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Research paper

Molecular and cellular interplay in virus-induced tumors in solid organ recipients

Alessia Gallo[a,*], Monica Miele[b], Ester Badami[b], Pier Giulio Conaldi[a]

[a] Department of Laboratory Medicine and Advanced Biotechnologies, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy
[b] Ri.MED Foundation, Palermo, Italy

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ABSTRACT

Patients following solid organ transplantation show a higher risk of developing cancer compared to the general population. Elevated risk is likely due to the interplay of a combination of factors, such as chronic inflammation, coexisting medical conditions, immunosuppressive regimen and persistent infection with oncogenic viruses. In addition, the tumor microenvironment plays a pivotal role in cancer progression, by driving recruitment and *in situ* differentiation of anti-inflammatory cells of the adaptive and innate immune system such as regulatory T cells, Th17, Dendritic Cells, Myeloid Derived Suppressor Cells, Type 2 Macrophages. Here we discuss the molecular role and the contribution to oncogenesis of Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8) and Hepatitis C virus (HCV) in immunocompromised patients and describe how these viruses may contribute to oncogenesis both directly and indirectly.

1. Introduction

Patients with end-stage organ failure resort to transplantation as a treatment of choice, and even if life expectancy is extended, the risk of poor outcomes remains high. Despite the vast effort put into finding the best match between organ donors and recipients before transplantation, there is no perfect match, apart from identical twins. The result is a lifelong course of immunosuppressive medications to prevent organ rejection but, as a consequence, this leaves the patient with a weakened immune system.

Among the most common immunosuppressants prescribed for solid organ transplant (SOT) recipients, there are: 1) calcineurin inhibitors, which inhibit the action of the enzyme calcineurin, activating T-cells [1]; 2) macrolides, such as cyclosporine, tacrolimus, and sirolimus [2], which interfere with the production and release of interleukin-2 (IL2), affecting the immune response mediated by antigen-specific cytotoxic T lymphocytes, but not the humoral immunity; 3) antimetabolites, such as mycophenolate mofetil, which inhibit purine production and impair cell proliferation [3], exerting the strongest effect on proliferating activated T and B lymphocytes; and 4) immunosuppressive monoclonal antibodies, such as basiliximab, through the binding of the IL-2 receptors, which impair normal function of cell surface markers, thus inhibiting stimulation of T lymphocyte clones directed against foreign antigens [4].

Following transplantation, and over the course of their lives, these patients are at higher risk for many types of cancer (risk increased by 15–30 times for children, and twice for those transplanted at over the age of 65), compared with the general population [5]. Persistent infection with oncogenic viruses, chronic inflammation, and coexisting medical conditions are generally considered the major causes of an elevated risk of developing cancer.

The immune system has a key role in controlling cancer onset and progression. Recognized as "non-self," cancer cells trigger immune responses, characterized by the infiltration of various immune cells (tumor infiltrating lymphocytes – TILs), which can affect tumor progression. As a response, tumors develop a number of strategies to evade immune surveillance by inhibiting, for example, recruitment, activation, proliferation and function of cytotoxic CD8+ T lymphocytes and NK cells, and by enhancing expansion of immunosuppressive populations such as Th2, Th17, regulatory T cells (Treg), anti-inflammatory type-2 macrophages (M2), tolerogenic Dendritic Cells (DCs), and myeloid-derived suppressive cells (MDSC) [6]. Neoplastic cells thus establish a pro-oncogenic microenvironment where tumor-specific inflammatory T lymphocytes become hyporesponsive to cancer cells.

A large number of viruses have been described as oncogenic in animals, but with evidence of a clear association with the development of tumors in humans in only a few of them. It has been proposed that these viruses can contribute to carcinogenesis in humans by: (i) directly

* Corresponding author at: Department of Laboratory Medicine and Advanced Biotechnologies, IRCCS-ISMETT, via Tricomi 5, 90127 Palermo, Italy.
E-mail address: agallo@ismett.edu (A. Gallo).

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inducing the expression of specific oncogenic proteins, and (ii) by transforming the recipient cells through an indirect virus-induced chronic infectious and inflammatory mechanism [7]. Indeed, it is known that several viruses with different replication mechanisms contribute to oncogenesis in immunosuppressed patients, both directly and indirectly [8]. Among them, in this mini review we explore the molecular role and the contribution to oncogenesis of the Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8), and hepatitis C virus (HCV) in immunocompromised patients.

2. Epstein-barr virus (EBV)

EBV is widespread globally, with 90% of adults presenting serological evidence of exposure. EBV is also implicated in carcinogenesis and the development of Hodgkin's disease, non-Hodgkin's lymphoma, and other manifestations of post-transplant lymphoproliferative disease (PTLD), as well as nasopharyngeal cancers and leiomyosarcomas [9]. EBV-induced B lymphocyte transformation is a complicated process, and involves changes in many genes and pathways related to the interaction between the virus and the host. The manifestation of EBV-related tumors often varies according to the patient's immune status regarding either HIV infection or transplant-related immunosuppression [10]. Generally, virus infection or reactivation of latent infection alone is not sufficient to promote cancer, but the rapidity with which some EBV-associated malignancies occur after transplantation is also consistent with the idea that other elements, such as the immunosuppressive microenvironment, local autocrine/paracrine loops, and host-derived factors are involved [11].

PTLDs occur on average in 1%–16% of SOT recipients. The risk depends on the type of transplanted organ, type of immunosuppression, exposure to lymphocyte-depleting antibody therapies (anti-thymocyte globulin and OKT3), and the immune status of the donor and recipient, with the highest risk in EBV-seronegative recipients of EBV-seropositive donors [12]. Most of the PTLDs, particularly those occurring early after transplantation, are associated with EBV primary infection and are mainly characterized by the broad type III latency expression pattern [13], similarly to *in vitro* grown EBV-immortalized lymphoblastoid cell lines (LCLs). The resolution of a high percentage of PTLD cases in response to a reduction in immunosuppression, particularly of anti-T-cell agents that impair EBV-specific T-cell-mediated immune surveillance, strongly suggests that the state of immunosuppression is among the most important permissive factors for PTLD development [14]. The immunosuppressive state creates an environment in which a weak or absent response of viral specific circulating T-cells against EBV allows unchecked viral replication and cell transformation, leading to the progression of uncontrolled EBV-driven lymphoproliferation [15]. Immunosuppressive therapy reduction is the first line of treatment for PTLD to reawaken the virus-specific T-cell population, but dose reduction carries the risk of graft rejection. In an alternative approach, adoptive transfer of *in vitro*-grown allogeneic or autologous EBV-specific cytotoxic T lymphocyte clones (CTLs) has proven successful, and is increasingly used for the prevention and treatment of PTLD in allogenic stem cell and SOT recipients [16,17].

EBV encodes a series of proteins that are able to up-regulate the production of several soluble factors, inducing the growth and/or survival of lymphoid cells, transcription and anti-apoptotic factors that can promote tumor progression through autocrine and paracrine pathways, and suppression of host anti-tumor immunity.

LMP-1, a latent cycle protein, is the main driver of the increased expression and local release of cytokines and chemokines that may be functionally relevant for B-cell growth and survival, such as IL-6 and IL-10 [18].

Historically, overproduction of IL-6, a B-cell growth factor, has been associated with the pathogenesis of lymphoid malignancies [19]. It has been shown that IL-6 promotes the growth of EBV-infected B cells in an autocrine feedback loop, and patients with PTLD produce abnormally high levels of IL-6 [20]. A tumorigenic role for IL-6 in PTLD was also suggested by experiments in which EBV-transformed B cells were transfected with human IL-6 cDNA: transfection significantly increased the proliferation of these cells *in vivo* and *in vitro* [21]. A phase I-II clinical trial has reported that neutralization of IL-6 by anti-IL-6 monoclonal antibodies in PTLD induced a clinical response [22]. Alternatively, IL-6 has been shown to inhibit immune effector functions, such as natural killer (NK) cell activity, and cytotoxic functions of splenocytes in athymic mice, thereby permitting tumor development [23]. Furthermore, immunosuppressive drugs may contribute to increased IL-6 levels in transplant recipients since cyclosporine A has been shown to enhance IL-6 production in T cells and monocytes [19]. The production of pro-survival cytokines, such as IL-10, produced by Th2 cells, B cells, DC, and monocytes can regulate the growth and differentiation of cytotoxic T cells and B cells. B cell lymphomas isolated from transplant recipients with PTLD constitutively produce human IL-10, and utilize this cytokine as an autocrine growth factor in spontaneous LCL [24]. Increase in IL-10 production can also be induced in B cells by the viral latent membrane protein latent membrane 2A (LMP-2A) through activation of PI3-kinase [20]. Later, the same group demonstrated that the PI3K-regulated kinase, Bruton's tyrosine kinase (BTK), is responsible for phosphorylating STAT3, which ultimately mediates the LMP2A-dependent increase in IL-10 production. In light of the use of BTK inhibitors in clinical trials, these findings potentially highlight novel pharmaceutical approaches to treat EBV-associated lymphomas that express LMP2A [25]. EBV has evolved several tactics to prevent apoptosis of the infected cell in order to augment viral persistence [26]. Only when host cells receive sufficient survival signals do they become immortalized. A functional bcl-2 homolog encoded by BHRF1, as a latent and lytic gene encoding a 17-kDa component of the restricted early antigen complex (EA-R), can inhibit apoptosis induced by a range of stimuli at least in part by binding to the pro-apoptotic protein Bim [27]. The structure of BHRF1 in complex with Bim confirms that BHRF1 can counteract Bim directly [28]. These findings may facilitate the exploitation of small-molecule inhibitors of BHRF1 to improve the poor prognosis in EBV-associated diseases, since BHRF1 confers strong chemoresistance, and current small molecules inhibitors of Bcl-2 do not target BHRF1 [28].

PTLD prognosis is highly influenced by stromal and immune cells of the local niche in which the tumor cells reside. Though the immune responses in post-transplant patients are profoundly altered due to the chronically administered immunosuppressive regimen, infiltration of CTL is associated with favorable prognosis and, conversely, infiltration of regulatory Treg cells was limited, with consequent release of B cells from inhibition and promotion of PTLD development [29]. In PTLD patients, increased expression of PDL1, a marker of T cell exhaustion, was observed in tumor biopsies [30]. Accumulation of immune-regulatory macrophages (M2) has also been associated with worse disease outcome in EBV+ patients, and possibly contribute to tissue remodeling and tumor progression, as opposed to pro-inflammatory M1 macrophages [31]. It is still a matter of debate whether M2 macrophages are recalled to the tumor tissue from the periphery or develop *in situ*. The latter hypothesis is supported by evidence that EBV encodes for IL10, a cytokine that drives macrophage polarization into M2 [32].

Other gene products encoded by the EBV genome include miRNAs [33]. EBV has the largest reservoir of miRNAs among human herpesviruses known to date. EBV encodes at least 44 miRNAs, which can potentially regulate hundreds of genes, but their identities are just beginning to emerge. It has been established that virally encoded miRNAs participate in viral-host cell interactions, including immune evasion, prolongation of survival of infected cells, and regulation of viral genes, and potentially contribute to the pathogenesis of viral-associated disease [34]. Accumulated evidence has shown that EBV miRNAs promote survival and proliferation of infected B cells early during infection, as well as in tumor cells [35]; moreover, viral miRNAs were also found to modulate immune evasion [36]. A recent study on EBV B cell lines

derived from PTLD patients found that host microRNA-194 participates in regulation of IL-10, suggesting a role for EBV in changing the cellular microenvironment through modulation of the miRNA network [37]. Also, onco-miRNAs miR-21 and -155 activate cell growth, and both miRNAs have been described as essential for growth of EBV-infected LCLs. Transgenic expression of hsa-miR-21, 155, and the miR-17–92 cluster leads to high-grade B cell lymphomas in animal models [38,39], while a constitutive expression of miR-155 in B cells leads to uncontrolled proliferation of pre-B cells, and subsequent malignancy [40]. It has also been shown that viral miRNAs, usually expressed by human EBV-transformed LCLs, are also packaged into exosomes. We have previously demonstrated that two miRNAs (ebv-miR-BART3 and ebv-miR-BHRF1-1) are more abundant in the exosomes, suggesting a microvesicular viral microRNA-specific transfer [41]. In recent years, exosomes have emerged as critical mediators of intercellular communications between cancer and stromal cells that may generate a local microenvironment conducive to tumor growth and diffusion [42]. EBV affects exosome content and functions, and virally modified exosomes can contain the viral oncoproteins LMP1 and LMP2, and virally encoded miRNAs that contribute to viral persistence and pathogenesis [43].

As discussed briefly in this section, EBV is able to arrange complex interactions with the cellular microenvironment to support growth and survival of transformed B cells (Fig. 1), favoring an escape from immune surveillance. Indeed, novel therapeutic approaches are emerging that mainly target the cellular and molecular interplay between EBV and the tumor microenvironment.

3. Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8)

Kaposi's-sarcoma-associated herpesvirus, or HHV8, is of the human γ-herpesvirus family. The International Agency for Research on Cancer (IARC) recognized KSHV as a group I carcinogen [44] based on the data from clinical studies, both cohort and case-control reports, involving patients with long-term immunodeficiency, such as HIV infection and SOT patients. KSHV is the etiological agent of Kaposi's sarcoma (KS), a highly inflammatory vascular tumor, defined by characteristic spindle cells [45]; for primary effusion lymphoma (PEL), a peculiar liquid-phase lymphoma arising and growing in the body cavities [46], and multicentric Castleman's disease (MCD) [47]. Primary KSHV infection transmitted from a seropositive donor to a seronegative liver transplant recipient can cause a severe non-malignant illness that is associated with high mortality [48]. As a herpesvirus, KSHV has a life cycle characterized by two phases, latent and lytic [49,50] and, like other herpesvirus, establishes latent infection in its host following an acute infection. When latency is disrupted, KSHV switches to a lytic life cycle, expressing all of its viral genes and producing infectious virions. Though the virus is interested in keeping and maintaining the host alive, the development of a lifetime latency in the host is the result of a delicate balance between the latency-lytic switch and host immune surveillance [50]. Alteration of the host immune surveillance system breaks the balance, either reactivating KSHV or allowing primary infection, and induces KS [51,52]. Though KSHV-associated cancers are commonly associated with latent-infected cells, KSHV shows a unique characteristic, among the herpesviruses, of contributing to tumorigenesis with the lytic cycle, and not only requiring it for progeny virus production [53]. Lytic replication contributes to tumorigenesis by providing a proinflammatory and proliferative environment [54]. In addition, KSHV is unique because it has a broader range of cell tropism, and is able to infect B cells, endothelial cells, epithelial cells, and monocytes [55,56]. For example, KSHV infection of human monocytes upregulates expression of PD-L1, a marker of cellular exhaustion, and recently recognized as a target for cancer treatment, likely representing a mechanism of escape from immune surveillance to sustain survival of the virus and tumor progression [57]. Despite different mechanisms of infection, it has been shown that KSHV has the same strategies as other viruses to invade host cells, and to activate the same pathways for inducing the host cells proliferation, transformation, and escape from host immune responses [58].

During the latency phase, KSHV encodes for a limited set of viral genes. Among them, latency-associated nuclear antigen 1, LANA-1, has been suggested as an oncogene by definition [59]. LANA-1 is a multifunctional major viral latent protein, responsible for the maintenance of the viral episome and homologous to EBNA-1, EBV nuclear antigen 1 [60], with which it shares the role of being an oncogene [61,62]. LANA-1 is found in all KSHV-related tumors, e.g., KS, PEL, and MCD [63], and affects the host transcriptional status through many pathways. P53 and pRb are the two most important tumor suppressors inactivated by the

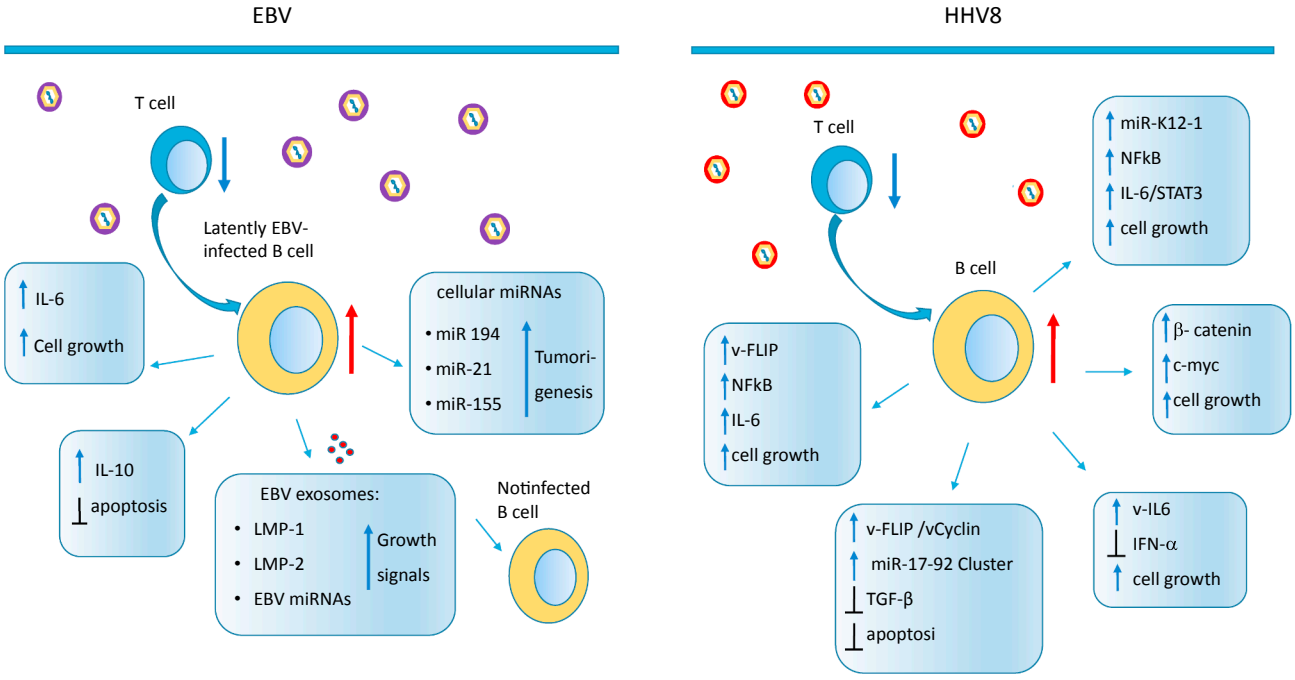

Fig. 1. Schematic representation of the main molecular and cellular pathways affected by EBV (left panel) and KSHV (right panel) infection in an immunosuppressed environment.

binding of LANA-1 [64,65]. LANA-1 is known to affect proliferation by binding and sequestrating GSK-3β, with the result of upregulating cyclin D, an important gene for proliferation [66]. In KSHV-transformed metanephric mesenchymal cells, it has been identified as a novel viral oncogenic signaling pathway affected by LANA-1. In fact, Liang et al. found that the axis BMP-Smad1-Id signaling is upregulated by LANA-1 binding with Smad1, and thus contributing to the oncogenicity [67]. Nevertheless, it has been postulated that LANA-1 is necessary but not sufficient for full cellular transformation [59].

During latency, KSHV also encodes for other gene products believed to be important for lymphomagenesis, such as viral cyclin, v-Cyc, and viral FLICE inhibitory protein v-FLIP [68]. V-FLIP is a potent activator of NF-kB, and able to induce the production of IL-6, a strong B-cell growth-promoting cytokine [69]. By activating the NF-kB pathway, v-FLIP inhibits the expression of lytic genes through the suppression of the AP-1 pathway, and blocks RTA (replication and transcription activator) transactivation in the lytic gene promoter as well [70,71]. V-FLIP and v-cyclin are also able to augment transcription from the miR-17–92 promoter, which in turn strongly down-regulates TGF-β signaling [72], usually involved in the suppression of cell growth and promotion of apoptosis [73].

Though there is the traditional concept that lysis does not contribute to oncogenesis because it leads to the death of the host cell, recent evidence suggests that the KSHV lytic phase plays a pivotal role in tumorigenesis. Martin et al. [74] described how the administration of anti-viral drugs, known to block only the lytic phase and not the latent one, were able to reduce the incidence of KS in AIDS patients. Montaner et al. [75] postulated the central role of a KSHV lytic gene, the viral receptor coupled to the protein G (vGPCR), in the development of KS. This receptor activates AKT, an important kinase that is part of the PIK3-AKT-mTOR pathway [76], and subsequently causes release of IL-6 and stimulates VEGF production in both paracrine and autocrine manners for cell growth and survival. Clinical studies have demonstrated that mTOR inhibition results in skin KS regression in transplant patients [77]. It has recently been reported that KSHV infection of endothelial cells induces the cytokine angiopoietin-2 (Ang-2), which works as a chemoattractant of monocytes into tumors [78]. Additionally, KSHV + endothelial cells also secrete such cytokines as IL-6, IL-10, and IL-13, that synergistically promote polarization of monocytes into tumor associated macrophages (TAMs), which sustain tumor growth, angiogenesis and metastasis formation [79].

Interestingly, KSHV encodes for a viral cytokine named v-IL6, which is usually secreted from B-cells after KSHV infection [80]. V-IL6 is found highly expressed in PEL and MCD [81,82], but rarely in KS [83]. V-IL6 can block the antiviral activity of IFN-α [84], and induce the host cell to productive IL-6-mediated cell proliferation in PEL cells [85].

Another interesting oncogenic strategy implemented by KSHV is the use of microRNAs. KSHV encodes for 12 pre-miRNAs. Of the 12 pre-miRNAs, 10 are clustered and located in the sequence between kaposin and ORF71 in the latency-associated region and target the host immune system, cell cycle regulation, and apoptosis [86,87]. Two pre-miRNAs, miR-K10 and miR-K12, are located, respectively, within the ORF of kaposin and within the coding region or the 3′UTR of the KSHV K12 gene, and are both upregulated in response to lytic induction [87,88]. Five miRNAs – miR-K12-10b, miR-K12-12*, miR-K12-1*, miR-K12-5, and miR-K12-3 originating from this cluster were detected in the peripheral blood of a patient with KS–associated herpesvirus inflammatory cytokine syndrome after a liver-kidney transplant [89]. The remaining ten pre-miRNAs (miR-K1 through K9 and miR-K11) are clustered within a viral intron located between ORF71 and kaposin [90], and show a primary function during latency. They are not affected during the lytic phase [87]. In particular, miR-K9 and miR-K3 directly and indirectly target the RTA gene, suppress reactivation of the lytic phase [91], and contribute to the maintenance of the latency phase. Of note, miR-K12-1 was reported to directly activate NF-kB/IL-6/STAT3 signaling and, thus, functions as an oncogene [92]. The other main function of viral miRNAs is to act as human cellular miRNA analogs. Examples of miRNA using this mechanism of action are miR-K10a, miR-K3, miR-K11, analog of miR-142-3p, miR-155, and miR-23 [93–95].

The metabolic changes occurring within the tumor microenvironment strongly influence disease outcome. KSHV + infected cells transport viral microRNAs to neighbor cells via exosomes, driving a metabolic alteration towards an aerobic glycolysis in the non-infected cells, growth of infected cells, and viral spread. This is not mediated by newly-formed viral particles, and thus eludes immune surveillance [96].

All the oncogenic mechanisms driven by KSHV described above are potentially dangerous, especially in those patients who are immunocompromised, such as SOT patients (Fig. 1), and thus develop an immune-inflammatory network permissive to malignant outgrowth, and fail to eradicate virus-transformed clones [97]. Proliferating B-cells are controlled by cytotoxic T-cell (CTL) responses, and in the case of KSHV infection, KSHV-infected B cells produce high levels of human and viral IL-6, which stimulate B cells to grow and survive [59]. Myoung and Ganem, in 2011, proposed the most convincing evidence of the fundamental role of the T-cell in regulating the reactivation of KSHV [98]. The experiments showed that culture of human tonsillar B cells and T cells exposed to KSHV results in a latent infection of B cells without production of virions. The addition of an immunosuppressant in order to prevent the risk of organ rejection, causing an inhibition of T cells, resulted in a spontaneous lytic production, demonstrating that continuous presence of functional T cells is required for active suppression. This is in line with clinical evidence linking immunosuppression and KS incidence in immunosuppressed patients [51,52].

4. Hepatitis C virus (HCV)

Hepatitis C virus (HCV) establishes chronic liver infection in the majority of patients, with an estimated 150 million cases worldwide, making it the second leading cause of cancer mortality globally [99]. Chronic infection causes long-term inflammation and consequently liver lesions associated with steatohepatitis, fibrosis and, eventually, cirrhosis or HCC [100]. New generation direct acting antivirals (DAAs) mark an important milestone in the treatment of HCV infection, achieving sustained virological response (SVR) rates of more than 90% in patients with chronic hepatitis in an interferon-free regimen, as opposed to pegylated interferon (PegIFN-α)/ribavirin therapy [101].

DAA clinical trials are relatively recent, and there is no definitive information on long-term side effects [102]. Recently, two studies were conducted on a group of HCV + patients with prior history of treated HCC. Quite unexpectedly, the authors observed, alongside viral clearance, increased rates of tumor recurrence in patients following successful treatment for HCC, and within months of exposure to DAA treatment [103,104]. The risk of HCC persists in cirrhotic patients infected with HCV even after curative treatment with DAA. A recently emerging question is what the role of DAA therapy in HCC is after achieving SVR in patients with HCV cirrhosis. Tumor recurrence after DAA therapy might be due to the concurrence of a number of factors: inhibition of immunosurveillance caused by the therapy itself; loss of a protective effect from chronic inflammation; down-regulation of IFN genes expression; clearance of HCV, which keeps at bay dedifferentiation of hepatocytes into neoplastic cells; and lesions undiagnosed before start of treatment. These data prompt the need to carefully re-evaluate new approaches of treatment combining DAAs with alternative therapies, such as cellular therapies, that take into consideration HCC relapse or exacerbation or even *de novo* occurrence, as described by others [105].

Liver transplantation is still used as a curative remedy, extending patients' life expectancy. However, in HCV patients, reinfection recurs in virtually all patients, aided by the regimen of immunosuppression administered to transplanted patients. Recently, a study was conducted

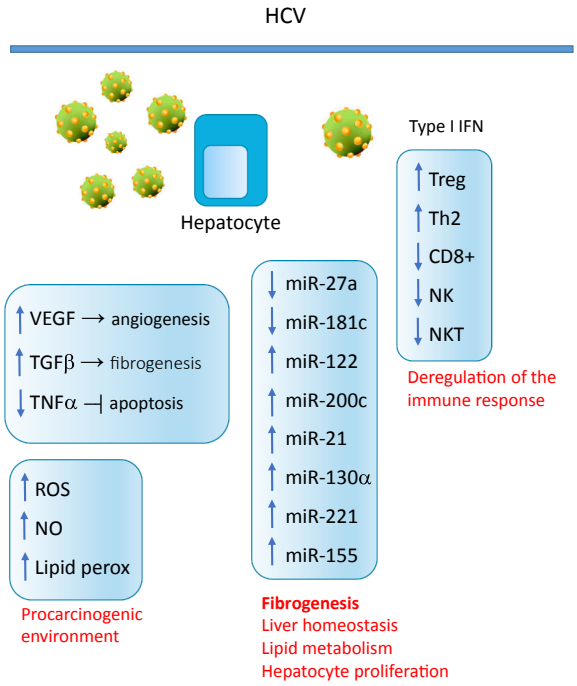

Fig. 2. Schematic representation of the main molecular and cellular pathways affected by HCV infection.

that analyzed the long-term (> 5 years) survival rate in liver transplant patients comparing HCV + HCC + and HCV − HCC + groups of patients. It was shown that the coexistence of HCC and HCV resulted in the worst outcomes in terms of long-term patient and graft survival, with double the risk of mortality. HCV + patients had lower survival post-transplantation, while HCC alone did not show a major impact on survival. Patient survival decreased in the HCC + HCV + group, and this was dependent on HCV recurrence [106].

There is no direct evidence that HCV can cause HCC as it does not integrate in the host genome. However, chronic HCV infection has been associated with an increased risk of developing HCC. HCV infection increases the risk of HCC by 14- to 22-fold compared with HCV-negative patients [107]. This is likely induced through inflammation and cirrhosis.

A close association between HCV infection and HCC is recognized, and is dependent on environmental, viral, and host factors (Fig. 2). Chronic inflammation caused by infection damages hepatocytes at metabolic and genetic levels, leading to apoptosis. Liver regeneration occurs in an HCV-infected microenvironment, and tends to induce more genetic alterations and consequent neoplastic transformation of hepatocytes, and carcinogenesis [108]. HCV interferes with both innate and adaptive immunity by blocking, for example, the production of type I interferons, and favoring the expansion of anti-inflammatory T-cell subsets, such as Th2 and Treg, and also by impairing the anti-viral functions of cytotoxic CD8 lymphocytes and NK cells [109,110]. Cirrhotic HCV patients are characterized by tumor infiltrating lymphocytes (TILs) that accumulate in the liver but do not succeed in viral clearance, and instead establish chronic inflammation. Increasing evidence indicates the immunosuppressive nature of the local environment in tumors. For example, augmented secretion of IL-17 by CD4 + T cells has been associated with increased post-transplant HCC recurrence [111]. Accumulation of CD8 + T cells in the liver of HCV + HCC + patients is associated with HCC progression, and is considered a prognostic factor for post-transplant/resection of tumor recurrence [112]. HCV + HCC + patients are characterized by increased inflammatory CD8 + cells and decreased NK and NKT cells, known to patrol the host for cancer immunosurveillance [113]. Treg cells usually infiltrate HCC, and a predominance of Treg over CD8 + T cells is associated with a worse prognosis [114]. Treg cells promote hyporesponsiveness to tumor cells, thus producing an overall detrimental effect and cancer development. The levels of Treg cells have indeed been correlated with HCC stages [115]. Myeloid-derived suppressive cells (MDSC) sustain an anti-inflammatory immune microenvironment by suppressing the function of effector T cells [116]. Within the liver tumor microenvironment, DCs also contribute to tumor progression as they are reduced in number and present reduced pro-inflammatory function, resulting in an immune response to neoplastic cells that is not strong enough [117]. Progression from cirrhosis to HCC in HCV + patients is the result of the effects of chronic inflammation combined with a deregulated immune response to cancer. HCV promotes a procarcinogenic environment inducing the release of reactive oxygen species (ROS), nitric oxide species, peroxidated lipids, and aberrant expression of cytotoxic cytokines [118]. Additionally, immune surveillance is deregulated, leading to higher rates of cancer cells that escape immune pressure, favoring progression of cancer. Many inflammatory cytokines, including TNF-α, interleukin (IL)-1, IL-23, IL-6 and lymphotoxins (LTs) α and β have been implicated in chronic liver inflammation and HCC progression [119]. HCV-related HCC depends on a fine balance between pro- and anti-inflammatory cytokines. For example, a high ratio between TNF-α and IL-10 is observed in the sera of HCC patients [120]. HCC is triggered indirectly by the status of chronic inflammation maintained by the host immune system, but also directly by HCV, which interferes with hosts regulatory pathways of tumor suppression. HCV viral structural and non structural proteins induce proliferation of hepatocytes, contributing to tumor initiation, and deregulate pathways maintained by RAF/MAPK/ERK, NF-κB, and JAK/STAT3, which are known to be associated with particularly aggressive liver cancer [121]. Equally important in cancer progression is inhibition of the apoptosis by HCV. For example, the HCV NS5A protein counteracts the apoptotic effect of tumor necrosis factor (TNF)-α by blocking the activation of caspase-3, and inhibiting the proteolytic cleavage of the death substrate poly (ADP-ribose) polymerase (PARP1) [122]. Though the HCV genome does not integrate into host DNA, some of the targets of HCV proteins are host tumor suppressors and proto-oncogenes [123]. Additionally, chronic inflammation tends to transform the TGF-β activity from tumor-suppressor to pro-fibrogenic, increasing the risk of HCC. The HCV protein also promotes angiogenesis and spread of metastasis through hepatic blood vessels by indirectly inducing up-regulation of vascular endothelial growth factor (VEGF) [124], which is considered a prognostic factor of HCC progression [125]. The HCV core protein induces production of TGF-β, a cytokine involved with progression of liver fibrosis. High levels of TGF-β have been observed in the sera and livers of chronic HCV + patients [126]. Major producers of this cytokine are HCV-infected hepatocytes, Kupffer cells, and liver-infiltrating lymphocytes. TGF-beta activates quiescent hepatic stellate cells to differentiate into myofibroblasts, and initiates the release of profibrogenic mediators, inflammatory cytokines, and chemokines, exacerbating liver inflammation and fibrogenesis [127]. TGF-β also acts as an immunosuppressor, thus favoring the immune escape of neoplastic transformed cells [128].

Among a number of miRNAs implicated in the HCV life cycle, probably the most well-known is miR-122, the function of which is to increase HCV replication in target cells [129]. Several phase I/II clinical trials using silencing of miR-122 to treat HCV infection have shown to be effective, with reduced viral titers even after discontinuation of treatment [130]. However, miR-122 has also been associated with proteins involved in HCC, and it has been shown that miR-122-knockout mice develop liver cancer [131]. Other miRNAs correlated with hepatocellular carcinoma exacerbation are miR-27a and miR-181c [132,133]. These miRNAs, downregulated in HCV patients, are involved in the metabolism of lipids and control of hepatic cell proliferation. In HCV infected patients a number of miRNAs are found to be up-regulated, such as miR-200c, miR-21, miR-130α, miR-221, and miR-155, and as they are correlated with fibrogenesis, they have also been

used as serum biomarkers predictive of disease progression [134–136].

5. Conclusion

In conclusion, in immunosuppressed patients, such as solid organ recipients, EBV, KSHV/HHV8, and HCV can contribute to carcinogenesis either by directly inducing the expression of specific oncogenic proteins and transforming the recipient cells or indirectly by establishing a chronic inflammatory microenvironment that persistently damages the local tissue. Also, the immune system, and in particular, the recognition of the “non-self”, has a key role in controlling tumor initiation and progression. Some of the most intriguing mechanisms that can contribute to oncogenesis in immunosuppressed patients, driven by three viruses, involve many cytokines able to create a chronic inflammatory microenvironment. A central role is played by immune cells, such as T lymphocytes, the function of which is altered by long-term immunosuppressive regimens and chronic infection, having consequences on the overall host welfare and tumor progression.

Finally, the central role of miRNAs has been demonstrated, both host and viral miRNAs, as players in the regulation of the viral lifecycle and infection, and tumor initiation and progression.

All the oncogenic mechanisms driven by EBV, KSHV, and HCV described above are potentially dangerous, especially in immunocompromised solid organ recipients, leading to the development of an immune-inflammatory network permissive to malignant outgrowth, and failing to eradicate virus-transformed clones.

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Conflict of interest

The authors declare no conflicts of interest.

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