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## Human inborn errors of immunity to oncogenic viruses

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### Abstract

Oncoviruses are viruses that can cause tumors. Seven viruses are currently recognized as oncogenic in humans: Epstein Barr virus (EBV), Kaposi sarcoma-associated herpesvirus (KSHV, also known as HHV8), human papillomaviruses (HPVs), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus-1 (HTLV-1), and Merkel cell polyomavirus (MCPyV). The clinical phenotypes resulting from infection with these oncoviruses range from asymptomatic infection to invasive cancers. Patients with inborn errors of immunity (IEI) are prone to the development of infectious diseases caused by a narrow or broad spectrum of pathogens, including oncoviruses in some cases. Studies of patients with IEI have deepened our understanding of the non-redundant mechanisms underlying the control of EBV, HHV8 and HPV infections. The human genetic factors conferring predisposition to oncogenic HBV, HCV, HTLV-1 and MCPyV manifestations remain elusive. We briefly review here what is currently known about the IEI conferring predisposition to severe infection with oncoviruses.

### Introduction

Oncoviruses are viruses that can cause tumors. An estimated 20% of the global cancer burden is due to infectious agents. Rous sarcoma virus (RSV) was the first oncogenic virus to be described, in the early 1900s. Vilhelm Ellerman and Oluf Bang in one study, and Peyton Rous in another demonstrated that leukemia and sarcoma could be transmitted between chickens by the injection of a cell-free tumor extract [1,2]. Two decades later, Richard Shope discovered the first mammalian oncovirus, Shope's papillomavirus virus (SPV), better known nowadays as cottontail rabbit virus (CRPV) [3]. Shope demonstrated

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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that horns and cutaneous warts in cottontail rabbits were driven by a virus. Peyton Rous subsequently demonstrated that SPV could induce cancers in inoculated rabbits [4]. Epstein Barr virus (EBV), also known as human herpesvirus (HHV) 4, was the first human oncogenic virus to be discovered, in 1964, when virus-like particles were observed directly, by electron microscopy, in cultured Burkitt's lymphoma cells [5]. Seven viruses are now recognized to be oncogenic in humans: EBV, Kaposi sarcoma-associated herpesvirus (KSHV, also known as HHV8), human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus-1 (HTLV-1), and the Merkel cell polyomavirus (MCPyV). The tumorigenic process ultimately leading to invasive cancers is based principally on a lack of viral control over periods of years to decades before the onset of cancer. All human oncoviruses promote tumor development, but infection does not lead to cancer if an effective host immune response develops. Indeed, seroprevalence for human oncoviruses ranges from 2% to >90% of human populations worldwide, with considerable differences between geographic areas (e.g. HHV-8, HCV, HTLV-1), but the prevalence of the associated cancers is much lower [6]. Host responses are, therefore, heterogeneous, and this heterogeneity can be effectively deciphered through genetics. Over the last few decades, studies of inborn errors of immunity (IEI) underlying susceptibility to oncovirus infections have deepened our understanding of the non-redundant antiviral immune responses preventing persistent active infection leading to transformation, particularly for EBV, HHV-8 and HPVs. We aim here to review current knowledge on this topic, focusing on patients who have developed virus-induced tumors or cancers.

## DNA oncoviruses

**Inborn errors of immunity to gamma-herpesviruses**—EBV and HHV8 are  $\gamma$ -herpesviruses, and thus belong to the only subfamily of herpesviruses with oncogenic properties. They are mostly transmitted through saliva. EBV is the most prevalent member of this subfamily, with seropositivity for this virus exceeding 90% in the adult population worldwide [7], whereas the seroprevalence of HHV8 ranges from <20% to >40%, depending on the geographic area considered [8]. EBV infection is usually asymptomatic in children, but may be associated with mononucleosis in adolescents and adults; HHV8 infection is usually asymptomatic in both children and adults.

**1- EBV:** After primary infection, EBV remains latent in the infected host. EBV can cause cancers if the infection is not kept under control, as in immunocompromised patients. It has been associated with several human cancers, including Hodgkin's lymphoma, B-, T-, and natural killer (NK) cell lymphomas, smooth muscle tumors, nasopharyngeal and gastric cancers. Some IEI confer a predisposition to severe EBV infection, and to associated cancers and immunopathological features, with very high penetrance [9,10]. Hemizygous loss of function (LOF) mutations of *SH2 Domain Containing 1A (SH2D1A)* cause X-linked lymphoproliferative disease 1 (XLP1), which consists of EBV-driven fulminant or severe mononucleosis with clinical features of hemophagocytic lymphohistiocytosis (HLH) [11,12]. HLH is a form of hyperinflammation caused by an uncontrolled and ineffective immune response, resulting in tissue damage and organ failure. *SH2D1A* is the only gene associated with selective susceptibility to EBV. It encodes the SH2 domain-containing cytoplasmic adaptor protein SAP (SLAM-associating protein). SAP is produced only in T

lymphocytes and NK cells. It links SLAM family receptors (including SLAM, 2B4, NTB-A, Ly-9 and CD84) to the intracellular signaling network. SLAM family receptors are broadly expressed in the immune system. They are homotypic receptors, except for 2B4, which recognizes CD48. Cytotoxic lymphocytes require SAP for signaling downstream from 2B4 and NTB-A, and for an appropriate response to EBV-infected B cells. Consequently, SAP-deficient CD8<sup>+</sup> T and NK cells display normal cytotoxic responses against various targets, but a selective failure to respond to EBV-infected B cells [13,14]. Accordingly, mutations in genes impairing T and NK cell cytotoxicity (e.g. PRF1) predispose to HLH, which is often triggered by EBV [15]. Together, this suggests a major role of cytotoxicity to prevent control EBV infection.

All the other IEI conferring a strong predisposition to EBV-induced diseases, including oncogenesis, also confer predisposition to other infections, including viral and bacterial infections. These genetic disorders include X-linked MAGT1 (magnesium transporter 1) deficiency, and autosomal recessive (AR) CD27, CD70, TNFRSF9 (TNF receptor superfamily member 9, also known as CD137), ITK (IL-2-inducible tyrosine kinase), CTPS1 (CTP synthase 1) and RASGRP1 (RAS guanyl releasing protein 1) deficiencies. CD27 is a costimulatory receptor constitutively expressed on naïve and some memory T cells, and on memory B cells and subsets of NK cells. CD70 is the ligand of CD27; it is strongly expressed on activated and EBV-infected B cells [16,17]. CD27 costimulation is, thus, required for the optimal recognition and elimination of EBV-infected B cells by T cells [18]. TNFRSF9 on T cells is induced upon activation, and acts as a costimulatory molecule [19,20]. The ligand of TNFRSF9 (TNFSF9) has yet to be linked to EBV susceptibility, but is expressed on activated lymphocytes and antigen-presenting cells [19]. LOF mutations of the *ITK*, *MAGT1*, *CTPS1* and *RASGRP1* genes impair T-cell activation and proliferation after TCR triggering. Mutations of the *ITK* gene impair PLC- $\gamma$ 1 phosphorylation and the downstream activation of calcium fluxes and IP3 production. MAGT1 deficiency also results in impaired PLC- $\gamma$ 1 activation downstream from the TCR [21], together with a congenital disorder of glycosylation affecting a restricted subset of glycoproteins, including NKG2D, CD28 and CD70 [22]. CTPS1 deficiency impairs T-cell proliferation after TCR activation due to the impairment, but not total abolition of cytidine 5' triphosphate synthesis [23]. RASGRP1 is a guanine nucleotide exchange factor. RASGRP1-deficient T cells display impaired MAP kinase pathway activation and proliferation after TCR engagement [24].

Finally, other combined immunodeficiencies (CIDs), such as AR DOCK8, CORO1A, STK4 and CARMIL2 deficiencies, or autosomal dominant (AD) PIK3CD deficiency, are frequently associated with EBV viremia and, occasionally, with EBV-induced tumors [25]. In particular, CARMIL2 deficiency impairs NF- $\kappa$ B activation downstream from CD28, and is often associated with EBV-driven leiomyoma, a rare smooth muscle tumor [26,27]. It remains unclear why CARMIL2-deficient patients develop these EBV<sup>+</sup> smooth muscle tumors (SMTs) whilst remaining resistant to EBV-induced lymphoma, despite the detection of EBV viremia in most patients tested. Interestingly, EBV<sup>+</sup> SMTs have also been reported in several RASGRP1-deficient patients [28,29], suggesting a link between these two molecules in inducing this rare tumor. Suboptimal T-cell activation and proliferation can underlie EBV susceptibility, as illustrated by EBV viremia in many CIDs. Studies of IEI conferring a predisposition to severe EBV infection have demonstrated the crucial role of

signaling by the TNF family receptors CD27 and TNFRSF9 in the control of EBV by CD8<sup>+</sup> T cells. Susceptibility to EBV-induced lymphoma in MAGT1-deficient patients can be explained by an impairment of CD70 expression [22], but further studies are required to determine the reasons for the very high penetrance of EBV-related cancers in patients with RASGRP1, ITK or CTPS1 deficiencies, relative to other T-cell defects (e.g. CARMIL2, DOCK8) known to result in a failure to control EBV replication, but less often leading to lymphoma development.

**2- Kaposi sarcoma-associated herpesvirus (KSHV or HHV8):** Three oncogenic phenotypes are related to HHV8: Kaposi sarcoma (KS), which is an endothelial cell cancer; primary effusion lymphoma (PEL), and multicentric Castlemans disease (MCD), both of which are B cell-derived cancers [30]. KS is the most prevalent of these phenotypes, and four forms have been described: epidemic in patients with acquired immunodeficiency due to HIV, iatrogenic in patients undergoing solid organ transplantation, endemic in sub-Saharan Africa, and classic in elderly men from Mediterranean countries and Eastern Europe [8]. No major difference in histological features has been observed between the four forms of KS, all display spindle-shaped cells, inflammation, and angioproliferation with erythrocyte extravasation, suggesting that similar pathogenic mechanisms are at work.

Three AR IEI have been shown to underlie KS — interferon gamma receptor 1 (IFN $\gamma$ R1), stromal interaction molecule 1 (STIM1) and OX40 deficiencies — in three single case studies. The patients with IFNGR1 and STIM1 deficiencies developed aggressive, systemic KS, and died. The patient with OX40 deficiency developed cutaneous KS and recovered following treatment (IFN- $\alpha$ , vinblastine, etoposide, and pegylated liposomal doxorubicin hydrochloride) [31]. Cutaneous KS has also been reported in three patients with X-linked IEI: Wiskott-Aldrich syndrome (XL-WAS, in one child, and in one adult, who developed T-cell lymphoma) and X-linked immunodeficiency with an Mg<sup>2+</sup> defect, Epstein-Barr virus infection, and neoplasia (XMEN, 1 patient) due to a large deletion of *MAGT1*. Complete remission was achieved in two of these patients, following hematopoietic stem cell transplantation (HSCT, XL-WAS), or treatment (chemotherapy, PegIntron and IVIG, XMEN) [32,33]. Finally, one adult patient with CTLA4 haploinsufficiency was recently reported to have cutaneous and nodal KS [34].

The patient with IFNGR1 deficiency also developed MSMD, the classical clinical expression of this IEI, and had CD4<sup>+</sup> T-cell lymphopenia, a more unusual immunological phenotype, at the time of KS. STIM1 is constitutively expressed in T cells and is the main activator of the Ca<sup>2+</sup> channel ORAI1 following TCR stimulation, whereas OX40 expression is induced on activated T lymphocytes and acts as a costimulatory molecule following TCR activation. XR-WAS affects cells of both the innate and adaptive immunity systems, including myeloid cells, NK cells, B and T cells. The immunological phenotype of patients with MAGT1 and CTLA4 deficiencies included very low naïve CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts. These data highlight the crucial role of T cells, including OX40-dependent T-cell immunity in particular for protection against HHV8. No IEI has yet been associated with HHV8-positive MCD and PEL. Further studies are required, for a comprehensive dissection of the molecular and immunological pathways controlling HHV8 infection, with a view to preventing KS, MCD and PEL.

**Inborn errors of immunity to HPVs**—HPVs were discovered in the 1960s. Five HPV genera ( $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\mu$ - and  $\nu$ -) have been described, and more than >200 genotypes reported, with either cutaneous ( $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\mu$ - and  $\nu$ -) or mucosal ( $\alpha$ -) tropism. HPV infections are usually asymptomatic or self-healing, but persistent infections can lead to debilitating benign tumors or invasive cancers. Only the  $\alpha$ - and  $\beta$ -HPV genera are oncogenic, with genotypes associated with a low or high risk of cancer. Seroprevalence is variable, with <40% and 20-65% of the general population seropositive for oncogenic  $\alpha$ -HPV and  $\beta$ -HPVs, respectively [35].

**1- Alpha-HPVs:**  $\alpha$ -HPV is the only HPV genus capable of infecting the skin, laryngeal or genital mucosa. HPV6 and HPV11 are the most frequent low-risk HPVs associated with benign anogenital condyloma, and rare cases of Buschke-Löwenstein tumor (anogenital mucosa) or recurrent respiratory papillomatosis (RRP). HPV16 and HPV18 are the two principal high-risk oncogenic HPVs, and are responsible for the vast majority of cervical and anogenital cancers. In rare cases,  $\alpha$ -HPVs may also cause Bowen disease, a cutaneous squamous cell carcinoma (SCC) mostly affecting the nails.

AD gain-of-function mutations of *CXCR4* are associated with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome. Between 60 to 80% of patients with WHIM syndrome develop warts following  $\alpha$ -HPV infection [36], and about 16% of these patients go on to develop HPV-related cancers [36]. The immunological phenotype is characterized by neutropenia, low counts of DC, memory B cells and naïve CD4<sup>+</sup> and CD8<sup>+</sup> T cells. GATA2 haploinsufficiency is also frequently associated with HPV infection (>50%), and frequently with genital cancers [37,38]. Low monocyte, DC, B-cell, CD4<sup>+</sup> T-cell and NK cell counts are the most common immunological features of the patients. Warts are also reported in >40% of patients with AR DOCK8 deficiency, which is characterized by T and NK cell lymphopenia, and some patients develop HPV-induced malignancies [39]. DOCK8 deficiency compromises the survival of T and NK cells during cell migration in collagen dense tissues, and DCs migration to lymph nodes, probably accounting for the susceptibility of patients to cutaneous virus infections [40,41]. Thus, the three IEI associated with the highest penetrance of severe HPV infection simultaneously impair the functions of both T cells and antigen-presenting cells (APCs). Cutaneous warts have been reported in 30% of patients with AD CARD11, XLR MAGT1 and AR CARMIL2 deficiencies [22,42,43]. In particular, two patients with CARMIL2 deficiency had recurrent condyloma, and one patient with MAGT1 deficiency had perianal condyloma. Three patients with AR complete CD28 deficiencies have recently been reported. These patients had severe common warts, with one patient displaying “tree man syndrome”, consisting of benign but devastating giant and disseminated HPV2<sup>+</sup> cutaneous horns [44]. Interestingly, CD28, MAGT1, CARD11 and CARMIL2 deficiencies all impair signaling via CD28 [22,26,43], a major T-cell costimulatory molecule recognizing CD80/CD86 on antigen-presenting cells (APCs). Moreover, a number of other IEI, affecting primarily either T cell differentiation or activation, were associated with severe skin or anogenital warts with various penetrance, and, in a few cases, malignancies. These IEI are reviewed elsewhere [35]. One example is the recently reported XL-SASH3 deficiency. Three out of the four patients with SASH3 deficiency developed severe cutaneous warts. SASH3 is associated with neutropenia, B, T,

and NK cell lymphopenia and a defect in TCR signaling leading to a decreased proliferative capacity [45]. Another example is AR ICOS deficiency in two patients who developed HPV-induced vulvar carcinoma and pre-auricular squamous cell carcinoma, respectively [46]. Nevertheless, HPV susceptibility is not common in ICOS deficiency. Finally, five patients with Netherton syndrome (NS), due to mutations of *SPINK5*, have developed HPV-related cancers, including two with Buschke-Löwenstein tumor and SCC [47-49]. In one case, SCC was caused by both  $\alpha$ - and  $\beta$ -HPVs [47]. NS was recently classified as an IEL, as patients are sensitive to cutaneous infections and have low counts of B cells with an immature phenotype and impaired NK cell cytotoxic activity [50,51]. Together, these data suggest that the control of  $\alpha$ -HPVs requires intact APC and T-cell compartments, particularly for CD4<sup>+</sup> T cells. Evidence has also recently been obtained for a major role of the CD28 costimulation pathway.

**2- Beta-HPV:** Epidermodysplasia verruciformis (EV) is a rare disease first reported in 1922. It is characterized by persistent disseminated flat warts and tinea versicolor-like lesions following  $\beta$ -HPV infection. EV may be isolated, occurring in the absence of other infectious manifestations, or syndromic, with a broader infectious phenotype. In 2002, the first two IEL underlying isolated EV were identified with the discovery of AR deficiencies of *TMC6* and *TMC8*, encoding EVER1 and EVER2 [52,53]. In 2018, a third IEL underlying isolated EV was discovered: CIB1 deficiency [54]. EVER1, EVER2 and CIB1 form a complex, the exact function of which remains unknown. Abnormal zinc homeostasis has been described in EVER1/2 deficiencies, suggesting a possible mechanism for the lack of control of  $\beta$ -HPV infection in EV patients. However, no zinc homeostasis defect was detected in CIB1-deficient cells. Moreover, EVER1, EVER2, and CIB1 are targeted by the HPV-E5 and -E8 proteins, suggesting that they act as restriction factors against HPVs. All cases of syndromic EV reported to date were associated with broadly impaired T-cell immunity [53], whereas no abnormalities of T- and B-cell immunity were reported in patients with isolated EV, suggesting a pathogenic mechanism involving a skin-intrinsic defect, probably related to keratinocytes. About 30-40% of patients with EV go on to develop SCC. Interestingly, to our knowledge, all the patients with EV reported to have SCC to date had the isolated form. This may reflect the younger age of patients with syndromic EV, the nature of the genetic defect underlying isolated EV, or both.

**Inborn errors of immunity to HBV—**HBV is a DNA virus from the Hepadnaviridae first discovered in 1965. It displays human-to-human transmission, mostly via blood or intimate contact. According to the World Health Organization, more than 257 million people worldwide were infected with HBV in 2017 (World Health Organization report, 2017). Age at contamination affects the likelihood of chronic disease development and cancer. Over 90% of individuals infected during infancy display progression to lifelong chronic infection, whereas acute infection is usually asymptomatic or resolves spontaneously in adults [56]. However, about 5% of infected adults develop chronic hepatitis, which can lead to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). In very rare cases, HBV infection can lead to acute liver failure [57]. HBV causes 20% of liver cancers in developed countries, and 65% of those occurring in developing countries [58]. Some HBV variants and HBV genome integration have been reported to increase the risks of HCC development

[58,59]. Over the last 15 years, many genome-wide association studies (GWAS) have been performed to identify genetic factors associated with clearance, chronic infection, cirrhosis and/or HCC development [60]. Only associations of variants of *STAT4* and some HLA-class II genes with a higher risk of developing HBV-related HCC have been replicated in different cohorts [60]. Only a very small number of patients with IEI have been reported to display HBV disease, and causality remains to be demonstrated in these cases. Two patients with agammaglobulinemia developed HBV hepatitis, and one patient with hyper-IgM syndrome had HBV-induced HCC [61,62]. One patient with CVID developed HBV cirrhosis, and one recovered [63]. HBV cirrhosis has been reported in two of 27 patients with CIB1 deficiency [54]. Further investigations are required to determine the physiological mechanisms underlying predisposition to HBV infection and disease progression.

**Inborn errors of immunity to Merkel cell polyomavirus**—Merkel cell polyomavirus (MCPyV) was discovered in 2008 [64]. It is a ~5400-base pair non-enveloped double-stranded circular DNA virus from the Polyomaviridae family [65]. Seroprevalence for MCPyV in the adult population ranges from 60 to 100%, depending on the geographic area considered [66]. MCPyV causes Merkel cell carcinoma (MCC), a rare but aggressive type of skin cancer. The genome of MCPyV is found to have been integrated into the genome of the patient in ~80% of MCC cases [64,67]. Accidental viral integration, disrupting the viral cycle but not the expression of the ST and truncated LT oncogenic proteins, leads to transformation [65]. MCC is a disease of the elderly, with a prevalence in the population peaking at the age of 75-80 years. Risk factors for MCC include acquired immunodeficiencies, such as HIV infection/AIDS and organ transplantation, suggesting that an ineffective immune response against MCPyV increases the risk of transformation [65]. Very little is known about the human genetics of susceptibility to MCPyV. The disease is sporadic, and no familial cases have been reported, to our knowledge. A few cases in children and young adults have been reported, with an estimated prevalence of MCC infection of ~1 in 100,000,000 before the age of 30 years [68]. The sporadic nature of MCC and its late onset probably reflect the need for long-term MCPyV infection before incidental viral integration. As a result, MCC would be expected to segregate with incomplete penetrance, even in individuals poorly controlling the infection. To our knowledge, only one case of MCC has been linked to a primary immunodeficiency in a 55-year-old woman with GATA2 deficiency [69,70]. This patient had B-cell and CD4<sup>+</sup> T-cell lymphopenia, low NK cell counts, monocytopenia and hypogammaglobulinemia. She also suffered from neurofibromatosis type 1 (NF1), which may have contributed to MCC development. The son of this patient also had GATA2 deficiency, but did not develop MCC and died from severe respiratory infection at the age of 22 years. The available evidence, including the very early onset of idiopathic cases and the higher susceptibility in patients with acquired immunodeficiency, strongly suggests that inborn errors of immunity can underlie sporadic MCC, as highlighted by a single case report.

### RNA oncoviruses

**Inborn errors of immunity to HCV**—HCV is a 9.6 kb positive single-stranded RNA flavivirus discovered in 1989. Contamination occurs through contact with infected blood. More than 170 million individuals worldwide are infected with HCV [58]. Chronic hepatitis

develops in 50-80% of infected individuals, some of whom develop liver fibrosis and cirrhosis, sometimes decades after primary infection. HCV is the second most important risk factor for HCC, after HBV, accounting for 10-20% of cases. Genome-wide association studies (GWAS) have investigated the genetic factors conferring predisposition to HCV infection *per se* or to the fibrosis/cirrhosis phenotype. The major genetic discovery has been the association between the *IFNL* locus and the spontaneous clearance of HCV infection or response to treatment [71,72]. Associations have been found between other loci and fibrosis development, but have yet to be validated biologically [73,74]. In addition, some patients with antibody deficiencies have suffered HCV infections after blood or immunoglobulin transfusions. The main causes of antibody deficiencies are XLA, CVID, hyper-IgM syndrome and congenital hypogammaglobulinemia. Various outcomes were observed for HCV infection in these patients, including spontaneous recovery, recovery after treatment, chronic active hepatitis, cirrhosis and end-stage liver failure [75-78]. More recently, two patients with GOF *STAT1* mutations and HCV cirrhosis have been described [79]. One patient with *CIB1* deficiency died from HCV-induced hepatocarcinoma [54], and one patient with *CD40L* deficiency received a liver transplant following end-stage liver failure due to chronic HCV disease [80]. Given the small number of patients and the lack of clinical and immunological phenotypes common to the various IEI, it is difficult to draw any firm conclusions as to whether the severe HCV infection was coincidental or genuinely genetically driven by these IEI. Additional investigations will be required to dissect the genetics determinants of anti-HCV immune responses and oncogenesis.

**Inborn errors of immunity to HTLV1**—HTLV1 is a ~9000-base oncoretrovirus discovered in 1980 [81]. The number of patients infected with HTLV1 was estimated at between five and ten million worldwide in 2012, with clusters of high endemicity [82]. HTLV1 mostly infects CD4<sup>+</sup> T cells, and, to lesser extent, other lymphocytes and myeloid cells. Infection requires cell-to-cell contact and generally occurs via breast-feeding, sexual intercourse or exposure to contaminated blood. HTLV1 seropositivity therefore typically clusters within families. Most people with HTLV1 infection remain asymptomatic, but about 5% of infected individuals develop adult T-cell leukemia (ATL), at reported median ages of between 45 and 70 years. Another 3% develop HTLV-1-associated myelopathy–tropical spastic paraparesis (HAM/TSP), a progressive inflammatory disease of the central nervous system (CNS) that causes weakness or paralysis of the legs, lower back pain and urinary symptoms [83]. HTLV-1 may also cause inflammatory syndromes in several organs, and confers predisposition to infection with certain pathogens [83]. The interindividual variability of clinical progression probably reflects age at infection (infancy vs. adulthood) [81], and host genetic factor conferring predispositions to different disease outcomes. ATL is more likely to occur in patients infected during childhood, whereas HAM is more likely in patients infected later in life. The host genetic determinants underlying predisposition to HTLV1 infection and disease progression remain largely unknown. One study based on genome-wide linkage linked predisposition to HTLV1 infection in children to the 6q27 and 2p25 regions, but the molecular basis of infection was not determined [84]. The HLA-A\*02 and HLA-C\*08 alleles have been shown to be associated with lower proviral load and a lower risk of HAM/TSP in Japanese populations [85,86]. By contrast, HLA-B\*54 was found to be detrimental and associated with a higher viral load [86]. The protective or detrimental

effects of these HLA alleles were enhanced by the presence of the *KIR2DL2* gene, encoding an inhibitory killer immunoglobulin-like receptor (KIR) expressed on NK cells and CD8<sup>+</sup> T cells [87]. However, this reported lower proviral load and lower risk of HAM/TSP in HLA-A\*02<sup>+</sup> individuals was not confirmed in a Caribbean population [88]. Thus, the host genetics of severe outcome of HTLV-1 infection remains poorly understood.

## Conclusion

Age at infection with oncoviruses varies considerably, from early childhood to adulthood, depending on the mode of transmission and endemic distribution of the virus concerned. Even in the absence of genetic diagnosis, IEI conferring a predisposition to multiple infectious agents are usually detected in infancy, and close follow-up and preventive actions and/or treatment are initiated. The specific mode of inheritance and preventive actions may help to limit the incidence of oncovirus infections in patients with IEI, but they complicate the study of genetic determinism. This is particularly true for HBV, HCV and, to lesser extent, HTLV-1. However, the study of IEI has improved our understanding of the immune response required for the optimal control of some oncovirus infections, and associated cancer risks. In the context of EBV and HHV8 infections, studies of IEI have highlighted the essential role of T lymphocytes, and particularly of CD8<sup>+</sup> T/NK cells for EBV and CD4<sup>+</sup> T cells for HHV8, in the control of infection. The control of HPV infections requires functional keratinocyte-intrinsic immunity ( $\beta$ -HPVs) and T cell-dependent adaptive immunity ( $\alpha$ - and  $\beta$ -HPVs). Requirement of T cell costimulation pathways are different for protection against EBV and HPV. CD27 or CD137 costimulation deficiencies underlie severe EBV infection, while deficiencies of CD28 costimulation axis underlie susceptibility to  $\alpha$ -HPV infection. Interestingly, cancer penetrance is never complete in patients with IEI infected with the oncovirus to which they are susceptible (e.g. lymphoma and genes predisposing to EBV infection). This suggests that the IEI only impair infection control, and that transformation requires other genetic (inherited or somatic) or environmental factors, or both. Further studies of patients with idiopathic severe oncovirus infections will undoubtedly shed more light on the immune mechanisms underlying oncovirus control. These studies will enable physicians to identify populations of patients at risk of specific cancers, and may pave the way for novel therapeutic strategies.

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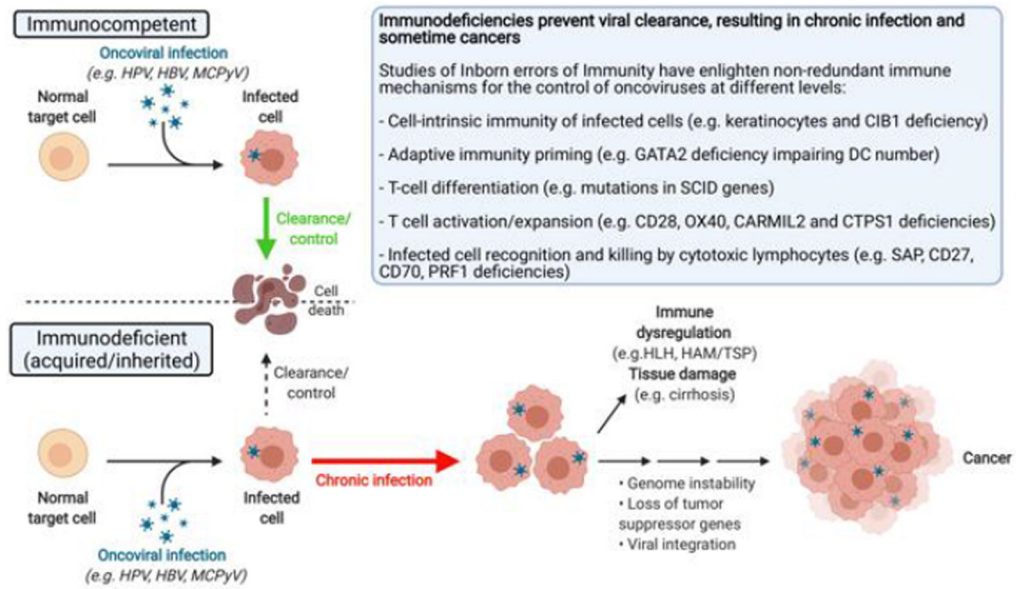
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**Figure :** Schematic representation of the oncogenic process in immunocompetent and immunodeficient individuals. Insights in non-redundant immune mechanisms for the control of oncoviruses gained from the study of inborn errors of immunity are listed in the upper right box. Most of them come from the genetic studies of HPV, EBV, and to lesser extend HHV8 infections. Genetic factors predisposing to severe HBV, HCV, MCPyV and HTLV1 remain largely unknown.