Early B cell differentiation in Merkel cell carcinomas: clues to cellular ancestry

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Running title

Early B cells as putative origin of Merkel cell carcinomas

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Abstract

Merkel cell carcinoma (MCC) is a highly malignant neuroendocrine non melanoma skin cancer, which is associated with the Merkel cell polyoma virus (MCPyV). Recently, expression of the terminal desoxynucleotidyl transferase (TdT) and the paired box gene 5 (PAX 5) has been consistently reported in the majority of MCCs. We tested 21 MCCs for the expression of MCPyV, TdT, PAX5, IgG, IgM, IgA, kappa and lambda by immunohistochemistry and assessed IgH and Igk rearrangement in all 21 MCCs.

All of the MCCs revealed specific expression of PAX5 and 72.8% of the MCCs expressed TdT. In addition, most of the MCC revealed specific expression of one or more Ig subclasses and kappa or lambda. One MCC did reveal monoclonal IgH and Igk rearrangement next to 2 other MCCs showing Igk rearrangement.

Since co-expression of TdT and PAX5 under physiological circumstances is restricted to pro/pre- and pre-B cells we propose - based on our results - that the cell of origin of MCC is a pro/pre- or pre-B cell rather than the postmitotic Merkel cells. MCPyV infection and transformation of pro-/pre- B cells is likely to induce the expression of simple cytokeratins as has been shown for SV40 in other non epithelial cells. This model of cellular ancestry of MCC might impact therapy and possibly helps to understand why approximately 20% of MCC are MCPyV negative.
Introduction

Merkel cell carcinoma (MCC) is a highly malignant non melanoma skin cancer characterized by the expression of neuroendocrine markers, i.e. CD56, chromogranin A and synaptophysin and a typical dotlike perinuclear expression of cytokeratin 20 (CK20) (1). MCC occurs mainly in elderly or immunosuppressed patients and its clinical prognosis is very poor (1). The recent finding of the Merkel cell polyomavirus (MCPyV) in MCC has substantially contributed to the understanding of the etiopathogenesis of this malignancy (2). Since 2008 MCPyV DNA has been detected in approximately 80% of more than 1000 MCCs yet tested. MCPyV has been shown to be integrated in the MCC genomes by diverse molecular techniques (2-6).

MCC was first introduced by Toker in 1972 as a trabecular carcinoma of the skin (7). Dense core granules were identified in 3 MCCs which was confirmed by subsequent immunohistochemical studies testing neuroendocrine and simple epithelium markers (8-13). Based on the similarity of the expression patterns, MCC is considered to be most closely related to Merkel cells, which are located at the epidermal dermal junction and are supposed to function as noticceptive receptors of the skin. However, serious doubts on this theory have been postulated - also based on histomorphological growth patterns- and an alternative proposal suggesting a role for a pluripotent stem cell in the dermis as cells of origin of MCC still remains to be proven (14).

In the past years, evidence is accumulating that MCC express early B cell lineage markers (15–22). For example, specific expression of terminal desoynucleotidyl transferase (TdT) as assessed by immunohistochemistry, which normally is restricted to thymocytes and precursors of lymphocytes in the bone marrow, has been reported in 72.5% (95/131) of MCCs (15–19). In addition, a number of studies have reported immunostaining of the B-cell specific activating protein (BSAP; syn: PAX5) in 83.6% (102/122) of MCCs (16, 19–22).
Coexpression of TdT and BSAP under physiological circumstances is restricted to pro/pre-B cells and pre-B cells. Pre-B cells exhibit immunoglobulins and in addition rearrangement of the IgH and Igk locus. Here we examined 21 MCCs for the expression of TdT, PAX 5 (BSAP), IgG, IgM, IgA, kappa, and lambda by immunohistochemistry. In addition, clonal rearrangement of the IgH and Igk locus was tested in all MCCs in order to find further evidence for our assumption that MCCs possibly derive from pro/pre- or pre-B cells.

**Materials and Methods**

**Patients and tissues**

Formalin-fixed and paraffin-embedded (FFPE) tissues of resection specimens of 21 MCCs were included in this study. All respective tumors had been excised for diagnostic and therapeutic reasons. Eighteen specimens were obtained from the Maastricht Pathology Tissue Collection (MPTC). All use of tissue and patient data was in agreement with the Dutch Code of Conduct for Observational Research with Personal Data (2004) and Tissue (2001, www.fmwv.nl). Three MCC were collected at the Institute of Pathology, University Hospital Freiburg, Germany, which had been previously tested for the presence of MCPyV (23).

MCC diagnoses were previously defined by histology and immunohistochemistry for CK20, CD56, synaptophysin and chromogranin A in routine diagnostic. The histology of all MCCs included in this study has been reviewed by two expert dermatopathologists (V.W. and A.z.H.). The patient group consisted of 9 men (age range: 63 - 93 years, mean: 78.3 years) and 12 women (age range: 60 – 93 years, mean: 76.2 years). Only MCC tissues were included in this study of patients with no history of other haematological oncologic disease. Further details of clinico-pathologic parameters are included in Table 1. Serial sections of all specimens were used for H&E staining, immunohistochemistry and DNA isolation.
Immunohistochemistry

The following antibodies and dilutions were used in this study: anti-MCPyV (clone: CM2B4) dilution 1:50, Santa Cruz, Inc., USA; anti-TdT “Ready to use Antibody”; anti-PAX5 (clone: DAK-Pax5), “Ready to use Antibody”; anti-IgA dilution 1:20000; anti-IgG dilution 1:20000; anti-IgM dilution 1:2000; anti-kappa dilution 1:40000; anti-lambda dilution 1:40000, all DAKO, Glostrup, Denmark. All immunohistochemical stainings were performed on a Dako Autostainer Link 48™ using the EnVision FLEX™ visualization Kit K8008 DAKO according to standard diagnostic routine protocols and manufacturers’ instructions.

DNA extraction and immunoglobulin light chain restriction

First, an H&E stain of the selected specimens was reviewed (V.W., A.z.H). Five 10µm-thick consecutive sections were cut from each paraffin block of formalin-fixed tissue and if needed microdissection was performed. After deparaffinization, the tissues were lysed by proteinase K overnight until complete tissue lysis, and DNA was extracted using QUIAmp mini kit (Qiagen) or Maxwell 16 FFPE Plus LEV DNA isolation kit (AS1135), Promega. Purified DNA was measured in a spectrophotometer (Nano-drop, 2000; Thermo Scientific) and directly used for PCR. Detection of clonal immunoglobulin gene recombinations was performed according to an established and validated protocol (24) in a routine diagnostic setting in the nationally accredited diagnostic molecular pathology laboratory of the Department of Pathology, Maastricht University Medical Center, Maastricht, the Netherlands.
Results

MCPyV, PAX5 and TdT expression in MCCs

The presence of MCPyV was assessed by the expression of the large T antigen (LTAg) as tested by immunohistochemistry. Eighteen MCCs (85.7%) were tested positive for LTAg expression. Of the 21 MCCs, 13 revealed very strong nuclear expression of the LTAg, 2 moderate nuclear expression and 3 weak nuclear expression (Fig. 1; Table 1). In these MCPyV-positive cases LTAg expression was homogenous and found in all tumor cells. Three MCCs were completely negative for LTAg expression.

Specific nuclear expression of PAX5 was seen in all MCCs, of which 10 MCCs revealed strong PAX5 expression, 6 moderate and 5 weak (Table 1).

Specific nuclear TdT expression was detected in 16 MCCs (76.2%), of which 6 were strongly, 2 moderately and 8 weakly expressing TdT. Five MCCs were completely negative for TdT expression. Although no correlation was observed between PAX5, TdT and LTAg expression it is of interest that when PAX5 expression was high, TdT expression was low and vice versa. MCCs could be grouped according to TdT and PAX5 expression (see Tabel 1): TdT high, PAX5 low expression and TdT expression equally to PAX5 expression. In addition the third and also largest group of MCC showing a lower TdT expression compared to PAX5 expression.

Expression of immunoglobulins and kappa and lambda in MCCs

Testing 21 MCCs for the expression of Igs by immunohistochemistry revealed that almost all MCCs did show Ig expression of one or more Ig subclasses to variable extent (Fig. 1A). In detail, 10 (47.6%) MCCs were expressing IgA, 10 (47.6%) MCCs were expressing IgG, 5 (23.8%) MCCs were tested positive for IgM expression to a varying degree. In addition, 7 (33.3%) MCCs revealed kappa, and 12 (57.1%) MCCs revealed lambda expression.
Expression was membranous or cytoplasmic and only strong expression intensity was scored as positive. The percentage of tumor cells expressing Ig or kappa or lambda did show marked diversity among the MCCs. Details are summarized in Table 1. Noteworthy, all of the MCPyV-negative MCC (n= 3) did not show expression of Ig or kappa or lambda.

Molecular testing of IgH and Igk rearrangement in MCCs

According to the specimen control size ladder 18 of the 21 MCCs revealed sufficient DNA quality to proceed with molecular testing (Table 1). Analysis of IgH and Igk rearrangements in MCCs according to van Dongen and colleagues (24) identified a monoclonal IgH locus rearrangement combined with a monoclonal Igk rearrangement in one case (case no. 38-20, see Fig. 1B, Table 1). Furthermore, light chain restriction was found in 2 additional cases (case no. 15-18 and 21-11; Table 1). All MCCs revealing molecular rearrangements were restricted to the group of MCC with low TdT and high PAX5 expression.
Discussion

At present, profound doubts are challenging the concept that the postmitotic Merkel cells are the cells of origin of MCC, which has been proposed in the early 1980ies (8-13, 25, 26). The recently discovered MCPyV has been shown to play an important role in the etiopathogenesis of the majority of MCCs. Of interest, MCPyV can not be detected in non-neoplastic Merkel cells adjacent to MCPyV-positive MCCs (26). Based on MCC-mouse models it has been speculated that the cell of origin of MCC derives from epidermal stem cells or other primitive totipotent stem cells (reviewed in 25 and 26).

However, none of the previous reports on the cellular origin of MCCs took into account that in a significant number of MCCs, TDT and PAX5 are expressed consistently, i.e. in 72.5% and 83.6% of cases respectively. Here we assessed TDT and PAX5 expression in 21 MCCs and indeed were able to confirm these previous results. Specific nuclear expression of TdT was found in 16 of 21 MCCs (76.2%) and all of the 21 MCCs revealed specific nuclear PAX5 expression. Under physiological conditions co-expression of TDT and PAX5 is restricted to pro/pre- and pre-B cells. In addition to TDT and PAX5 expression, pro/pre- and pre-B cells are characterized by the expression of immunoglobulins (Igs) and VJH clonal rearrangements. Taken together, the obtained data on TdT and PAX5 expression in MCCs might either reflect an epiphenomenon in the course of malignant transformation or be of meaningful significance possibly pointing to the cellular ancestry of MCC. In order to assess further pro/pre- and pre-B cells differentiation in MCCs we examined the expression of immunoglobulins (IgA, IgG and IgM), kappa and lambda and in addition B-cell clonality in MCC tissues.

Indeed we were able to show strong expression of immunoglobulins or kappa/lambda in a significant number of MCCs. Only strong membranous or cytoplasmic Ig and/or kappa/lambda staining of the MCC cells were considered as positive expression. Although this is the first report to show Ig expression by immunohistochemistry in FFPE tissues of
MCCs it is not the first report on Igs and kappa/lambda expression in MCCs on the transcriptional level. Recent cDNA microarray analyses have shown that the expression of certain Igs is strongly up-regulated. Comparing the transcriptional expression profiles of MCC cell lines versus that of cell lines of small cell lung cancer Van Gele and colleagues have shown a 100 fold increase in membrane-bound and secreted immunoglobulin gamma heavy chain in MCC cells (27). In addition, Paulson and colleagues identified transcriptional expression of the IgJ polypeptide and Ig kappa constant as genes most highly upregulated in good prognosis tumors (28). Thus, the immunohistochemical expression data of Ig and kappa/lambda are in line with previous observations on the transcriptional level. Although only a minority of the MCCs in this study did show B-cell clonality, the finding of B-cell clonality in 3 MCCs (14.3%) strongly points to pro/pre- or pre B-cells as the cells of origin of MCCs.

B-lymphocyte development is a timely regulated specific process controlled by protein products of functionally rearranged Ig heavy (H) and light (L) chain genes. This process of Ig rearrangement begins in pro-B cells at the IgH locus (29).

Based on our results we propose that pro/pre- or pre-B cells, which either or not have yet started the process of Ig rearrangement turn into a tumor cell as the starting point of MCC (Fig. 2). Although other transforming events may be considered, MCPyV is the main suspect to transform pro/pre- and pre-B cells. More than 80% of MCCs harbor the recently discovered Merkel cell polyomavirus in its integrated form and in addition reveal oncogenic mutations in the large T antigen of MCPyV. It is likely that MCPyV-transformation leads to spontaneous loss of cytokeratin and neuroendocrine marker gene expression control and thus the expression of simple cytokeratins and neuroendocrine markers is induced in pro/pre- and pre-B cells. At least, the induction of cytokeratin expression in cytokeratin-negative cells upon infection with another polyomavirus, i.e. SV40, has been shown previously (30).

Phylogenetically MCPyV is closely related to SV40 and thus shares the same set of
transformation relevant genes. Moreover it has been shown that e.g. JC polyomaviruses preferentially infect stem cells or progenitor cells (reviewed in 25). The finding of Ig and kappa and lambda expression in MCCs on the protein level, as has been described in two previous independent cDNA microarray studies on the transcriptional level strongly support our model. Clonal IgH and Igk rearrangement in MCCs as found in our study in addition highly substantiates our model. The relative low number of 3 MCCs revealing B cell clonality might indicate that the transforming event, i.e. MCPyV infection, of pro/pre- or pre- B cells occurs prior to the start of Ig rearrangement. The fact that all MCCs carrying IgH or Igk rearrangements are in the group of MCCs with lower TdT than PAX5 expression also supports our hypothesis. In addition, the striking histological similarity of pro/pre- and pre-B cells and the intermediate type of MCC further supports this hypothesis. The proposed model can also help to understand why there are MCPyV-positive and MCPyV-negative MCCs and why most MCCs reveal a lymphoma-like growth pattern in the skin and only a very small minority of MCCs being connected to the epidermis. MCCs are almost always haematologically disseminated at the time of diagnosis. Identifying pro/pre- or pre-B cells as the cellular ancestors of MCCs is also expected to impact current treatment regimens of MCC which is of major significance in the context of the very poor prognosis for MCC patients after primary MCC diagnosis. Next to this it might also influence the current understanding of the cellular ancestry of other neuroendocrine cancers such as small cell lung cancer in which to a lesser extent TdT and PAX5 expression has been observed (18,19).
References


Figure legends:

Figure 1: Histomorphology, immunohistochemistry and IgH and Igk rearrangement of MCC 38

A: HE: Hematoxylin-Eosin showing an intermediate type of MCC; MCPyV: merkel cell polyo-mavirus as determined by CM2B4 antibody directed against large T antigen of MCPyV; CK20: cytokeratin 20 showing the typical perinuclear dotlike expression pattern as reported in MCC; specific nuclear TdT (terminal desoxynucleotidyl transferase) expression; specific nuclear PAX5 (paired box gene5) expression in all MCC cells; specific membranous IgG and kappa expression in contrast to no expression of lambda according to the \(v_K/\text{intron k}\) deleting element as tested by Igk rearrangement (Table 1).

B: Assessment of IgH FR2 (upper panel) and Igk B (lower panel) rearrangements reveals B-cell clonality in MCC 38 (see also Table 1) as compared to the respective monoclonal and polyclonal controls. The red stars indicate the MCC38 either in IgH FR2 or in Igk B.

Figure 2: Proposed model of cellular ancestry and etiopathogenesis of Merkel cell carcinomas

MCPyV infects, integrates and transforms pro/pre- or pre-B cells inducing the expression of simple cytokeratins, i.e. cytokeratin 20 (CK20) according to the previously reported induction of cytokeratins by SV40 in non- epithelial cells (30). The level of TdT and PAX 5 expression in the MCCs is likely to reflect the state of B-cell maturity (pro/pre- or pre-B cell) at the time point of MCPyV-infection. The right panel shows the histology and immunohistochemistry of MCC 11 (Table 1). Double arrows in the left panel indicate strong expression, one arrow moderate expression.
<table>
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<th>Age</th>
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<th>Molecular Pathology</th>
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**Legend:**
- **Pat ID:** Patient Identification Number
- **Gender:** M = Male, F = Female
- **Age:** Age in years
- **Histo.:** Histological Grade
- **Immunohistochemistry:**
  - **MCPyV:** MCPyV (Epstein-Barr Virus) positivity
  - **TdT:** Telomerase activity
  - **PAX5:** PAX5 gene expression
- **Molecular Pathology:**
  - **IgA, IgG, IgM:** Immunoglobulin expression
  - **Ig kappa, Ig lambda:** Immunoglobulin expression
  - **SCS-ladder:** SCS-ladder expression
  - **IgH, Igk:** Immunoglobulin expression

**Notes:**
- Authors and references are not provided in the table.
- The table details the presence and intensity of various molecular and histological markers across different patient samples.
Tabel 1: Clinico-pathological, immunohistochemical and molecular pathology data of 21 MCCs.

Abbreviations used: m: male; f: female; histol: histology; int.: intermediate; s.c.: small cell; TdT: terminal desoxynucleotidyl transferase; PAX5: paired boxe gene 5; BSAP: B cell specific activating protein; -: negative; + weak expression; ++: moderate expression; +++: strong expression; expression of Ig’s and kappa and lambda is given as percentage tumor cells expressing respective Ig’s or kappa and lambda; p: polyclonal; m: monoclonal; m*: vk/intron k deleting element; SCS ladder: specimen control size ladder indicating whether DNA quality is sufficient in order to inteprete results. y: sufficient DNA quality; n: not sufficient DNA quality; n.i.: not informative.
Fig. 1A

- HE
- MCPyV
- CK20
- TdT
- PAX5
- IgG
- lambda
- kappa

Fig. 1B

- IgH FR2 monoclonal control
- IgH FR2 polyclonal control
- IgH FR2 MCC 38
- IgH FR2 water control
- IgK B monoclonal control
- IgK B polyclonal control
- IgK B MCC38
Figure 2

Protein expression and clonality

- TdT
- Pax 5
- IgVH

- Pro/pre-B cell
  - TdT
  - Pax 5
  - IgVH

- Pre-B cell
  - TdT
  - Pax 5
  - IgVH

Infection
Integration
Transformation by

MCPyV-positive Merkel cell carcinoma

MCPyV

CK20

HE

TdT

IgM

PAX5

IgVH+/

IgVH-/+
Early B-cell differentiation in Merkel cell carcinomas: clues to cellular ancestry

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