Ig in MCC is sparse. Van Gele et al. performed gene-expression profiling of classical (MCPyV-positive) MCC cell lines and variant (MCPyV-negative) MCC cell lines. Hereby, the expression of Membrane-bound and secreted immunoglobulin gamma heavy chain (IgH3G) in the classical MCC cell lines was 100-fold higher as compared to the variant MCC cell lines. Importantly, IgH3G expression was the single most predictive gene for differentiating classical and variant MCCs (Van Gele et al., 2004). In another transcriptome-wide study of 35 primary MCCs, Paulson found IgL and Ig-kappa constant mRNA to be sig-
markers, authors significantly up-regulated in MCCs with a good prognosis (Paulson et al., 2011). In addition, we recently demonstrated IgA, IgG and IgM expression by immunohistochemistry in the majority of MCC cases. Of note, two MCPyV-positive cases showed clonal IgH and Ig kappa rearrangement (Zur Hausen et al., 2013). A recent study by Murakami et al. confirms this data: Using IHC, one or more of the tested immunoglobulins (IgG, IgA, IgM, Igk) was expressed in 70% of MCPyV-positive MCCs (14/20), while none of the MCPyV-negative MCCs expressed any immunoglobulin (p < 0.0003). In addition, the authors identified a MCPyV-positive case with monoclonal IgH recombination. (Murakami et al., 2014).

C-KIT expression is frequently observed in MCCs, while it is not expressed in MCs (Su et al., 2002). Overall, the meta-analysis of KIT expression in MCC reveals 63% (204/324) KIT positive MCCs (Table 1). Though critical for early B-cell maturation, C-KIT has also been proven to be important in certain non-hematological malignancies, including melanoma. In non-hematologic malignancies, the C-KIT signaling pathway is exploited through mutations and overexpression of c-kit. Contrarily, C-KIT could not be found to harbor functional mutations nor gene amplifications in MCC (Erstad and Cusack, 2014; Swick et al., 2013).

Data on the expression of the C-KIT ligand SCF in MCC is limited to three studies, in which the detection rates vary considerably (9–94%). While one group reported co-expression of KIT and SCF in 15.6% (5/32), another group detected it in 75% of the cases (12/16). The functional relevance of the ligand receptor interaction was subsequently shown in the MCC cell line MCC-1. Exogenous administration of SCF increased proliferation of MCC-1, while blockage of KIT signaling reduced proliferation (Krasagakis et al., 2011). In non-hematologic malignancies, activation of the C-KIT signaling pathway is not achieved by autocrine signaling, but by overexpression and functional mutations in c-kit itself. Although this autocrine

![Fig. 2. Overview of the different stages of B-cell development with their respective surface markers (Nagasawa, 2006), nuclear markers and V(D)J rearrangement. B-cell markers yet also reported to be expressed in MCCs are highlighted in bold.](image)

### Table 1

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tested positive, N</th>
<th>Total tested, N</th>
<th>Percentage present</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD56</td>
<td>15</td>
<td>15</td>
<td>100</td>
<td>(McNiff et al., 2005)</td>
</tr>
<tr>
<td>BCL-2</td>
<td>15</td>
<td>16</td>
<td>94</td>
<td>(Verhaegen et al., 2014)</td>
</tr>
<tr>
<td>PAX-5</td>
<td>128</td>
<td>143</td>
<td>89.5</td>
<td>(Zur Hausen et al., 2013; Kolhe et al., 2013; Dong et al., 2005; Mhawech-Fauceglia et al., 2007; Murakami et al., 2014)</td>
</tr>
<tr>
<td>TdT</td>
<td>122</td>
<td>187</td>
<td>65.2</td>
<td>(Zur Hausen et al., 2013; Kolhe et al., 2013; Murakami et al., 2014; Buresh et al., 2008; Sur et al., 2007; Sidirooulos et al., 2011; Bhatia et al., 2010)</td>
</tr>
<tr>
<td>KIT</td>
<td>204</td>
<td>324</td>
<td>63</td>
<td>(McNiff et al., 2005; Verhaegen et al., 2014; Kolhe et al., 2013)</td>
</tr>
<tr>
<td>SCF</td>
<td>32</td>
<td>128</td>
<td>25</td>
<td>(Kartha and Sundram, 2008; Waltari et al., 2011; Krasagakis et al., 2009)</td>
</tr>
</tbody>
</table>
Table 2
Summary of supportive and contradictory arguments for the different hypotheses on the cell of origin of MCC.

<table>
<thead>
<tr>
<th>Putative Cell of Origin</th>
<th>Supportive Arguments</th>
<th>Contradictory Arguments</th>
</tr>
</thead>
</table>
| Merkel Cell             | 1. Neuroendocrine granules  
                         | 2. CK20 and CD56 expression  
                         | 3. Clinical characteristics | 1. Epidermal location  
                         | 2. Postmitotic  
                         | 3. Gene-expression profile |
| (Epi-)dermal stem cell  | 1. Neuronal cell markers  
                         | 2. CK14 expression  
                         | 3. SOX-2 expression  
                         | 4. Mitotic potential | 1. Expression of B-cell markers |
| B-cell                  | 1. B-cell specific lineage factors  
                         | 2. Expression of Ig  
                         | 3. IgH and Igx rearrangement  
                         | 4. MCC regression with idelalisib treatment | 1. Neuroendocrine granules  
                         | 2. Location of MCPyV transduction |
| Dermal fibroblasts      | 1. Dermal fibroblasts are a target of MCPyV infection | 1. Gene-expression profile  
                         | 2. Neuroendocrine differentiation  
                         | 3. Expression of B-cell markers |

loop could possibly be a target for MCC therapy, current clinical experience does not provide a clear picture. While one group could show clinical remission, a phase II trial could not prove imatinib to be efficient (Samlowski et al., 2010).

Recently, knockdown of bcl-2 in Merkel cell lines has been shown to result in cell death. Importantly, these finding could be phenocopied by the potent pan-BCL-2 inhibitor ABT-263, which led to the induction of apoptosis in 10 out of 11 cell lines.

5. Conclusion

Although our knowledge of the underlying etiopathogenesis of MCC has changed tremendously with the recent discovery of MCPyV, the cell of origin of MCC still remains to be defined. Initially, the MC was assumed to be the cellular origin of MCC. However, this view has been discarded based on the data summarized in this review. Alternatively, epidermal stem cells and epidermal precursors have been discussed as possible cellular origin of MCC. We suggest that MCC originates from a pre/pro or pre-B-cell, which is mainly based on descriptive data yielded by IHC and also on molecular data (Zur Hausen et al., 2013). Descriptive data, in combination with molecular analyses, has been successfully used in the identification of the cellular origin of Non-Hodgkin lymphomas. Indeed, the current WHO classification of malignant lymphomas is largely based on this combination of descriptive and molecular data (Swerdlow and Harris, 2008). However, one should be aware of the fact that a possible transformation-related phenotype switch might impact the interpretation of these findings.

In contrast to MCs, early B-cells hold the capacity to differentiate into different cell types, which is a necessary and important characteristic of tumorigenesis (Visvader, 2011). The combined synthesis of critical early B-cell markers, including TdT, PAX-5, KIT and SCF in a majority of MCCs, strongly suggest B-cells as the cellular origin of MCC. Furthermore, preliminary data from our lab also points to the consistent and strong expression of RAG-1 in 81% (18/22) of MCCs. Molecular data on the expression of Ig transcripts, also in addition to monoclonal Ig gene rearrangement in some cases, further supports the hypothesis that early B-cell constitute the cellular origin of MCC (Zur Hausen et al., 2013; Murakami et al., 2014). On the other hand, it needs to be noted that Ig expression, though most prominent in B-cells, can also be found in some non-hematological malignancies (Chen et al., 2007). According to the pre-/pro-B-cell hypothesis, the respective stage of early B-cell development at which the transforming event takes place will affect the phenotype, as well as the protein expression profile.

Moreover, the pre/pro B-cell as the cellular origin also explains why most MCCs are located within the dermis and subcutis, without revealing contact to the epidermis, where MCs or epidermal stem cells resides (Fig. 1). Yet, it is unknown where the putative cell of origin of MCC is infected and transformed by MCPyV. In the case of pre/pro B-cells, it seems most likely that this infection/transformation occurs in the skin or blood. Previously, it has been shown that pre/pro B-cells enter the blood circulation (Pilarski et al., 1985; Krumbholz et al., 2008). Very recently, we assessed the presence of pre/pro B-cells in sun damaged skin and were able to demonstrate by TDT and PAX5 IHC double staining the presence of circulating pre/pro B-cells in sun damaged skin (unpublished data). These findings help to understand why MCPyV-negative MCCs do carry a genomic UV damage signature and still reveal the consistent expression of early B-cell markers. In addition, it helps to understand why MCC are sometimes found as collision tumors with BCC or SCC of the skin.

Expression of CK20 in MCC is considered to be the signpost of epithelial origin. However, CK20 expression is variable and can be induced in non-epithelial cells. Indeed, Simian virus 40 (SV40), a closely related polyomavirus, is able to induce expression of cytokeratins in non-epithelial cells (Knapp and Franke, 1989). In addition, also non-Hodgkin lymphomas and leukemias can express cytokeratins (Adams et al., 2008). Similarly, the expression of NCAM, also known as CD56, in MCC does not necessarily indicate its neuroendocrine origin, since CD56 is strongly associated with natural killer (NK) cells and the respective lymphomas (McNiff et al., 2005). Notably, NK cells originate from pre-/pro- B-cells.

Furthermore, MCPyV is present in approximately one third of chronic lymphatic leukemia (CLL) cases, a malignancy that frequently occurs together with MCC (Barroeta and Farkas, 2007). Lastly, integration of MCPyV into the host DNA of CLL cells was demonstrated by fluorescence in situ hybridization (Haugg et al., 2011).

In conclusion, several lines of evidence suggest that MCC originates from pre/pro- or pre-B-cells. At the same time, there are many unresolved issues and contradictory findings that need to be verified and addressed by functional in vitro studies before any hypothesis can be proven (Table 2). The correct identification of the cellular origin of MCC may allow to develop novel and more adequate therapeutic regimens for this highly malignant cancer.

In order to proof any of the suggested hypotheses functional in vitro studies are needed.

Conflicts of interest

The first authors, co-authors and corresponding author declare no conflicts of interest, relevant financial activities outside the submitted work or any related intellectual property.