Chapter 16
Interplay Between Microenvironmental Abnormalities and Infectious Agents in Tumorigenesis

Qing Zhu, Feng Gu, Caixia Zhu, Yuyan Wang, Fang Wei, and Qiliang Cai

Abstract Emerging evidence has shown that the cell of microenvironmental abnormalities is a key factor that controls many cellular physiological processes including cellular communication, homing, proliferation, and survival. Given its central regulatory role, it is therefore not surprising that it is widely exploited by infectious agents for inducing pathogenesis. In the past decade, a number of oncogenic pathogens including viruses, bacteria, and parasites are demonstrated to take advantage of the tumor microenvironmental factors including hypoxia, oxidative stress, and cytokines, to create an extracellular environment more favorable for pathogen survival and propagation and escape from the host immune surveillance. Here we summarize and highlight the current understanding of the interplay between common tumor microenvironmental factors and oncogenic pathogens in promoting tumorigenesis.

Keywords Tumor microenvironment • Pathogen • Oncogenesis

Qing Zhu and Feng Gu equally contributed to this work.

Q. Zhu • F. Gu • C. Zhu • Y. Wang • Q. Cai (✉)
Key Laboratory of Medical Molecular Virology (Ministries of Education and Health), School of Basic Medical Sciences, Fudan University, Shanghai 200032, People's Republic of China
e-mail: qiliang@fudan.edu.cn

F. Wei (✉)
ShengYushou Center of Cell Biology and Immunology, School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai 200240, People's Republic of China
e-mail: fangwei@sjtu.edu.cn

© Springer Nature Singapore Pte Ltd. 2017

Q. Cai et al. (eds.), *Infectious Agents Associated Cancers: Epidemiology and Molecular Biology*, Advances in Experimental Medicine and Biology 1018,
DOI 10.1007/978-981-10-5765-6_16

16.1 Introduction

Oxygen and glucose are not only essential nutrients but also key microenvironment factors to maintain cell survival. Imbalance between nutrients supply and demand can lead to nutrient stress within regions of tumor tissues. The growth of solid tumors, which are significantly different from the normal tissues, possesses the characteristic of rapid expansion of tumor mass and chaotic growth of tumor vasculature [1, 2]. Thus, excessive metabolism rate of tumor cells and insufficient blood supply could profoundly influence the tumor microenvironment where forms hypoxia and glucose starvation. To survive in hypoxia and glucose starvation stress, tumor cells have evolved strategies of adaptive cellular response by acting on various signaling pathways that are responsible for angiogenesis, glucose metabolism, cell proliferation, and apoptosis [3, 4]. Importantly, increasing evidence suggests that these adaptive strategies in cancer cells profoundly drive tumor growth and aggressive progression [1, 4, 5]. In addition, the consequence of limitation on the uptake of oxygen and glucose has also been shown to associate with the physiochemistry change within tumor microenvironment such as increase of acidic (H^+) concentration and ROS production [6]. Conversely, these physiochemistry changes acting as a selective stress influence cellular signaling pathways and can be exploited in tumorigenesis. Together, nutrient stress (hypoxia or glucose starvation) in synergizing with the accompanied production of metabolites constitutes a unique tumor microenvironment where it produces a potent selective stress in driving carcinogenesis.

Distinct from noninfectious agent-associated cancer, pathogen–host interaction has been causally demonstrated in the carcinogenesis of pathogen-associated cancer [7]. The hemostasis of both extracellular and intracellular metabolic environment is equally essential for oncogenic pathogen survival, especially for virus that absolutely relied on cells for living. Whether these oncogenic pathogens are directly capable of sensing changes in extracellular or intracellular microenvironment remains to be exploited. However, the factors including low oxygen and ROS generation have been indicated to influence virus replication and virions production [8]. On the other hand, emerging evidence has also suggested that many oncogenic pathogens participate in modulating key signaling pathways and gene expression that triggered cellular response to metabolic stress. The adaptive genetic alteration of signaling pathways by oncogenic pathogens may reflect the interaction between pathogen-associated cancer cells and tumor microenvironment. Therefore, it is highly possible that some of these oncogenic pathogens have evolved their own unique adaptive mechanisms. The pathogen-specific subversion response of signaling pathway not only facilitates the survival of infected cells under stress but also promotes pathogen-mediated oncogenesis. Hence, the understandings of these pathogen-associated critical signaling pathways in adaption to hypoxia and glucose starvation stress will not only expand the oncogenesis mechanism induced by pathogen in a microenvironment base but will also favor the identification of both

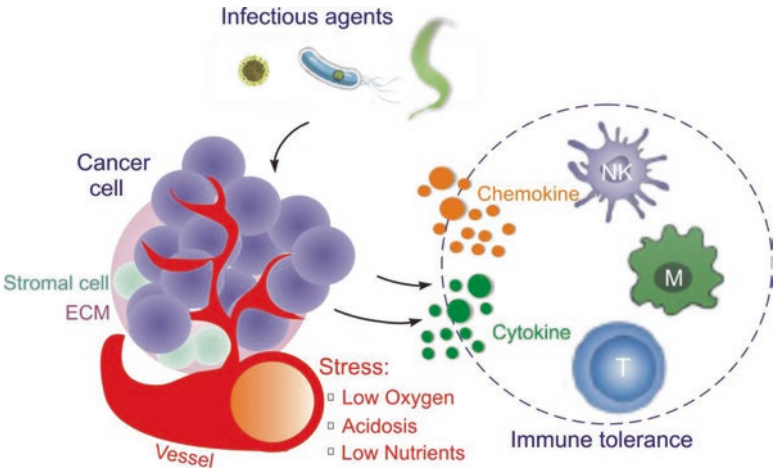

Fig. 16.1 Schematic representation of microenvironmental abnormalities including immune (immune cells, cytokines, and chemokines) and nonimmune (extracellular matrix, stromal cells, blood vessels) components associated with infectious agents (virus, bacterium, and parasite)

pathogen and microenvironment based on potential therapeutic targets for the treatment of pathogen-associated cancer (Fig. 16.1).

In this review, we summarize the key cellular adaptive signaling pathways that are modified by oncogenic pathogens and highlight the common or unique mechanisms utilized by these oncogenic pathogens for oncogenesis.

16.2 Pathogen-Mediated Alteration of Hypoxic Signaling and Response to Hypoxic Stress

Cellular oxygen homeostasis is highly dependent on the regulation of oxygen-sensitive signaling pathway. Accumulated evidence has strongly shown the activated oxygen-sensitive signaling is the first line to respond to hypoxic stress within tumor microenvironment [9–11]. Activations of hypoxia-inducible factor 1 (HIF-1) and HIF-dependent downstream gene are the master regulatory pathway during hypoxia. In addition, mTOR kinase signaling pathway and unfolded protein response (UPR) are another two oxygen-sensitive signaling that are individually activated under the condition of severe and durative hypoxia stress [11]. Therefore, it is not surprising that most oncogenic pathogens are involved in the deregulation of key molecules in controlling these hypoxic signaling pathways.

16.2.1 Deregulation of HIF-Dependent Hypoxic Signaling

HIF-1, which consists of a constitutively expressed β-subunit and an inducible α-subunit, is a central transcriptional factor of HIF-dependent signaling in response to hypoxia stress [12]. The modulation of HIF-1 is mainly through the stability and availability of the inducible subunit HIF-1α. The stabilization of HIF-1α is oxygen-dependent and is tightly regulated in the presence of oxygen [13]. More recently, it has been proven that many oncogenic viruses can directly enhance the accumulation of HIF-1α and promote its transcriptional activity through various mechanisms even in normoxia [14]. Given the role of HIF-1α in inducing the expression of proangiogenic factors, the subversion of HIF-1-dependnent angiogenesis has been deeply involved in oncoprotein-stimulated tumor angiogenesis.

16.2.1.1 Synthesis of HIF-1α Protein

Activation of growth factor signaling pathways including MAPK signaling, PI3K/Akt signaling, and TSC/mTOR signaling has been indicated to be involved in the synthesis of HIF-1α protein [15]. Several oncogenic viruses have been found to hijack these signaling pathways to enhance the synthesis of HIF-1α protein in hypoxia or normoxia. For instance, KSHV vGPCR-mediated paracrine secretion can activate TSC/mTOR signaling and mTOR-dependent upregulation of HIF-1α/HIF-2α [16]. Similarly, EBV-encoded latent membrane protein LMP-1 is also shown to induce the activation of p42/p44 MAPK signaling pathway to promote the synthesis of HIF-1α proteins [17], and HPV16-encoded E6 associate with ERK1/2 signaling pathway to enhance HIF-1α accumulation [18]. In addition, some viral oncoproteins are shown to regulate HIF-1α at a transcription level. For example, HTLV encodes Tax to promote the expression and DNA-binding activity of HIF-1α by means of activating PI3K/Akt signaling [19]. EBV-encoded LMP-1 is also shown to enhance the stability of HIF-1α RNA transcripts through ERK1/2 and STAT3 signaling targeting the expression of RNA-destabilizing proteins TTP and PUM2 [20].

16.2.1.2 Stability of HIF-1α Protein

The accumulation of HIF-1α protein not only depends on the constitutive synthesis of HIF-1α but also requires the modulation of HIF-1α degradation. The degradation of HIF-1α is primarily induced by PHD/HIF/VHL pathway in an oxygen-dependent manner [21, 22]. The tumor suppressor VHL acts as an E3 ubiquitin ligase to induce prolyl-hydroxylated HIF-1α for ubiquitylation and in turn proteasomal degradation. The hydroxylation of HIF-1α in the specific proline residue is mediated by oxygen-sensor prolyl hydroxylase (PHD) enzymes. Interestingly, increasing evidences have shown that oncogenic viruses have exploited diverse strategies to interfere PHD/

HIF/VHL pathway. For instance, both KSHV-encoded LANA and EBV-encoded LMP-1 have been demonstrated to induce the proteasome-mediated degradation of HIF-1α suppressor. LANA can stimulate the degradation of HIF-suppressor VHL and p53, which is dependent on the recruitment of Cul5-Elongin BC complex by the cytokine signaling-box motif within LANA [23]. In contrast, LMP-1 can induce the degradation of oxygen-sensor PHD1 and PHD3 via recruitment of Siah1 E3 ubiquitin ligase [24]. Distinct from LANA and LMP-1, KSHV-encoded IFN-regulatory factor 3 (vIRF3), a viral homologue of cellular IRF gene, can stabilize HIF-1α protein through forming a complex with HIF-1α, although the machinery of the inhibition of HIF-1α degradation remains unclear [25]. The EBV oncoproteins EBNA3 and EBNA5 are shown to bind to PHD1 and PHD2 for blocking the hydroxylation of HIF-1α [26]. Interestingly, in order to stabilize HIF-1α, the HBV-encoded HBx not only blocks the formation of VHL-HIF complex but also induces interaction between MTA1/HDAC and HIF-1α to promote the deacetylation of HIF-1α within the oxygen-sensitive domain [27, 28].

16.2.1.3 Transcriptional Activity of HIF-1α

In addition to the accumulation of HIF-1α protein, the regulators of HIF-1α transcriptional activity including nuclear translocation, and interaction with coactivators, DNA-binding capacity also plays a critical role in activating HIF signaling, which is targeted by different viral proteins [29]. For example, KSHV-encoded LANA and vIRF3 have been reported to promote nuclear accumulation of HIF-1α [23]. EBV oncoprotein LMP-1 enhances DNA-binding ability of HIF-1α to hypoxia-responsive DNA elements within the VEGF promoter [17], while HBx enhances the transcriptional activity of HIF-1α through the activation of p42/p44 MAPK signaling, leading to the interaction between HIF-1α and coactivator CREB-binding protein [30]. In addition, some viral oncoproteins are also involved in stimulating HIF-1α activity through posttranslational modification. For instance, the p38/MAPK signaling activated by KSHV vGPCR can phosphorylate HIF-1α and enhance its transcriptional activity [31], and HPV E7 prevents deacetylation of HIF-1α through dissociation with histone deacetylases HDAC1, HDAC4, and HDAC7 [32].

16.2.2 Deregulation of HIF-Independent mTOR Signaling

It has been demonstrated that the adaptive response to hypoxia stress involves not only stimulation of angiogenesis but also inhibition of protein synthesis [33]. mTOR kinase signaling pathway, as a central regulator of protein synthesis that integrates various physiological signals [34], has been shown to respond to hypoxia and restrain the growth of tumor [33]. mTOR-mediated protein synthesis is a process involving the phosphorylation of the eukaryotic initiation factor 4E binding protein

1 (4E-BP1) and the p70 ribosomal S6 kinase 1(S6K1) [34]. These two are critical effectors of the downstream of mTOR signaling and responsible for the initiation process of translation. It has been shown that inhibition of mTOR by hypoxia involves three hypoxia-inducible proteins REDD1, BNIP3, and PML [35–37]. Both REDD1 and BNIP3 can directly suppress mTORC1 activity by disrupting Rheb-mTOR interaction, whereas REDD-mediated downregulation of mTORC1 by hypoxia is dependent on TSC1/TSC2 complex (a negative regulator of mTOR). In view of the fact that the deregulation of mTOR signaling appears in many advanced cancers [38, 39], the constitutive activation of mTOR could be an adaptive strategy in response to hypoxia. Intriguingly, a growing number of evidence has shown the positive regulation of mTOR activity by several oncogenic viruses. For instance, HPV16-encoded E6 and HBV-encoded HBx are shown to target TSC1/TSC2 complex for stimulating protein synthesis. Moreover, HPV16 E6 not only induces the activation of mTOR/SK61 signaling, which is dependent on the disruption of TSC2 by E6-tuberin interaction and the proteasomal degradation of tuberin [40], but also enhances Atk/mTOR activity to initiate cap-dependent translation [41]. For HBV, the overexpression of HBx activates TSC1/mTOR/SK61 signaling by means of IKKβ [42]. Meanwhile, HCV NS5A-mediated activation of mTOR presents a positive effect on two key translation initiation-associated proteins S6 K1 and 4EBP1, by which NS5A promotes the dissociation of FKBP38 from mTOR by competitive binding to mTOR [43, 44]. This indicates to some extent that activation of mTORC1 and protein synthesis could be potent strategies targeted by oncogenic viruses in response to hypoxia. Nonetheless, the increasing severity and duration of hypoxia will conversely cause the suppression of protein synthesis in most cells. Therefore, the mTOR signaling is also a critical regulator in hypoxia toleration. However, whether the subversion of mTOR signaling by oncogenic virus for carcinogenesis will still benefit to the survival of tumor cells during severe hypoxia remains elusive. It is likely that the oncogenic virus will shift the regulatory mechanism of mTOR signaling or constitutively activate mTOR-dependent protein synthesis to promote viral replication in response to sever hypoxia.

16.3 Pathogen-Mediated Alteration of ROS Signaling and Response to Oxidative Stress

Mounting evidence has indicated the excess generation of intrinsic or extrinsic ROS in cancer cells. It has been proven that several factors including mitochondrial dysfunction and oncoprotein activity contribute to the accumulation of ROS [45]. In tumor microenvironment, hypoxia stress and glucose starvation have been clearly linked to the induction of intracellular ROS production [46, 47]. The constitutive production of ROS (i.e., hydroperoxides) and the consequence of oxidative stress will cause DNA damage and genomic instability and trigger the normal cell death signaling. To date it is well known that oxidative DNA damage caused by ROS will

activate p53 signaling through the enhancement of p53 stability and DNA-binding activity [48], which is tightly modulated by negative regulator MDM2 (an ubiquitin E3 ligase) and ATM (an important sensor of DNA damage) [49, 50]. Different from the effect on normal cells, it has been well established that the oxidative stress in microenvironment profoundly contributes to tumor progression by affecting cell proliferation, apoptosis sensitivity, and genome stability [45]. Therefore, adaptive genetic change to subvert the death signaling induced by oxidative stress has evolved in tumorigenesis.

Since the tumor suppressor p53 is demonstrated as a central regulator in both cell cycle arrest and apoptosis and is potently activated in response to oxidative stress [51], several viruses have been found to evolve an adaptive mechanism to directly block p53 function. For example, the expression of vIRF1 encoded by KSHV can attenuate ATM/p53-mediated DNA damage response through directly blocking ATM-mediated phosphorylation of p53 on serine 15 which in turn increases the degradation of p53 by MDM2. In addition, vIRF1 can also reduce the transcriptional activation of p53 [52]. In contrast, EBV-encoded lytic protein BZLF-1 can induce the degradation of p53 in ATM-dependent DNA damage response which is independent of MDM2 [53]. The deregulation of p53-dependent oxidative stress response is also found in HCV infection. The overexpression of DHCR24 induced by HCV infection can suppress the activation of p53 through the accumulation of p53-MDM2 complex, although the specific viral protein involved in this process remains unknown [54]. In addition, KSHV-encoded LANA and some structural proteins expressed during the late stage of lytic replication have been found to inhibit p53-mediated apoptosis [55, 56]. Both EBV nuclear antigen 3C and viral oncoprotein LMP-1 have also been shown to be involved in repressing p53-induced apoptosis and transcriptional activity [57–59]. However, despite that the activation of p53 signaling has been linked to multiple types of DNA damage, how p53 is regulated by viral oncogene and in turn responsible for oxidative DNA damage is still elusive and requires to be further investigated.

16.4 Cross Talk Between Pathogens and Cytokines in Tumor Microenvironment

Cytokines and chemokines, existing in tumor microenvironment, are a series of small proteins that exert great effects on host response to pathogen infection. Despite antiviral activity induced by cytokines and chemokines, extensive evidence demonstrates that some pathogens, especially oncogenic viruses and bacteria, utilize cytokines and chemokines to promote tumor progression [60, 61]. Here, we summarized and highlighted several cytokines and chemokines that play a vital role in tumorigenesis during infection of oncogenic pathogens (Fig. 16.1).

16.4.1 IL-6

Interleukin 6 (IL-6), secreted by a variety of host cells such as T cells, macrophages, fibroblasts, and malignant cells, is a multifunctional inflammatory cytokine, inducing various biological effects including tumorigenesis [62]. Increasing evidence indicates that IL-6 has a strong link with pathogen-mediated carcinomas. For example, it has been found that IL-6 acts as an autocrine growth factor targeted by EBV to promote immortalization of B cells and tumor growth [63–65]. In contrast, KSHV encodes viral IL-6 (vIL-6), sharing about 25% homology with human IL-6 (hIL-6). Different from hIL-6, vIL-6 stimulates almost each type of cells through directly binding to gp130 without hIL-6 receptor [66]. vIL-6 is able to promote the growth and survival of PEL cells and tumorigenesis of nude mice [67, 68]. Blockading vIL-6 expression or neutralizing antibody against gp130 could efficiently inhibit the growth of PEL cells [69, 70]. Further studies revealed that vIL-6 blocks IFN signaling, which contributes to tumor cell proliferation [71]. In addition, miRNA K12-1, a viral miRNA encoded by KSHV, was found to activate NF-κB/IL-6/STAT3 pathway to promote tumorigenesis [72]. In the HPV-associated cervical cancer, recent studies reported that IL-6/STAT3 is activated by the E6 oncoprotein encoded by high-risk HPV for tumorigenesis [73, 74], while HBV-encoded X protein modulates IL-6 to promote the progression of liver cancer [75]. In the HTLV-1-associated T-cell malignancy, the viral protein Tax is shown to enhance the expression of IL-6 receptor and leads to the malignant growth of T cells [76]. In the bacterium-associated cancers, *Helicobacter pylori*, a gram-negative microaerophilic bacteria, is found to parasitize in the stomach and results in chronic gastritis that is intensely associated with gastric neoplasm [77]. Several reports indicated that the interplay between *H. pylori* and TLR2 induces the expression of IL-6 and subsequently activates IL-6/STAT3 signaling pathway, which strongly contributes to immortality of gastric cancer cells. Interestingly, TLR2 is also directly upregulated by STAT3 in gastric tumors [78–81]. Therefore, TLR2/IL-6/STAT3 pathway may form a positive loop to promote gastric tumorigenesis [77].

16.4.2 IL-10

Interleukin 10 (IL-10), initially identified as an inhibitor of cytokine synthesis, has been shown to play a vital role in regulating cell differentiation and immune response, including limiting inflammatory response to pathogens and thereby reducing damage to host [82, 83]. However, it is also reported that IL-10 is utilized by various viruses to favor viral survival and pathogenesis, among which some even encode IL-10 homologs. For instance, EBV encodes vIL-10, imitating biological activities of cellular IL-10, to inhibit cytokine synthesis and regulate immune response [83]. In addition, vIL-10 prevents EBV-infected B cells from being eliminated by NK cell and protects antigen-specific T-cell proliferation by

downregulating MHCII antigen on monocytes and ultimately maintains EBV latent infection [84, 85]. On the other hand, human IL-10 (hIL-10) expression is also induced in the EBV-infected B cells. Evidence shows that hIL-10 is upregulated by latent membrane protein 1(LMP-1) via p38/SAPK2 pathway [86]. Another mechanism study revealed that EBV transcription factor Zta, previously recognized as a master regulator of EBV productive cycle, is also involved in the expression of hIL-10 [87]. Furthermore, EBV-encoded small RNA, EBER, was found to induce hIL-10 through RIG-I-mediated IRF3 pathway [88]. For another herpesvirus, KSHV was found to force PEL cells to release hIL-10 into culture supernatant. Moreover, neutralizing antibodies against IL-10 and IL-10 receptor shows that IL-10 is critical for the progression of PEL [67]. In the HPV-associated malignant cervical cancer, HPV drives immune cells to produce IL-10 to facilitate viral persistence and tumorigenesis [89]. During chronic HBV infection, high production of IL-10 suppresses the biological activity of $CD8^+$ and $CD4^+$ T cells, which favors the progression of tumorigenesis [90, 91]. Recently, it has been found that HTLV-1 bZIP factor (HBZ) upregulates T-cell immunoglobulin and ITIM domain (TIGIT) and enhances expression of IL-10 for evading host immune response [92].

16.4.3 IL-13

Interleukin 13 (IL-13) is known as inflammation regulatory factor, mainly generated by B cells, T cells, and NK cells [93]. The main function of IL-13 is to induce IgE switching and CD23 expression in B cells, promoting antigen presentation ability of MHCII, inhibiting inflammation in human monocytes, and suppressing apoptosis [94–97]. Increasing evidence has shown that IL-13 collaborates with various viruses including EBV, KSHV, and HTLV-1 to promote tumorigenesis [61, 98–101]. In the EBV-associated Hodgkin lymphoma, the expression of IL-13 is upregulated, and the underlying molecular mechanism is that Zta serving as a EBV lytic protein elicits IL-13 production via directly binding to IL-13 promoter. Furthermore, neutralizing antibody against IL-13 suggests that IL-13 is vital for proliferation and latency of EBV-immortalized lymphoblastoid cell lines [98]. STAT6, a key downstream effector of IL-13, is a remarkable transcriptional factor whose constitutive phosphorylation has been indicated in controlling tumorigenesis [102]. Our group found that the constitutive phosphorylation of STAT6 is due to autocrine/paracrine of IL-13 and downregulation of SHP1 mediated by KSHV, which is closely associated with oncogenesis. Strikingly, neutralizing antibody against IL-13 suppresses the proliferation and survival of PEL, suggesting IL-13 plays a significant role in KSHV-associated latency and subsequent tumorigenesis [61]. Though previous studies reveal that IL-4, sharing the same receptor IL-4Rα/IL-13Rα1 with IL-13, also leads to the phosphorylation of STAT6, we found that IL-4/STAT6 pathway is negatively regulated in the KSHV-infected cells through dephosphorylation of STAT6 by latency-associated nuclear antigen (LANA), an important viral oncoprotein for maintaining viral latency [103, 104]. Similar to the effect of EBV and

KSHV, HTLV-1 Tax protein also induces production of IL-13, which is capable of promoting cell proliferation and anti-apoptosis of infected cells in an autocrine manner [96, 97, 99, 105]. This indicates that IL-13 is often targeted by oncogenic virus for host immune escape and cell survival.

16.4.4 IL-8

Chemokines are a large family of small proteins that regulates inflammation. The main property of chemokines is to attract immune cells to the site of inflammation, resulting from various causes including infection, autoimmune disease, and carcinomas [106]. Interleukin 8 (IL-8), a member of CXC chemokine subfamily, is responsible for recruiting neutrophils and T lymphocytes to the site of inflammation. Extensive evidence demonstrates that IL-8 is closely implicated in tumorigenesis such as breast cancer, gastric cancer, and pancreatic cancer [107–109]. Thus, it is not surprising that IL-8 was also found to participate in pathogen-related tumorigenesis. For example, EBV-encoded Zta protein activates IL-8 through binding to two elements within IL-8 promoter and subsequently upregulates IL-8 production, which is crucial for NPC development by recruiting infiltrates around infected cells [110]. In contrast to EBV, KSHV adopts different mechanisms to regulate IL-8 expression. It has been demonstrated that LANA-1 boosts IL-8 production to assist KSHV-infected cells in evading host immune response [111]. Similarly, in the context of lung adenocarcinomas, HPV16 infection upregulates IL-8 expression and in turn promotes angiogenesis and metastasis through inducing MMP2 and MMP9 [112], while the downregulation of IL-8 in the HPV-immortalized exocervical cells or primary keratinocytes could create a favorable microenvironment for HPV infection and subsequent tumorigenesis [113, 114]. In addition, previous studies showed that HCV infection could upregulate IL-8 expression and contribute to host immune tolerance and viral pathogenesis [115]. Interestingly, the similar phenomenon occurs to HBV, which was found to increase viral tolerance to IFN-α by inducing IL-8 production [116]. HTLV-1 also encodes Tax oncoprotein to activate IL-8 production and in turn contribute to HTLV-1-associated pathogenesis [117]. In bacteria-associated cancer, the discoveries from gastric epithelial cells exposed to *Helicobacter pylori* indicate that bacterial infection could also upregulate the expression of IL-8. The fact that high production of IL-8 is tightly associated with tumor cell proliferation, angiogenesis, and metastasis suggests that IL-8 plays a key role in *H. pylori*-associated gastric cancer [118–121].

16.4.5 CCL20

CCL20 is a member of CC chemokine subfamily and acts as a potent chemotaxin of immature dendritic cells, B lymphocytes, and T lymphocytes [122]. The main characteristic of CCL20 is to recruit immune cells to the site of inflammation, and in turn it is also involved in host immune response and tumorigenesis, such as breast adenocarcinoma, hepatocellular carcinoma, and pancreatic cancer [123–125]. Many reports have indicated that CCL20 is connected with pathogen-related tumorigenesis. For instance, in the EBV-positive Burkitt lymphoma (BL) cells or EBV-negative cells overexpressing LMP-1, the production of CCL20 is highly upregulated, indicating viral oncoprotein LMP-1 is involved in inducing chemokine CCL20 [126]. In addition, CCL20 is also upregulated by another EBV latent antigen called EBNA1 [127]. Further studies showed that high-level CCL20 could recruit Treg and is capable of inhibiting $CD4^+$ and $CD8^+$ T cells [127, 128]. By which, EBV-infected cells can inhibit host immune response and may promote tumorigenesis. Similarly, overexpressions of CCL20 and its receptor CCR6 are also observed in both KSHV-positive cells and HTLV-1-infected cells, which may drive virus-infected cells to migrate in an autocrine or paracrine manner. In contrast, high-risk HPVs were also found to escape immune response by downregulating CCL20 through E6 and E7 proteins [129].

16.5 Remarks and Perspectives

It is well known that metabolic stress within solid tumors is characterized by hypoxia, nutrient deprivation, oxidative stress, and lactic acidosis as a hostile microenvironment for the survival of cancer cells. Nonetheless, these adverse microenvironments have been successfully exploited by cancer cells and have been converted as driving force in the initiation and progression of cancer. The same cases have been extended to the mechanism by which oncogenic pathogen utilized to involve in carcinogenesis. Here, we have summarized the potential roles of metabolic stress like hypoxia, glucose starvation, and ROS accumulation in promoting viral oncoprotein-induced adaptive signaling change and oncogenesis. Among these, extracellular lactic acidosis has also been confirmed as a potent metabolic stress that plays a multiple role in promoting cancer progression. However, rare information was reported about the interaction between oncogenic pathogens and lactic acidosis stress. In addition, the consequence of the interplay between oncogenic pathogen and metabolic stress microenvironment is complicated and elusive. For examples, although the metabolic stress environment could drive tolerance change of cancer cells, the adaptive response strategies exploited by virus may not stable but adjust to the severity and duration of metabolic stress. On ther other hand, the metabolic stress factors are not isolated but cross talked, which may imply a cooperative or opposed effect of these selective stress on the same viral-mediated

adaptive signaling pathway. Thus, a dynamic and comprehensive perspective in understanding oncogenesis mechanism induced by microenvironment abnormalities and oncogenic pathogen interaction will facilitate the development of a precise pathogen-specific therapeutic strategy.

Cytokines and chemokines are crucial factors that benefit not only hosts but also viruses. For hosts, cytokines and chemokines play a key role in regulating immune system, in order to limit and eliminate harmful pathogens. In contrast, for pathogens, many of them would adopt various mechanisms to evade host immune response by manipulating cytokines and chemokines. Moreover, many pathogens, in particular oncogenic viruses, even utilize cytokines and chemokines to promote persistent infection, even tumorigenesis [60]. In recent years, increasing evidence demonstrates the strong relationship between pathogens and carcinoma, and more and more cytokines and chemokines are proved to participate in pathogen-associated tumorigenesis, whereas the potential related to underlying mechanisms remains to be fully understood. As research exploited, more knowledge about virus-mediated tumorigenesis by manipulating cytokines and chemokines will be unveiled, and this knowledge could potentially be utilized to design therapies to defeat pathogen-related malignancies.

Acknowledgments The authors would like to apologize to the many researchers who have contributed to this area of research but have not been cited in this review due to space limitations. This work is supported by the National Key Research and Development Program of China (2016YFC1200400) and the National Natural Science Foundation of China (81471930, 81402542, 81672015). FW is a scholar of Pujiang Talents in Shanghai. QC is a scholar of New Century Excellent Talents in University of China.

References

1. Eales KL, Hollinshead KE, Tennant DA (2016) Hypoxia and metabolic adaptation of cancer cells. Oncogene 25:50
2. Pouyssegur J, Dayan F, Mazure NM (2006) Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature 441:437–443
3. Semenza GL (2012) Hypoxia-inducible factors in physiology and medicine. Cell 148:399–408
4. Rankin EB, Giaccia AJ (2016) Hypoxic control of metastasis. Science 352:175–180
5. Fang JS, Gillies RD, Gatenby RA (2008) Adaptation to hypoxia and acidosis in carcinogenesis and tumor progression. Semin Cancer Biol 18:330–337
6. Patel A, Sant S (2016) Hypoxic tumor microenvironment: opportunities to develop targeted therapies. Biotechnol Adv 34:803–812
7. McLaughlin-Drubin ME, Munger K (2008) Viruses associated with human cancer. Biochim Biophys Acta 3:127–150
8. Purushothaman P, Uppal T, Verma SC (2015) Molecular biology of KSHV lytic reactivation. Virus 7:116–153
9. Bruick RK (2003) Oxygen sensing in the hypoxic response pathway: regulation of the hypoxia-inducible transcription factor. Genes Dev 17:2614–2623
10. Ratcliffe PJ (2013) Oxygen sensing and hypoxia signalling pathways in animals: the implications of physiology for cancer. J Physiol 591:2027–2042

11. Wouters BG, Koritzinsky M (2008) Hypoxia signalling through mTOR and the unfolded protein response in cancer. Nat Rev Cancer 8:851–864
12. Wang GL, Jiang BH, Rue EA, Semenza GL (1995) Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A 92:5510–5514
13. Lee JW, Bae SH, Jeong JW, Kim SH, Kim KW (2004) Hypoxia-inducible factor (HIF-1) alpha: its protein stability and biological functions. Exp Mol Med 36:1–12
14. Zhu C, Zhu Q, Wang C, Zhang L, Wei F, Cai Q (2016) Hostile takeover: manipulation of HIF-1 signaling in pathogen-associated cancers (review). Int J Oncol 49:1269–1276
15. Masoud GN, Li W (2015) HIF-1alpha pathway: role, regulation and intervention for cancer therapy. Acta Pharm Sin B 5:378–389
16. Jham BC, Ma T, Hu J, Chaisuparat R, Friedman ER, Pandolfi PP, Schneider A, Sodhi A, Montaner S (2011) Amplification of the angiogenic signal through the activation of the TSC/mTOR/HIF axis by the KSHV vGPCR in Kaposi's sarcoma. PLoS One 6:0019103
17. Wakisaka N, Kondo S, Yoshizaki T, Murono S, Furukawa M, Pagano JS (2004) Epstein-Barr virus latent membrane protein 1 induces synthesis of hypoxia-inducible factor 1 alpha. Mol Cell Biol 24:5223–5234
18. Liu F, Lin B, Liu X, Zhang W, Zhang E, Hu L, Ma Y, Li X, Tang X (2016) ERK signaling pathway is involved in HPV-16 E6 but not E7 Oncoprotein-induced HIF-1alpha protein accumulation in NSCLC cells. Oncol Res 23:109–118
19. Tomita M, Semenza GL, Michiels C, Matsuda T, Uchihara JN, Okudaira T, Tanaka Y, Taira N, Ohshiro K, Mori N (2007) Activation of hypoxia-inducible factor 1 in human T-cell leukaemia virus type 1-infected cell lines and primary adult T-cell leukaemia cells. Biochem J 406:317–323
20. Sung WW, Chu YC, Chen PR, Liao MH, Lee JW (2016) Positive regulation of HIF-1A expression by EBV oncoprotein LMP1 in nasopharyngeal carcinoma cells. Cancer Lett 382:21–31
21. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, Ratcliffe PJ (1999) The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature 399:271–275
22. Semenza GL (2001) HIF-1, O(2), and the 3 PHDs: how animal cells signal hypoxia to the nucleus. Cell 107:1–3
23. Cai Q, Murakami M, Si H, Robertson ES (2007) A potential alpha-helix motif in the amino terminus of LANA encoded by Kaposi's sarcoma-associated herpesvirus is critical for nuclear accumulation of HIF-1alpha in normoxia. J Virol 81:10413–10423
24. Kondo S, Seo SY, Yoshizaki T, Wakisaka N, Furukawa M, Joab I, Jang KL, Pagano JS (2006) EBV latent membrane protein 1 up-regulates hypoxia-inducible factor 1alpha through Siah1-mediated down-regulation of prolyl hydroxylases 1 and 3 in nasopharyngeal epithelial cells. Cancer Res 66:9870–9877
25. Shin YC, Joo CH, Gack MU, Lee HR, Jung JU (2008) Kaposi's sarcoma-associated herpesvirus viral IFN regulatory factor 3 stabilizes hypoxia-inducible factor-1 alpha to induce vascular endothelial growth factor expression. Cancer Res 68:1751–1759
26. Darekar S, Georgiou K, Yurchenko M, Yenamandra SP, Chachami G, Simos G, Klein G, Kashuba E (2012) Epstein-Barr virus immortalization of human B-cells leads to stabilization of hypoxia-induced factor 1 alpha, congruent with the Warburg effect. PLoS One 7:27
27. Yoo YG, Cho S, Park S, Lee MO (2004) The carboxy-terminus of the hepatitis B virus X protein is necessary and sufficient for the activation of hypoxia-inducible factor-1alpha. FEBS Lett 577:121–126
28. Yoo YG, Na TY, Seo HW, Seong JK, Park CK, Shin YK, Lee MO (2008) Hepatitis B virus X protein induces the expression of MTA1 and HDAC1, which enhances hypoxia signaling in hepatocellular carcinoma cells. Oncogene 27:3405–3413

29. Kallio PJ, Okamoto K, O'Brien S, Carrero P, Makino Y, Tanaka H, Poellinger L (1998) Signal transduction in hypoxic cells: inducible nuclear translocation and recruitment of the CBP/p300 coactivator by the hypoxia-inducible factor-1alpha. EMBO J 17:6573–6586
30. Yoo YG, Oh SH, Park ES, Cho H, Lee N, Park H, Kim DK, Yu DY, Seong JK, Lee MO (2003) Hepatitis B virus X protein enhances transcriptional activity of hypoxia-inducible factor-1alpha through activation of mitogen-activated protein kinase pathway. J Biol Chem 278:39076–39084
31. Sodhi A, Montaner S, Patel V, Zohar M, Bais C, Mesri EA, Gutkind JS (2000) The Kaposi's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1alpha. Cancer Res 60:4873–4880
32. Bodily JM, Mehta KP, Laimins LA (2011) Human papillomavirus E7 enhances hypoxia-inducible factor 1-mediated transcription by inhibiting binding of histone deacetylases. Cancer Res 71:1187–1195
33. Liu L, Simon MC (2004) Regulation of transcription and translation by hypoxia. Cancer Biol Ther 3:492–497
34. Laplante M, Sabatini DM (2009) mTOR signaling at a glance. J Cell Sci 122:3589–3594
35. Brugarolas J, Lei K, Hurley RL, Manning BD, Reiling JH, Hafen E, Witters LA, Ellisen LW, Kaelin WG Jr (2004) Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex. Genes Dev 18:2893–2904
36. Bernardi R, Guernah I, Jin D, Grisendi S, Alimonti A, Teruya-Feldstein J, Cordon-Cardo C, Simon MC, Rafii S, Pandolfi PP (2006) PML inhibits HIF-1alpha translation and neoangiogenesis through repression of mTOR. Nature 442:779–785
37. Li Y, Wang Y, Kim E, Beemiller P, Wang CY, Swanson J, You M, Guan KL (2007) Bnip3 mediates the hypoxia-induced inhibition on mammalian target of rapamycin by interacting with Rheb. J Biol Chem 282:35803–35813
38. Connolly E, Braunstein S, Formenti S, Schneider RJ (2006) Hypoxia inhibits protein synthesis through a 4E-BP1 and elongation factor 2 kinase pathway controlled by mTOR and uncoupled in breast cancer cells. Mol Cell Biol 26:3955–3965
39. Populo H, Lopes JM, Soares P (2012) The mTOR signalling pathway in human cancer. Int J Mol Sci 13:1886–1918
40. Lu Z, Hu X, Li Y, Zheng L, Zhou Y, Jiang H, Ning T, Basang Z, Zhang C, Ke Y (2004) Human papillomavirus 16 E6 oncoprotein interferences with insulin signaling pathway by binding to tuberin. J Biol Chem 279:35664–35670
41. Spangle JM, Munger K (2010) The human papillomavirus type 16 E6 oncoprotein activates mTORC1 signaling and increases protein synthesis. J Virol 84:9398–9407
42. Yen CJ, Lin YJ, Yen CS, Tsai HW, Tsai TF, Chang KY, Huang WC, Lin PW, Chiang CW, Chang TT (2012) Hepatitis B virus X protein upregulates mTOR signaling through IKKbeta to increase cell proliferation and VEGF production in hepatocellular carcinoma. PLoS One 7:27
43. George A, Panda S, Kudmulwar D, Chhatbar SP, Nayak SC, Krishnan HH (2012) Hepatitis C virus NS5A binds to the mRNA cap-binding eukaryotic translation initiation 4F (eIF4F) complex and up-regulates host translation initiation machinery through eIF4E-binding protein 1 inactivation. J Biol Chem 287:5042–5058
44. Panda S, Vedagiri D, Viveka TS, Harshan KH (2014) A unique phosphorylation-dependent eIF4E assembly on 40S ribosomes co-ordinated by hepatitis C virus protein NS5A that activates internal ribosome entry site translation. Biochem J 462:291–302
45. Fiaschi T, Chiarugi P (2012) Oxidative stress, tumor microenvironment, and metabolic reprogramming: a diabolic liaison. Int J Cell Biol 762825:13
46. Marambio P, Toro B, Sanhueza C, Troncoso R, Parra V, Verdejo H, Garcia L, Quiroga C, Munafo D, Diaz-Elizondo J, Bravo R, Gonzalez MJ, Diaz-Araya G, Pedrozo Z, Chiong M, Colombo MI, Lavandero S (2010) Glucose deprivation causes oxidative stress and stimulates

aggresome formation and autophagy in cultured cardiac myocytes. Biochim Biophys Acta 6:509–518
47. Clanton TL (1985) Hypoxia-induced reactive oxygen species formation in skeletal muscle. J Appl Physiol 102:2379–2388
48. Martindale JL, Holbrook NJ (2002) Cellular response to oxidative stress: signaling for suicide and survival. J Cell Physiol 192:1–15
49. Haupt Y, Maya R, Kazaz A, Oren M (1997) Mdm2 promotes the rapid degradation of p53. Nature 387:296–299
50. Meek DW (2004) The p53 response to DNA damage. DNA Repair 3:1049–1056
51. Chen X, Ko LJ, Jayaraman L, Prives C (1996) p53 levels, functional domains, and DNA damage determine the extent of the apoptotic response of tumor cells. Genes Dev 10:2438–2451
52. Shin YC, Nakamura H, Liang X, Feng P, Chang H, Kowalik TF, Jung JU (2006) Inhibition of the ATM/p53 signal transduction pathway by Kaposi's sarcoma-associated herpesvirus interferon regulatory factor 1. J Virol 80:2257–2266
53. Sato Y, Shirata N, Kudoh A, Iwahori S, Nakayama S, Murata T, Isomura H, Nishiyama Y, Tsurumi T (2009) Expression of Epstein-Barr virus BZLF1 immediate-early protein induces p53 degradation independent of MDM2, leading to repression of p53-mediated transcription. Virology 388:204–211
54. Nishimura T, Kohara M, Izumi K, Kasama Y, Hirata Y, Huang Y, Shuda M, Mukaidani C, Takano T, Tokunaga Y, Nuriya H, Satoh M, Saito M, Kai C, Tsukiyama-Kohara K (2009) Hepatitis C virus impairs p53 via persistent overexpression of 3beta-hydroxysterol Delta24-reductase. J Biol Chem 284:36442–36452
55. Friborg J Jr, Kong W, Hottiger MO, Nabel GJ (1999) p53 inhibition by the LANA protein of KSHV protects against cell death. Nature 402:889–894
56. Chudasama P, Konrad A, Jochmann R, Lausen B, Holz P, Naschberger E, Neipel F, Britzen-Laurent N, Sturzl M (2015) Structural proteins of Kaposi's sarcoma-associated herpesvirus antagonize p53-mediated apoptosis. Oncogene 34:639–649
57. Yi F, Saha A, Murakami M, Kumar P, Knight JS, Cai Q, Choudhuri T, Robertson ES (2009) Epstein-Barr virus nuclear antigen 3C targets p53 and modulates its transcriptional and apoptotic activities. Virology 388:236–247
58. Cai Q, Guo Y, Xiao B, Banerjee S, Saha A, Lu J, Glisovic T, Robertson ES (2011) Epstein-Barr virus nuclear antigen 3C stabilizes Gemin3 to block p53-mediated apoptosis. PLoS Pathog 7:8
59. Li L, Li W, Xiao L, Xu J, Chen X, Tang M, Dong Z, Tao Q, Cao Y (2012) Viral oncoprotein LMP1 disrupts p53-induced cell cycle arrest and apoptosis through modulating K63-linked ubiquitination of p53. Cell Cycle 11:2327–2336
60. Mogensen TH, Paludan SR (2001) Molecular pathways in virus-induced cytokine production. Microbiol Mol Biol Rev 65:131–150
61. Wang C, Zhu C, Wei F, Zhang L, Mo X, Feng Y, Xu J, Yuan Z, Robertson E, Cai Q (2015) Constitutive activation of interleukin-13/STAT6 contributes to Kaposi's sarcoma-associated Herpesvirus-related primary effusion lymphoma cell proliferation and survival. J Virol 89:10416–10426
62. Sin S-H, Dittmer DP (2012) Cytokine homologs of human gammaherpesviruses. J Interf Cytokine Res 32:53–59
63. Yokoi T, Miyawaki T, Yachie A, Kato K, Kasahara Y, Taniguchi N (1990) Epstein-Barr virus-immortalized B cells produce IL-6 as an autocrine growth factor. Immunology 70:100
64. Tosato G, Tanner J, Jones K, Revel M, Pike S (1990) Identification of interleukin-6 as an autocrine growth factor for Epstein-Barr virus-immortalized B cells. J Virol 64:3033–3041
65. Cordano P, Lake A, Shield L, Taylor G, Alexander FE, Taylor PR, White J, Jarrett RF (2005) Effect of IL-6 promoter polymorphism on incidence and outcome in Hodgkin's lymphoma. Br J Haematol 128:493–495
66. Suthaus J, Adam N, Grötzinger J, Scheller J, Rose-John S (2011) Viral interleukin-6: structure, pathophysiology and strategies of neutralization. Eur J Cell Biol 90:495–504

67. Jones KD, Aoki Y, Chang Y, Moore PS, Yarchoan R, Tosato G (1999) Involvement of interleukin-10 (IL-10) and viral IL-6 in the spontaneous growth of Kaposi's sarcoma herpesvirus-associated infected primary effusion lymphoma cells. Blood 94:2871–2879
68. Aoki Y, Tosato G (1999) Role of vascular endothelial growth factor/vascular permeability factor in the pathogenesis of Kaposi's sarcoma-associated herpesvirus-infected primary effusion lymphomas. Blood 94:4247–4254
69. Zhang Y-J, Bonaparte RS, Patel D, Stein DA, Iversen PL (2008) Blockade of viral interleukin-6 expression of Kaposi's sarcoma–associated herpesvirus. Mol Cancer Ther 7:712–720
70. Drexler H, Meyer C, Gaidano G, Carbone A (1999) Constitutive cytokine production by primary effusion (body cavity-based) lymphoma-derived cell lines. Leukemia 08876924:13
71. Chatterjee M, Osborne J, Bestetti G, Chang Y, Moore PS (2002) Viral IL-6-induced cell proliferation and immune evasion of interferon activity. Science (New York, NY) 298:1432–1435
72. Chen M, Sun F, Han L, Qu Z (2016) Kaposi's sarcoma herpesvirus (KSHV) microRNA K12-1 functions as an oncogene by activating NF-κB/IL-6/STAT3 signaling. Oncotarget 7:33363–33373
73. Walboomer JM, Acos MV, Manos MM, Xavier Bosch F, Kummer JA (1999) Human papillomavirus is a necessary cause of invasive cervical cancer. Worldwide J pathol 189:12–19
74. Ren C, Cheng X, Lu B, Yang G (2013) Activation of interleukin-6/signal transducer and activator of transcription 3 by human papillomavirus early proteins 6 induces fibroblast senescence to promote cervical tumourigenesis through autocrine and paracrine pathways in tumour microenvironment. Eur J Cancer (Oxford, England : 1990) 49:3889–3899
75. Tang Y, Kitisin K, Jogunoori W, Li C, Deng C-X, Mueller SC, Ressom HW, Rashid A, He AR, Mendelson JS (2008) Progenitor/stem cells give rise to liver cancer due to aberrant TGF-β and IL-6 signaling. Proc Natl Acad Sci 105:2445–2450
76. Horiuchi S, Yamamoto N, Dewan M, Takahashi Y, Yamashita A, Yoshida T, Nowell MA, Richards PJ, Jones SA, Yamamoto N (2006) Human T-cell leukemia virus type-I tax induces expression of interleukin-6 receptor (IL-6R): shedding of soluble IL-6R and activation of STAT3 signaling. Int J Cancer 119:823–830
77. Uno K, Kato K, Shimosegawa T (2014) Novel role of toll-like receptors in helicobacter pylori-induced gastric malignancy. World J Gastroenterol 20:5244–5251
78. Tye H, Jenkins BJ (2013) Tying the knot between cytokine and toll-like receptor signaling in gastrointestinal tract cancers. Cancer Sci 104:1139–1145
79. Grivennikov SI, Karin M (2010) Dangerous liaisons: STAT3 and NF-κB collaboration and crosstalk in cancer. Cytokine Growth Factor Rev 21:11–19
80. Deng J-Y, Sun D, Liu X-Y, Pan Y, Liang H (2010) STAT-3 correlates with lymph node metastasis and cell survival in gastric cancer. World J Gastroenterol 16:5380–5387
81. Tye H, Kennedy CL, Najdovska M, McLeod L, McCormack W, Hughes N, Dev A, Sievert W, Ooi CH, T-o I (2012) STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. Cancer Cell 22:466–478
82. Fiorentino DF, Bond MW, Mosmann T (1989) Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J Exp Med 170:2081–2095
83. Moore KW, de Waal MR, Coffman RL, O'Garra A (2001) Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 19:683–765
84. Jochum S, Moosmann A, Lang S, Hammerschmidt W, Zeidler R (2012) The EBV immunoevasins vIL-10 and BNLF2a protect newly infected B cells from immune recognition and elimination. PLoS Pathog 8:e1002704
85. de Waal MR, Haanen J, Spits H, Roncarolo M-G, Te Velde A, Figdor C, Johnson K, Kastelein R, Yssel H, De Vries JE (1991) Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression. J Exp Med 174:915–924

86. Vockerodt M, Haier B, Buttgereit P, Tesch H, Kube D (2001) The Epstein-Barr virus latent membrane protein 1 induces interleukin-10 in Burkitt's lymphoma cells but not in Hodgkin's cells involving the p38/SAPK2 pathway. Virology 280:183–198
87. Mahot S, Sergeant A, Drouet E, Gruffat H (2003) A novel function for the Epstein–Barr virus transcription factor EB1/Zta: induction of transcription of the hIL-10 gene. J Gen Virol 84:965–974
88. Samanta M, Iwakiri D, Takada K (2008) Epstein-Barr virus-encoded small RNA induces IL-10 through RIG-I-mediated IRF-3 signaling. Oncogene 27:4150–4160
89. Prata TT, Bonin CM, Ferreira AM, Padovani CT, Fernandes CE, Machado AP, Tozetti IA (2015) Local immunosuppression induced by high viral load of human papillomavirus: characterization of cellular phenotypes producing interleukin-10 in cervical neoplastic lesions. Immunology 146:113–121
90. Das A, Ellis G, Pallant C, Lopes AR, Khanna P, Peppa D, Chen A, Blair P, Dusheiko G, Gill U (2012) IL-10–producing regulatory B cells in the pathogenesis of chronic hepatitis B virus infection. J Immunol 189:3925–3935
91. Xue H, Lin F, Tan H, Zhu Z-Q, Zhang Z-Y, Zhao L (2016) Overrepresentation of IL-10-expressing B cells suppresses cytotoxic CD4+ T cell activity in HBV-induced hepatocellular carcinoma. PLoS One 11:e0154815
92. Yasuma K, J-i Y, Takemoto K, Sugata K, Mitobe Y, Takenouchi N, Nakagawa M, Suzuki Y, Matsuoka M (2016) HTLV-1 bZIP factor impairs anti-viral immunity by inducing co-inhibitory molecule, T cell immunoglobulin and ITIM domain (TIGIT). PLoS Pathog 12:e1005372
93. Wynn TA (2003) IL-13 effector functions*. Annu Rev Immunol 21:425–456
94. de Waal MR, Figdor CG, Huijbens R, Mohan-Peterson S, Bennett B, Culpepper J, Dang W, Zurawski G, de Vries JE (1993) Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. Comparison with IL-4 and modulation by IFN-gamma or IL-10. J Immunol 151:6370–6381
95. Punnonen J, Aversa G, Cocks BG, McKenzie A, Menon S, Zurawski G, de Waal MR, de Vries JE (1993) Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. Proc Natl Acad Sci 90:3730–3734
96. Manna SK, Aggarwal BB (1998) IL-13 suppresses TNF-induced activation of nuclear factor-κB, activation protein-1, and apoptosis. J Immunol 161:2863–2872
97. Relić B, Guicheux J, Mezin F, Lubberts E, Togninalli D, Garcia I, van den Berg WB, Guerne P-A (2001) IL-4 and IL-13, but not IL-10, protect human synoviocytes from apoptosis. J Immunol 166:2775–2782
98. Tsai SC, Lin SJ, Chen PW, Luo WY, Yeh TH, Wang HW, Chen CJ, Tsai CH (2009) EBV Zta protein induces the expression of interleukin-13, promoting the proliferation of EBV-infected B cells and lymphoblastoid cell lines. Blood 114:109–118
99. Silbermann K, Schneider G, Grassmann R (2008) Stimulation of interleukin-13 expression by human T-cell leukemia virus type 1 oncoprotein tax via a dually active promoter element responsive to NF-κB and NFAT. J Gen Virol 89:2788–2798
100. Wäldele K, Schneider G, Ruckes T, Grassmann R (2004) Interleukin-13 overexpression by tax transactivation: a potential autocrine stimulus in human T-cell leukemia virus-infected lymphocytes. J Virol 78:6081–6090
101. Chung H-K, Young HA, Goon PK, Heidecker G, Princler GL, Shimozato O, Taylor GP, Bangham CR, Derse D (2003) Activation of interleukin-13 expression in T cells from HTLV-1-infected individuals and in chronically infected cell lines. Blood 102:4130–4136
102. Bruns HA, Kaplan MH (2006) The role of constitutively active Stat6 in leukemia and lymphoma. Crit Rev Oncol Hematol 57:245–253
103. Cai Q, Verma SC, Choi J-Y, Ma M, Robertson ES (2010) Kaposi's sarcoma-associated herpesvirus inhibits interleukin-4-mediated STAT6 phosphorylation to regulate apoptosis and maintain latency. J Virol 84:11134–11144

104. Wang C, Wei F, Cai Q (2016) Deregulation of IL-4/IL-13-induced STAT6 signaling in viral oncogenesis. Oncol Commun 1:e1131
105. Løvmo J, Blomhoff HK, Jacobsen SE, Krajewski S, Reed JC, Smeland EB (1997) Interleukin-13 in combination with CD40 ligand potently inhibits apoptosis in human B lymphocytes: upregulation of Bcl-xL and Mcl-1. Blood 89:4415–4424
106. Jundi K, Greene CM (2015) Transcription of interleukin-8: how altered regulation can affect cystic fibrosis lung disease. Biomol Ther 5:1386–1398
107. Matsuo Y, Ochi N, Sawai H, Yasuda A, Takahashi H, Funahashi H, Takeyama H, Tong Z, Guha S (2009) CXCL8/IL-8 and CXCL12/SDF-1α co-operatively promote invasiveness and angiogenesis in pancreatic cancer. Int J Cancer 124:853–861
108. Lu W, Pan K, Zhang L, Lin D, Miao X, You W (2005) Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor α and risk of gastric cancer in a Chinese population. Carcinogenesis 26:631–636
109. Freund A, Chauveau C, Brouillet J-P, Lucas A, Lacroix M, Licznar A, Vignon F, Lazennec G (2003) IL-8 expression and its possible relationship with estrogen-receptor-negative status of breast cancer cells. Oncogene 22:256–265
110. Hsu M, Wu SY, Chang SS, Su IJ, Tsai CH, Lai SJ, Shiau AL, Takada K, Chang Y (2008) Epstein-Barr virus lytic transactivator Zta enhances chemotactic activity through induction of interleukin-8 in nasopharyngeal carcinoma cells. J Virol 82:3679–3688
111. Li X, Liang D, Lin X, Robertson ES, Lan K (2011) Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen reduces interleukin-8 expression in endothelial cells and impairs neutrophil chemotaxis by degrading nuclear p65. J Virol 85:8606–8615
112. Shiau M-Y, Fan L-C, Yang S-C, Tsao C-H, Lee H, Cheng Y-W, Lai L-C, Chang Y-H (2013) Human papillomavirus up-regulates MMP-2 and MMP-9 expression and activity by inducing interleukin-8 in lung adenocarcinomas. PLoS One 8:e54423
113. Woodworth C, Simpson S (1993) Comparative lymphokine secretion by cultured normal human cervical keratinocytes, papillomavirus-immortalized, and carcinoma cell lines. Am J Pathol 142:1544
114. Huang S-M, McCance D (2002) Down regulation of the interleukin-8 promoter by human papillomavirus type 16 E6 and E7 through effects on CREB binding protein/p300 and P/CAF. J Virol 76:8710–8721
115. Polyak SJ, Khabar KS, Paschal DM, Ezelle HJ, Duverlie G, Barber GN, Levy DE, Mukaida N, Gretch DR (2001) Hepatitis C virus nonstructural 5A protein induces interleukin-8, leading to partial inhibition of the interferon-induced antiviral response. J Virol 75:6095–6106
116. Pollicino T, Bellinghieri L, Restuccia A, Raffa G, Musolino C, Alibrandi A, Teti D, Raimondo G (2013) Hepatitis B virus (HBV) induces the expression of interleukin-8 that in turn reduces HBV sensitivity to interferon-alpha. Virology 444:317–328
117. Mori N, Murakami S, Oda S, Prager D, Eto S (1995) Production of interleukin 8 in adult T-cell leukemia cells: possible transactivation of the interleukin 8 gene by human T-cell leukemia virus type I tax. Cancer Res 55:3592–3597
118. Asfaha S, Dubeykovskiy AN, Tomita H, Yang X, Stokes S, Shibata W, Friedman RA, Ariyama H, Dubeykovskaya ZA, Muthupalani S (2013) Mice that express human interleukin-8 have increased mobilization of immature myeloid cells, which exacerbates inflammation and accelerates colon carcinogenesis. Gastroenterology 144:155–166
119. Beales IL, Calam J (1997) Stimulation of IL-8 production in human gastric epithelial cells byhelicobacter pylori, IL-1β and TNF-α requires tyrosine kinase activity, but not protein kinase C. Cytokine 9:514–520
120. Kitadai Y, Haruma K, Sumii K, Yamamoto S, Ue T, Yokozaki H, Yasui W, Ohmoto Y, Kajiyama G, Fidler IJ (1998) Expression of interleukin-8 correlates with vascularity in human gastric carcinomas. Am J Pathol 152:93
121. Lee KE, Khoi PN, Xia Y, Park JS, Joo YE, Kim KK, Choi SY, Jung YD (2013) Helicobacter pylori and interleukin-8 in gastric cancer. World J Gastroenterol 19:8192–8202

122. Schutyser E, Struyf S, Van Damme J (2003) The CC chemokine CCL20 and its receptor CCR6. Cytokine Growth Factor Rev 14:409–426
123. Bell D, Chomarat P, Broyles D, Netto G, Harb GM, Lebecque S, Valladeau J, Davoust J, Palucka KA, Banchereau J (1999) In breast carcinoma tissue, immature dendritic cells reside within the tumor, whereas mature dendritic cells are located in peritumoral areas. J Exp Med 190:1417–1426
124. Shimizu Y, Murata H, Kashii Y, Hirano K, Kunitani H, Higuchi K, Watanabe A (2001) CC-chemokine receptor 6 and its ligand macrophage inflammatory protein 3α might be involved in the amplification of local necroinflammatory response in the liver. Hepatology 34:311–319
125. Kleeff J, Kusama T, Rossi DL, Ishiwata T, Maruyama H, Friess H, Büchler MW, Zlotnik A, Korc M (1999) Detection and localization of MIP-3α/LARC/exodus, a macrophage pro-inflammatory chemokine, and its CCR6 receptor in human pancreatic cancer. Int J Cancer 81:650–657
126. Okudaira T, Yamamoto K, Kawakami H, Uchihara JN, Tomita M, Masuda M, Matsuda T, Sairenji T, Iha H, Jeang KT (2006) Retracted: transactivation of CCL20 gene by Epstein–Barr virus latent membrane protein 1. Br J Haematol 132:293–302
127. Baumforth KR, Birgersdotter A, Reynolds GM, Wei W, Kapatai G, Flavell JR, Kalk E, Piper K, Lee S, Machado L (2008) Expression of the Epstein-Barr virus-encoded Epstein-Barr virus nuclear antigen 1 in Hodgkin's lymphoma cells mediates up-regulation of CCL20 and the migration of regulatory T cells. Am J Pathol 173:195–204
128. Satoh T, Wada R, Yajima N, Imaizumi T, Yagihashi S (2014) Tumor microenvironment and RIG-I signaling molecules in Epstein Barr virus-positive and -negative classical Hodgkin lymphoma of the elderly. J Clin Exp Hematopathol: JCEH 54:75–84
129. Jiang B, Xue M (2015) Correlation of E6 and E7 levels in high-risk HPV16 type cervical lesions with CCL20 and Langerhans cells. Genet Mol Res 14:10473–10481