Review

The Multifaceted Role of Protoparvoviruses in Human Cutaneous T Cell Lymphoma: From Candidate Causative Agents to Potential Oncolytic Virus Therapeutics

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Article

The Multifaceted Role of Protoparvoviruses in Human Cutaneous T Cell Lymphoma: From Candidate Causative Agents to Potential Oncolytic Virus Therapeutics

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Abstract: Cutaneous T cell lymphoma (CTCL) is a devastating, potentially fatal T lymphocyte malignancy affecting the skin. Despite all efforts, the etiology of the disease remains unknown. Infectious agents have long been suspected as factors or co-factors in CTCL pathogenesis. This review deals with the panel of bacterial and viral pathogens that have been investigated so far in an attempt to establish a potential link between infection/carriage and CTCL development. A special focus is given to a recently discovered human protoparvovirus, namely the cutavirus (CutaV), which has emerged as a plausible CTCL etiological agent. Available evidence in support of this hypothesis as well as alternative interpretations and uncertainties raised by some conflicting data are discussed. The complexity and the multifacetedness of the *Parvoviridae* family of viruses are illustrated by presenting another protoparvovirus, the rat H-1 parvovirus (H-1PV). H-1PV belongs to the same genus as the CutaV but carries a considerable potential for therapeutic applications in cutaneous lymphoma.

Keywords: cutaneous T cell lymphoma; infectious etiology; *Parvoviridae*; cutavirus; oncolytic H-1 parvovirus

1. Introduction

Cutaneous T cell lymphoma (CTCL) belongs to the heterogeneous group of primary cutaneous lymphomas (CL), the second most common extranodal non-Hodgkin hematological malignancy. CTCL accounts for approximately 75% of all CL [1]. The disease emerges through the clonal proliferation of CD4+CD8- T lymphocytes that home to the skin. The two major CTCL subtypes are mycosis fungoides (MF) characterized by the formation of patches, plaques and skin tumors, and Sézary syndrome (SS) with typical leukemic involvement and generally poor prognosis [2]. The incidence of CTCL increases with age. CTCL patients are likely to develop various secondary malignancies such as other non-Hodgkin lymphomas, melanomas, and lung or bladder cancer [3].

It has been suggested that antigen-driven T cell proliferation induced by medication use [4], genetic predisposition [5] or somatic mutations in signaling pathways [6] may contribute to CTCL pathogenesis. However, controversial data have been obtained and the etiology of the disease remains presently unknown. Going back to the 90s of the last century, Whittemore et al. were the first to raise the hypothesis that various infectious agents might be involved in CTCL development [7]. This review summarizes the current knowledge on CTCL infectious etiology and focuses in particular on the still putative role of some parvoviruses in the induction of CTCL carcinogenesis. A recently discovered intriguing property of other parvoviruses, namely to exert, in contrast, therapeutic effects in CTCL is also discussed.

2. Infectious agents involved in cutaneous lymphoma etiopathogenesis

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Infectious agents are known to induce cancers by acting in either direct or indirect ways. Direct carcinogenesis is exerted e.g. by the oncogenic viruses (papillomaviruses, polyomaviruses, retroviruses, herpesviruses, among others), which initiate infection leading, through direct virus-driven mechanisms, to cell malignant transformation. Indirect carcinogenesis is typically associated with chronic infection and inflammation. In CTCL, the malignant T cell population consists of various clones that share a common TCR-Vß epitope, in contrast to the malignant T lymphocyte clonal expansion characteristic for other lymphomas [8]. Since the ability to initiate polyclonal T cell expansion in a Vß-restricted manner is characteristic of pathogen-produced immunostimulatory molecules known as superantigens, the idea was launched that in CTCL carcinogenesis a bacterial and/or a viral superantigen may serve as the trigger of chronic antigen stimulation and excessive T cell proliferation.

2.1. Bacterial superantigens in CTCL

2.1.1. Staphylococcus aureus

A primary role of *S. aureus* in triggering CTCL carcinogenesis has not been proven so far. However, an association of CTCL clinical behavior with *S. aureus* colonization was noted. A trend towards higher antibiotics-sensitive *S. aureus* colonization was observed in CTCL patients in comparison with healthy control subjects, and colonization was suggested to be directly related to the body surface area of CTCL involvement [9]. Furthermore, a relationship between *S. aureus*-induced sepsis and lymphoma progression was found [10]. Conversely, treatment of infection with antibiotics was reported to lead to significant clinical improvement in *S. aureus*-colonized MF patients [11,12]. Based on the above, it was initially suggested that staphylococcal superantigens might be strongly and directly involved in CTCL pathogenesis. Indeed, the *S. aureus*-derived superantigen family of proteins is known to consist of at least 26 different paralogues, which exert their activities by crosslinking the major histocompatibility complex (MHC) type II molecules with the TCR-Vß, resulting in this way in aberrant T cell proliferation and proinflammatory cytokine release [13]. However, subsequent *in vitro* studies revealed that *S. aureus*-derived superantigens induce superantigen-responsive non-malignant T cell proliferation rather than direct CTCL cell growth stimulation [14]. Staphylococcal infection-associated tumor cell expansion in CTCL therefore seems to rely on the crosstalk between malignant and non-malignant T lymphocytes on the background of *S. aureus* superantigen-induced chronic antigen stimulation.

2.1.2. Borrelia burgdorferi

B. burgdorferi is another bacterial agent that was suspected to play a plausible role in CTCL etiology. *B. burgdorferi*-specific flagellin gene sequences were detected in approximately 18% of the MF cases registered in a Lyme disease-endemic area in Northeastern Italy, but in none of the healthy control biopsies [15]. This bacterial pathogen is known to affect the complement function by inactivating complement regulatory proteins [16]. Moreover, *B. burgdorferi* is capable of persisting in immunoprivileged sites [17], using various immune evasion mechanisms, including outer membrane antigenic variations [18]. It was suggested that *B. burgdorferi*, in particular in Lyme disease-endemic areas where long-term persistence-prone strains prevail, might possibly function as a co-factor in MF pathogenesis and lead, through long-lasting antigen stimulation, to the malignant accumulation of skin-homing CD4+ lymphocytes. Indeed, while the causal link between MF and *B. burgdorferi* remains controversial, some literature reports describe cutaneous lymphoma outcome improvement after *B. burgdorferi*-directed specific antibiotic therapy [19].

2.1.3. Chlamydia pneumoniae

Abrams et al. speculated that there might be an association between *C. pneumoniae* infection and CTCL development. The authors identified an effector molecule originally designated as Sézary T cell-activating factor (SAF). SAF was shown to be produced by mitogen-stimulated peripheral blood mononuclear cells (PBMC) from SS patients and to be able to induce interleukin-2 (IL-2) receptor

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expression on both normal and malignant T lymphocytes. Furthermore, this effector molecule strongly stimulated the proliferation of Sézary cells and, interestingly, could be found in keratinocytes, histiocytes and dendritic cells within the dermis and epidermis of SS patients. Since the attempts to isolate the coding gene from eukaryotic libraries failed, it was suggested that SAF was not a eukaryotic factor but rather a *C. pneumoniae*-associated protein [20,21]. Indeed, *C. pneumoniae* DNA was detected in skin and lymph node samples from MF and SS patients, respectively [21]. However, it has not been elucidated whether SAF is physically associated with the bacterium or produced during its life cycle. It could not be excluded either that SAF might still be a eukaryotic product, which possesses high affinity to localize within bacterial inclusions. *C. pneumoniae* involvement in CTCL etiopathogenesis remains therefore a controversy and needs further investigation.

2.2. Viral superantigens in CTCL

Further to the above presented bacterial agents, several viruses characterized by an ability to provide chronic immune stimulation have been studied for their potential involvement in CTCL development.

2.2.1. Retroviruses: human T-lymphotropic virus (HTLV)

In the 90s of the past century, the hypothesis arose that retroviral infection of skin- and lymph node-resident Langerhans cells might be the triggering event in CTCL development [22]. Retrovirus-like particles were indeed found in these cells [23], and in 1980, the first publication was released describing the detection and isolation from MF patient's PBMC of HTLV, the causative agent of human adult T cell leukemia and lymphoma (ATL) [24]. The HTLV etiology hypothesis was further strengthened by both the well-established significant clinical and histopathological similarities between CTCL and ATL and by several later discoveries. HTLV-specific sequences and reverse transcriptase activity were detected in a cell line derived from a SS patient [25] and in cultured PBMC from CTCL patients [26,27]. In contrast to the above reports, which speak in favor of HTLV association with CTCL pathogenesis, other studies failed to amplify HTLV-specific sequences from skin lesion- and PBMC-derived CTCL patient DNA [28–31]. In one 2010 study, Bonin et al. analyzed 83 skin biopsies from MF patients in comparison with 83 healthy subject skin samples. HTLV-I-like genomic sequences were found in 41% of the MF cases. Surprisingly, the frequency of HTLV-I detection in control biopsies was also substantial, thus questioning the direct role of this virus in CTCL carcinogenesis [32].

2.2.2. Herpesviruses: Epstein-Barr virus (EBV) and cytomegalovirus (CMV)

These viruses are known for their characteristic capacity for long-term persistence through the establishment of latent infection. It was therefore speculated that both EBV and CMV might readily exert chronic antigen stimulation leading to T cell hyperproliferation. Indeed, EBV and CMV genomic sequences and seropositivity were reported to be present in CTCL samples by various studies [33–36]. However, these data could not be reproduced by other groups who failed to trace a link between either EBV or CMV and CTCL [37,38]. Similar inconsistencies accompanied the attempts to link the Kaposi sarcoma-associated herpesvirus (KSHV, HHV-8) and the human herpesviruses 6 and 7 (HHV-6, HHV-7) to CTCL. While some groups could prove the prevalence of KSHV infection and the presence of virus-specific DNA in CTCL patient samples [39], others either observed a uniform negativity [34,40] or failed to confirm immunohistochemically the PCR-detected virus DNA positivity [37]. Only a small percentage, if any, of the samples tested was shown to be positive for HHV-6 or HHV-7 DNA [33,34,41,42], thus failing to support any significant role of these herpesviruses in CTCL pathogenesis.

Other viruses, namely the Merkel polyomavirus affecting the skin and possibly causing Merkel cell carcinoma, were also suggested as CTCL-triggering/associated agents. The link between this virus and CTCL was nevertheless unquestionably rejected [43].

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In this way, none of the bacterial or viral agents discussed above could show a convincingly consistent association with CTCL. Therefore, CTCL infectious etiology remained for decades a matter of speculation, until recently, when a novel viral candidate was discovered in MF specimens (see below). Infectious agents, of both bacterial and viral origin, which have been associated or investigated for an association with CTCL so far, are listed in Table 1.

Table 1. Infectious agents investigated for their association with CTCL pathogenesis.

Origin	Infectious agent	Taxonomical classification (Family)	References
Bacterial	*Staphylococcus aureus*	*Staphylococcaceae*	[9–14]
	Borrelia burgdorferi	*Borreliaceae*	[15–19]
	Chlamydia pneumoniae	*Chlamydiaceae*	[20,21]
Viral	Human T-lymphotropic virus (HTLV)	*Retroviridae*	[22–32]
	Epstein-Barr virus (EBV)	*Orthoherpesviridae*	[33–38]
	Human cytomegalovirus (CMV)	*Orthoherpesviridae*	[33–38]
	Kaposi sarcoma-associated herpesvirus (KSHV)	*Orthoherpesviridae*	[34,39,40],
	Human herpesvirus 6, 7 (HHV-6, HHV-7)	*Orthoherpesviridae*	[33,34,41,42]
	Merkel polyomavirus	*Polyomaviridae*	[43]
	Cutavirus (CutaV)	***Parvoviridae***	[54–61]

3. Parvoviruses associated with cutaneous lymphoma etiopathogenesis

3.1. The Parvoviridae family

Parvoviridae is a large and heterogeneous family of single-stranded DNA viruses that can infect both invertebrates (subfamily *Densovirinae*) and vertebrates (subfamily *Parvovirinae*). The linear, about 3.9-6 kb genome is protected by a non-enveloped icosahedral capsid with a diameter of approximately 26 nm. The parvoviral genome is divided into two major open reading frames (ORFs) that encode nonstructural (NS) and structural viral proteins (VP). The coding region of the parvoviral genome is flanked by terminal repeats folded into hairpin-like structures that can be either identical or not [44,45]. The parvoviral major nonstructural protein, NS1, is strongly involved in virus replication and pathogenicity through its broad-spectrum enzymatic and sequence-specific DNA binding activities [46,47]. Parvoviruses are ancient viruses: it is believed that they have been circulating in nature for 90 million years [48,49] acquiring various strategies for host adaptation and immune evasion. Parvoviruses are broadly distributed in nature: various animal hosts can be infected simultaneously by more than one parvovirus [50]. Most parvoviruses produce little or no disease in their hosts. However, some family members, in particular the canine parvovirus (CPV) [51] and the human parvovirus B19 [52] can cause up to severe clinical illness. For over three decades, the B19 parvovirus was the only known parvoviral human pathogen. This limitation was partly due to the difficulties in propagating parvovirus virions in cell cultures. However, in recent years numerous new techniques and approaches have been introduced into the laboratory routine, which led to the discovery of novel parvoviruses and the introduction of new genera and species into the *Parvovirinae* subfamily [53] (Table 2). The paragraphs below focus on recently discovered human parvoviruses named cutaviruses, in the context of their possible association with cutaneous lymphoma.

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Table 2. Current International Committee on Taxonomy of Viruses (ICTV) classification of the *Parvoviridae* family.

Family	***Parvoviridae***		
Subfamily	***Densovirinae***	*Hamaparvovirinae*	***Parvovirinae***
Genera (number)	11	5	**Protoparvovirus** * +10
Species (number)	37	37	**Protoparvovirus primate3** (cutavirus) **Protoparvovirus rodent1** (H-1 parvovirus) +89

* The heterogeneous Protoparvovirus genus incorporates 91 virus species, two of which, the cutavirus and the rodent H-1 parvovirus, play distinct roles (pathogenesis-associated and oncolytic, respectively) in cutaneous lymphoma (from Current ICTV Taxonomy Release | ICTV, accessed on 17.11.2023).

3.2. Cutavirus discovery

In 2016, Phan et al. described the genome of a new protoparvovirus (Table 2) that was detected through metagenomics analysis and nested PCR in human diarrhea samples and MF biopsies [54]. Seven genomic sequences were identified in fecal samples from children in Brazil and Botswana. The viruses were named cutaviruses (CutaV) and were found to share significant amino acid identity with bufaviruses, another recently discovered species belonging to the Protoparvovirus genus [55]. The study of Phan et al. analyzed a limited number of CTCL samples (17 in total), some of which (n=2) were processed for virion-associated nucleic acid enrichment. These data did not allow to determine whether CutaV DNA detection was merely associated with an ongoing replication or virion deposition in the skin or reflected a direct oncogenic role of the virus in CTCL. Furthermore, CutaV expression could not be convincingly shown in the transformed T lymphocytes infiltrating the MF-affected skin.

3.3. Cutavirus association with CTCL

While no direct pathogenic role of CutaV in CTCL could be concluded from the above study, a later work by Väisänen et al. suggested that dermal CutaV DNA carriage might indeed be strongly associated with cutaneous lymphoma. The authors set up a multiplex quantitative PCR and analyzed by this means malignant and non-malignant skin samples from 25 CTCL patients, as well as 98 healthy control subjects. CutaV DNA was detected in 16% (4/25) of the biopsies analyzed but, importantly, in none of the healthy control samples. Interestingly, positive samples were derived not only from MF but also from a SS patient [56]. CutaV association with CTCL was further demonstrated by another study that was launched to retrospectively analyze a large number of lesional skin samples from both patients with CTCL and those with cutaneous B cell lymphoma. A total of 189 (170 CTCL and 19 CBCL) tissue specimens from 130 (117 CTCL and 13 CBCL) patients were analyzed by real-time PCR. CutaV DNA was found in 6/189 CTCL biopsies and 6/130 CTCL patients. In contrast to CTCL-derived samples, none of the samples derived from B-cell lymphoma patients displayed CutaV DNA positivity [57].

Large plaque-type parapsoriasis is considered as a premalignant condition capable of developing into CTCL [58]. While Phan et al. failed to detect CutaV DNA in parapsoriasis samples [54], Mohanraj et al., in contrast, observed a significant association of CutaV carriage with plaque-type parapsoriasis. In contrast to the infrequent detection of other parvo- or other (herpes, polyoma) viruses, CutaV DNA was consistently found in skin biopsies and skin swabs from parapsoriasis patients, but only occasionally (1,96%) in healthy subjects, more particularly in the skin swab from a single healthy individual. Notably, half of the patients who carried CutaV DNA in the skin subsequently developed CTCL. The latter findings suggested the idea of using CutaV DNA carriage as a potential biomarker for cutaneous lymphoma development [59].

 doi:10.20944/preprints202401.1017.v1

The above presented observations hinted at a possible association of CutaV infection/carriage with CTCL (etio)pathogenesis. However, some recently published studies produced conflicting results. While Hashida et al. found a significant association of CutaV load with MF in a subset of Japanese patients [60], Bergallo et al. failed to detect the virus in 55 Italian patient skin specimens [61]. Further investigations are obviously needed in order to reveal a straightforward link between cutaviruses and CTCL, and elucidate whether these protoparvoviruses are a factor, a co-factor or a satellite in cutaneous lymphoma. As discussed below, parvoviruses are endowed with oncotropic properties, implying that their association with neoplastic tissues may be opportunistic rather than causative.

4. Parvoviruses with therapeutic potential in cutaneous lymphoma

4.1. The rat H-1 parvovirus

The rat H-1 parvovirus (H-1PV) is another member of the Protoparvovirus genus (Table 2). H-1PV was discovered in the late 50s in transplantable human tumor samples and was initially thought to be an oncogenic virus [62]. However, further observations revealed that virus infection was not an initiating event in carcinogenesis but rather an opportunistic process based on H-1PV natural tropism for human cancer cells [63]. It was subsequently shown that infection with this protoparvovirus may lead to the suppression of both virally or chemically-induced or spontaneously developed tumors in animal models [64,65]. This groundbreaking research inspired the idea that H-1PV may be successfully used as a selective cancer-killing agent and laid the ground of oncolytic parvovirotherapy. The numerous later investigations on H-1PV potential as cancer therapeutic demonstrated that this virus possesses a broad-range anticancer activities against various types of cancers both *in vitro* and in animal models [66–68]. Moreover, it was shown that the H-1PV-induced death of tumor cells may be immunogenic and trigger the mounting of an anticancer immune response [69,70]. In 2011, H-1PV became the first parvovirus, which was the subject of a bona fide clinical trial. The trial involved patients with progressive recurrent glioblastoma, who were treated with either local (intratumoral/intracerebral) or systemic (Intravenous) virus applications. The study demonstrated H-1PV excellent safety and tolerability in both applications. Furthermore, it provided first hints of H-1PV treatment-associated immune system stimulation and warming up of the tumor microenvironment [71]. Parvovirus outstanding tolerability, with no dose-limiting toxicities, was confirmed in a subsequent phase II trial in inoperable metastatic pancreatic cancer patients. Following virus administration, partial response associated with favorable immune modulation were observed in two out of seven patients enrolled [72]. Altogether, over a century of H-1PV research has convincingly demonstrated that this oncolytic parvovirus deserves to be considered for a clinical translation as cancer immunotherapeutic.

4.2. The potential of H-1PV against cutaneous lymphoma

Parvovirus therapeutic potential in some hematological malignancies has already been shown. In particular, it was demonstrated that H-1PV is able to cause B cell lymphoma regression and survival prolongation in animal models of Burkitt's lymphoma [73]. H-1PV infection of other types of blood cancer cells (diffuse large B cell lymphoma, large cell immunoblastic lymphoma, among others) similarly resulted in tumor cell death and reduction of cancer cultures viability [74]. Remarkably, H-1PV was capable of suppressing the proliferation not only of malignant B but also of T lymphocytes. Oncolysis was observed in T-cell acute lymphoblast leukemia (T-ALL) and, of note, in CTCL cells [74]. H-1PV infection of the SS-derived T-lymphoblast HH cells was characterized by efficient virus uptake, intracellular expression and replication and, ultimately, host cell killing with release of progeny infectious virions [74]. Further studies are required in order to substantiate H-1PV potential in CTCL treatment. However, first *in vitro* observations are promising and promote parvovirotherapy as a potential novel approach in cutaneous lymphoma. Thus, two *Parvovirinae* subfamily members, CutaV and H-1PV, belonging to the same - Protoparvovirus - genus seem to

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have distinct relationships with CTCL development. The pro-curative (oncolytic) effect of H-1PV on CTCL cells challenges the CutaV association with CTCL to be causative *versus* opportunistic.

5. Conclusions and future directions

Despite all efforts to identify an infectious agent of either bacterial or viral origin that might be involved in CTCL development, the trigger of this malignancy remains presently unclear. The recently discovered human cutaviruses emerged as sound candidates for an etiopathogenic role in this disease. However, existing study limitations and controversial results hint at the necessity to await further investigations in order to draw a straightforward conclusion. Further studies are similarly required, and worth being considered, to unravel the therapeutic potential of the oncolytic H-1 parvovirus in cutaneous lymphoma.

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