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REVIEW

Concise Review on Modulation Mechanism of Matrix Metalloproteinase via Oncoviruses in Aggressiveness of Malignancies

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Abstract: *Matrix metalloproteinases (MMPs) are a member of the protein family intimately associated with zinc-containing endopeptidases, which are the main proteases implicated in extracellular matrix (ECM) degradation. The high ability of MMPs in the degradation of extracellular proteins is an important event in many normal biological as well as pathologic processes, including tumor progression, tissue repair, wound healing, developmental morphogenesis, and inflammatory diseases. This review is focused on the description of the modulation mechanism of MMPs via oncoviruses. Up to now, a large number of oncogenic viruses have been detected and recognized as etiologic factors of multiple human cancers. Actually, by expression of several viral oncoproteins of tumorigenic viruses with the simple genetic system, we are able to deregulate or modulate the pathways of cell transformation procedure in malignancy. In brief, upregulated expression of MMPs genes by direct (through DNA binding) , as well as indirect interactions (by activating PI-3K/AKT, ERK/MAPK, IFN/JAK/STAT, JNK, NF-κB signaling pathways and/or immune response) with tumorigenic viruses, have a noticeable role in the proliferation of cells, as well as angiogenesis, mobility, EMT, invasiveness, and metastatic features. In fact, the growth of tumor-related researchers offers a future perspective for the efficiency of targeted, molecular-based therapies and its anticancer effects via diverse mechanisms such as the suppression of viral oncoproteins.*

Keywords: *Matrix Metalloproteinases (MMPs), Tumor Viruses, Tumor Progression*

INTRODUCTION

Matrix metalloproteinases (MMPs), form a family of zinc-dependent extracellular matrix (ECM) remodeling endopeptidase enzymes that play a role in a number of physiological processes, like the healing of wounds, organismal development, and effectors of immune responses, as well as in pathological conditions, like pulmonary dysfunctions, autoimmune diseases, and cancer [1,2]. To date, almost 25 various vertebrate MMPs have been recognized, including 23 members in humans [3]. Based on sequence homology and specificity for substrate, the MMPs family divides into six categories of stromelysins, collagenases, matrilysins, gelatinases, membrane-type as well as other non-classified MMPs [4]. Each of these groups has its subunits that perform unique functions [5]. Chemokines, cytokines, as well as growth factors, cell-to-to-cell adhesion molecules, and binding proteins, can be mentioned as other potential targets for MMP substrates [6]. The classification of MMPs is indicated in Table 1 shown [7-11]. Matrix metalloproteinase (MMPs) activity might be regulated at three transcription levels, production of enzymes like zymogens, which require activation, as well as co-expression of tissue inhibitors of metalloproteinases (TIMPs) [12,13]. MMPs transcription is perfectly controlled, and their expression level of them is low. TIMPs are endogenous suppressors of metalloproteinases that can inhibit the MMM's catalytic activity, therefore maintaining ECM homeostasis [14]. MMPs are produced in their inactive zymogenic forms (proenzymes or pro-MMPs), which are subsequently proteolytically activated by removing propeptides by other proteases [15]. The majority of MMPs are activated in the extracellular space via plasma, tissues, and microbial proteases. The rest of the activated MMPs like MT-MMPs, MMP-11, 23, and 28 possess a furin-dependent cleavage motif RXK/RR in the propeptide sequence, which are intracellularly

activated via furin-like proteases of Golgi [16]. Any disruption in the regulation of MMPs modulatory mechanisms may associate with the progression of the disease in pathological conditions [12].

Table 1: Classification of the main members of the MMP family by chromosomal location and the group of substrates

MMP number	MMP subclass/ Family/Group	MMP name	Substrates	Chromosome
MMP-1	Collagenases	Interstitial collagenase	Collagens (I,II,III,VIII a X); gelatin; aggrecan; L-selectin; IL-1β proteoglycans, entactin; ovostatin; MMP-2; MMP-9	11q22-q23
MMP-2	Gelatinases	Gelatinase A	Collagens (I,IV,V,VII,X,XI a XIV); gelatin; elastin; fibronectin; aggrecan; MBP; osteonectin; laminin-1; MMP-1; MMP-9; MMP-13	16q13
MMP-3	Stromelysins	Stromelysin 1	Collagens (III,IV.V, a IX); gelatin; aggrecan; perlecan; decorin; laminin; elastin; casein; osteonectin; ovostatin; antactin; plasminogen; MBP; IL-1β; MMP-2/TIMP-2; MMP-7; MMP8; MMP-9; MMP-13	11q23
MMP-7	Matrilysins	Matrilysins	Collagens (IV a X); gelatin; aggrecan; decorin; fibronectin; laminin; entactin; elastin; casein; transferrin; plasminogen; MBP; β4-integrin; MMP-1; MMP-2; MMP-9; MMP-9/TIMP-1	11q21-q22
MMP-8	Collagenases	Neutrophil collagenase	Collagens (I,II,III,V,VII,VIII a X); gelatin; aggrecan; fibronectin	11q21-q22
MMP-9	Gelatinases	Gelatinase B	Collagens (IV,V,VII,X a XIV); gelatin; entactin; aggrecan; elastin; fibronectin; osteonectin; plasminogen; MBP; IL-1β	20q11.2-q13.1
MMP-10	Stromelysins	Stromelysin 2	Collagens (III-V); gelatin; casein; aggrecan; elastin; MMP-1; MMP-8	11q22.3-q23
MMP-11	Stromelysins	Stromelysin 3	Unknown (casein)	22q11.2
MMP-12	Elastase	Metalloelastase	Collagen IV; gelatin; elastin; casein; fibronectin; vitronectin; laminin; entactin; MBP; fibrinogen; fibrin; plasminogen	11q22.2-q22.3
MMP-13	Collagenases	Collagenase-3	Collagens (I,II,III,IV,IX,X,a XIV); gelatin; plasminogen; aggrecan; perlecan; fibronectin; osteonectin; MMP-9	11q22.3
MMP-14	Membrane-MMP	MT1-MMP	Collagens (I-III); gelatin; casein; fibronectin; laminin; vitronectin; entactin; proteoglycans; MMP-2; MMP-13	14q11-q12
MMP-15	Membrane-MMP	MT2-MMP	Fibronectin; entactin; laminin; perlecan; MMP-2	16q12.2-q21
MMP-16	Membrane-MMP	MT3-MMP	Collagen III; gelatin; casein; fibronectin; MMP-2	8q21
MMP-17	Membrane-MMP	MT4-MMP	Gelatin	12q24
MMP-18	Collagenases	Collagenase-4	Unknown	Unknown
MMP-19	Other	RASI-1	Gelatin; tenascin; fibronectin; collagen IV; laminin; entactin; fibrin/fibrinogen; aggrecan	12q14
MMP-20	Other	Enamelysin	Amelogrenein; aggrecan; COMP	11q22
MMP-23	Other	Unnamed	Amelogenin	11q22
MMP-24	Membrane-MMP	MT5-MMP	Pro-MMP 2	20q11.2
MMP-25	Membrane-MMP	MT6-MMP	Pro-gelatinase A; fibrin; fibronectin; collagen IV; gelatin	16p/3.3
MMP-26	Matrilysins	Endometase, matrilysin-2	Gelatin Iα; P1; fibrinogen; fibronectin; vitronectin; β-casein	Unknown

MMPs AND TUMOR PROGRESSION

Cancer is the second factor of death globally, which is estimated to account for 9.6 million deaths in 2018 [17]. Recent two decades of biomedical research have led to large amounts of information about the molecular events which occur during carcinogenesis as well as signaling pathways involved in the progression of cancer. Complex molecular mechanisms play different roles in the tumor cells and the tumor environment associated with this process [18]. Several interactions of tumor cells with the involved environment of the tumor are crucial for the pathological changes observed during the transformation of cells and carcinogenesis in the extracellular matrix (ECM), as well as cytokines, growth factors associated with ECM, along with neighboring cells (neutrophils, endothelial cells, mast cells, macrophages, fat cells, and pericytes) [19-21]. Different steps of cancer consisting of migration, attack, metastasis, and angiogenesis are in interaction with the neighboring microenvironment [22]. MMPs are the main molecules in these processes, and since they break down numerous cell adhesion molecules, indicating their roles in the regulation of cell-to-to-cell, and cell-ECM interactions [23,24]. Previous researchers have identified that MMPs play an essential role in all phases of tumor maintenance and growth, including invasiveness, migration of tumor cells, evasion from apoptosis as well as immune surveillance, angiogenesis, and metastasis, so that all these major stages may be modulated by MMPs [25].

Interferon, interleukins, growth, factors, and extracellular MMP inducers secreted from tumor cells in a paracrine, manner stimulating adjacent host cells to generate the required MMPs. MMPs produced by normal cells can be bound and used on the surface of tumor cells [26]. MMPs gene expression and its activity increase in many types of cancers in humans. And this increased expression causes an increase in tumor size, invasion, and decreased survival [27]. Thus, MMPs are used as a novel and capable therapeutic target in different types and cancer phases [28]. MMPs use their proteolytic function to remove physical barriers, developing angiogenesis and tumor metastasis [29]. Tumor development and angiogenesis depend on the facilitated accessibility of signaling molecules. For example, cytokines and growth factors by MMPs enhance by making them available for tumor cells and their microenvironment [18]. This process is performed by releasing these factors from the ECM (VEGF, IGF, and bFGF) or via secreting them from the surface of the cell (HB-EGF, EGF, TGF-a) [4]. The release of endogenous angiogenesis suppressers can regulate angiogenesis perfectly, for instance, angiogenesis inhibitors like tumstatin, endostatin, angiostatin, and endorepellin [30]. Disruptions in the regulation of cell-cell and cell-ECM interactions by MMPs during the processing of E-cadherin and integrins, respectively, affect both cell phenotype (EMT) as well as increasing cell migration [31,32]. Almost all members of the MMP family have been reported to be dysregulated in human tumors, although MMPs such as MMP-1, -2, -7, -9, -13, and 14 are more important [33]. We have demonstrated the most noticeable MMPs, which are related to the phases of tumor growth, biological effects, and their consequences in Table 2.

Table 2: Key MMPs in relation to the stages of cancer progression, biological effect, and consequences

Function	MMP	Biological effect	Consequence	Reference
Cancer cell invasion	MT1-MMP, MMP-2 and MMP-9	Proteolytic	Breakdown physical barriers	[144]
Cancer cell proliferation	MMP-1, -2, -3, -7, -9, -11, -19	Cleavage of IGF binding proteins, Shedding of membrane, anchored ligands of EGFR, including HB-EGF, TGF-a and amphiregulin, Activation of TGF-β, Shedding of HB-EGF	Proliferation	[145-147] [148] [149] [150]
Cancer cell apoptosis	MMP-7 Several MMPs	Cleaving the Fas ligand Indirect activation of the serine/serine/threonine Akt ⁄ protein kinase B through the signaling cascades of EGFR and IGFR	Anti-apoptotic	[151] [147, 152]
Tumor angiogenesis	MMP-2, -9 MMP-3, -10, -11 MMP-1, -8, -13	Degradation of COL-IV, perlecan; release of VEGF and bFGF, respectively Degradation of COL-IV, COL-XVIII, perlecan; generation of tumstatin, endostatin, angiostatin and endorepellin, respectively	Upregulation of angiogenesis Downregulation of angiogenesis	[153, 154] [4, 155]
Cell adhesion, migration, and EMT	MMP-2 MT1-MMP MMPs MMP-2, -3, -9, -13, -14 MMP-1 and -7 MMP-28	Degradation of COL-IV; generation of cryptic peptides Degradation of laminin-5; generation of cryptic peptides Integrins as substrates Overexpression this MMPs associated with EMT, a highly conserved and fundamental process of morphological transition By cleavage E-cadherincontribute to morphological transition Proteolytic activation of TGF-β	Promote migration Induction of EMT; cell migration Powerful inducer of EMT, leading to cell migration	[156, 157] [158] [159] [160] [161]
Immune surveillance	MMP-9 MMP-9, -2, -14 MMP-7, -11, -1, -8, -3 MMP-7, -8	Cleavage of IL-2R alpha Release active TGF- β Release of a1-proteinase inhibitor Cleave several members of the CC (β-chemokine) and CXC (α-chemokine) chemokine subfamilies or to regulate their mobilization	Repress T-lymphocyte proliferation Abolish T-lymphocyte reaction against cancer cells Decrease cancer cell sensitivity to NK cells Affecting leukocyte infiltration and migration	[162] [163] [164] [165, 166]

ONCOVIRUSES

Approximately 20% of all human malignancies worldwide are associated with viruses [34]. Seven viruses have been implicated as oncogenic, including HPV, EBV, HCV, HBV, Kaposi's sarcoma-associated herpesvirus (KSHV), HTLV-1, and Merkel cell polyomavirus (MCV), which have been reported to be etiologically implicated in the maintenance and progression of human cancers [35]. However, viral oncogenesis processes

are a complex process, with induction of chronic inflammation conditions, disruption of cellular DNA repair mechanisms, interrupting host genetic and epigenetic integrity, and homeostasis, viral infection may result in genome variation and cell cycle deregulation. Viral 'oncoproteins' are capable of modulating or deregulating cellular signaling pathways, making changes in the expression of genes and microRNAs in either transcription or post-transcription, and disrupting tumor suppressor factors and proteins, which regulate cell polarity, immune response, signal transduction, and cell apoptosis. Genetic and epigenetic modifications caused via oncoviruses may be resulting in the morphology and variation of cancer stem cells, which are essential for the primary initiation, development, migration, invasiveness, and chemotherapy resistance of tumors. These molecular events underlying the interactions between oncoviruses that use specific cellular genes and cellular signaling pathways are important issues to research efforts [36-38]. MMPs have several specific biological actions in every cancer phase, from the beginning to the extension of pertinent metastases. Accordingly, this review's focus is on characterizing the mechanism of modulation or deregulation of MMPs by oncoviruses.

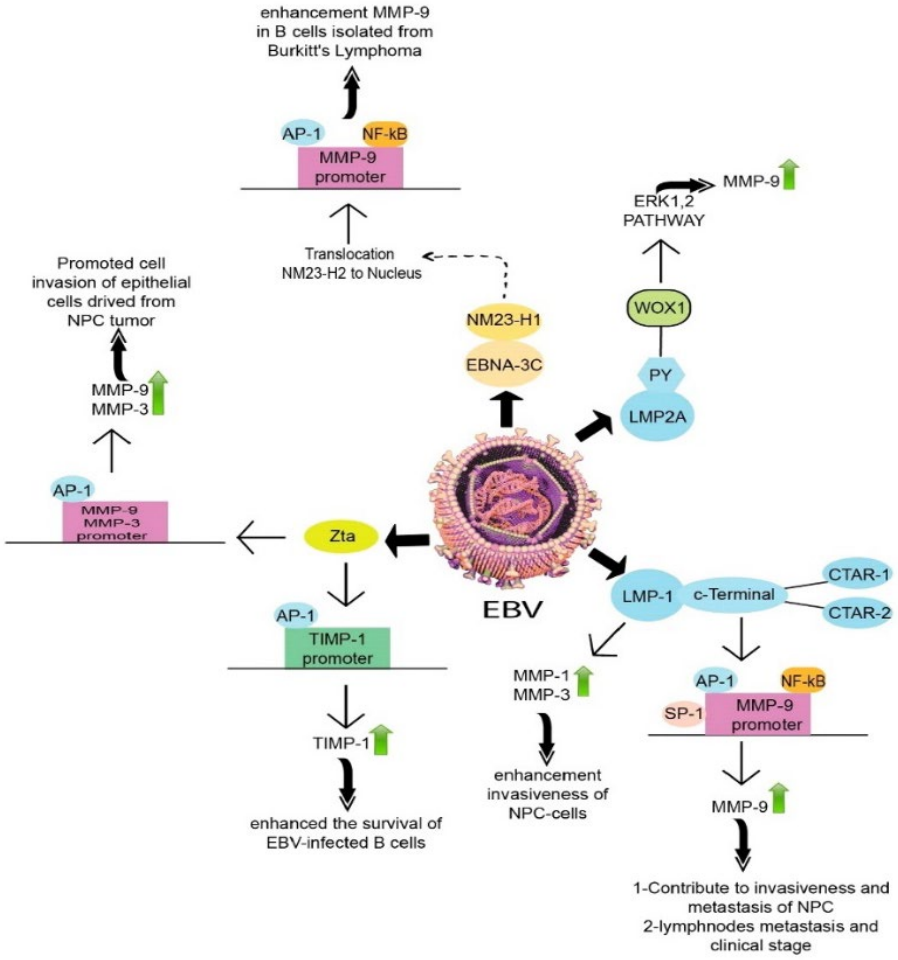
INTERACTION BETWEEN ONCOVIRUSES AND MMPs

Epstein-Barr virus

Epstein-Barr virus (EBV) is a linear dsDNA virus that belongs to the human gamma-herpesvirus family, playing a role in different B-cells lymphomas, including Hodgkin's lymphoma, Burkitt's lymphoma, post-transplant lymphoproliferative disorders, as well as other tumors like T-cell non-Hodgkin lymphomas and nasopharyngeal carcinoma [39]. In tumors associated with EBV, the virus leads to a latent infection expressing only a subset of 12 latent viral transcripts, two early RNAs (EBERs), three latent membrane proteins (LMPs), six nuclear antigens (EBNAs), and BARF transcripts. Out of these genes, EBNA1, EBNA-2, EBNA-3A, EBNA-3C, EBNA-LP, and LMP1 enable the virus to control a number of cellular signaling pathways associated with oncogenesis [40,41]. EBV LMP1 increases MMP-9 expression by recruitment of Sp-1, AP-1, and NF-kappa B transcription factors on MMP-9 promoter that is related to invasiveness and metastasis in EBV-associated NPC [42]. Previous research demonstrated that C-terminal activation regions 1 and 2 (CTAR-1 and CTAR-2), two crucial signaling domains within the carboxy terminus of LMP1, might activate the MMP-9 promoter and stimulate MMP-9 activity [43]. TANG Jian showed EBV-induced MMP-9 upregulation correlates with lymph node metastasis and clinical stage in NPC tumors [44]. Lee demonstrated that upregulation of MMP1 and MMP3 expression in LMP1-positive NPC tumors led to the enhancement of invasiveness in NPC cells [45]. BZLF1 (also known as Zta) is one of the critical inducers of EBV lytic cycle alteration and has been reported to trigger metastasis in epithelial cells [46, 47]. In vitro studies demonstrated that Zta stimulates MMP3 and MMP9 expression in epithelial cells derived from NPC tumors. Zta can activate the MMP3 promoter by AP-1 elements, and its DNA-binding domain is necessary for the process of promoter binding and MMP3 stimulation. Zta-enhanced cell migration requires MMP3 but not MMP9. Zta-elevated cell migration needs MMP3, but not MMP9. Therefore, the expression of both MMP3 and MMP9 is important for the co-expression of the two MMPs (MMP3 and MMP9) induced by Zta, which simultaneously promotes cell invasiveness of epithelial cells differentiated from NPC tumor [48]. Moreover, Zta protein via binding AP-1 site of its promoter increases TIMP-1 expression in EBV-infected B-cells as well as EBV-immortalized lymphoblastoid cell lines (LCLs). Upregulation of TIMP-1 expression through Zta enhances the maintenance of EBV-infected B-cells and promotes the progression of EBV-associated cancer [49]. EBNA3C regulates the transcription of numerous viral as well as cellular genes important for the process of immortalization by EBV in primary B-lymphocytes [50]. Nm23-H1 is a well-known metastasis inhibitor, and its low expression is correlated with metastatic tumor capability in different types of human carcinoma [51]. In vitro research showed the interaction of EBNA3C with Nm23-H1 leads to the translocation of Nm23-H1 to the nucleus and inhibits the antimotility effect. However, studies have shown that this interaction also can increase transcriptional activity on a related promoter of the target gene [52]. Interaction between EBNA3C and Nm23-H1 upregulates the expression of MMP-9 by binding the transcription factors AP-1 and NF-kB on its promoter in B-cells that were isolated from Burkitt's lymphoma [53]. LMP2A promotes cell transformation, migration, and invasion by affecting host cellular signaling pathways, mainly by its N-terminus, intracellular domain, which consists of an immunoreceptor tyrosine-based activation motif (ITAM), a YEEA motif, and two PPPPY (PY) motif [54,55]. LMP2A promotes invasion of NPC cells by the PY motif via stimulation of extracellular signal-regulated kinase (ERK)-1/2 as well as the downstream transcription factor Fra-1, therefore leading to upregulation of MMP9 expression [56]. WW domain-containing oxidoreductase WOX1, also called WWOX or FOR, is a candidate tumor inhibitor encoded by the human fragile WWOX gene, related to several signaling pathways modulating embryonic development, metabolism, cell proliferation, and apoptosis [53]. The function of WOX1 in cancer suppression is commonly used by stimulating apoptosis and sequestering some oncoproteins [57,58]. According to a previous study, the interaction of the tyrosine residue 33 of WOX1 and the PY

motif of LMP2A is needed for the LMP2A-induced ERK1/2-Fra-1-MMP9 pathway in NPC cells (Figure 1) [59]. Two SNPs (rs8113877T>G or rs17576A>G) of MMP-9 in ab_EBV positive individuals were associated with more possibility of progression to chronic lymphocytic leukemia in contrast to those individuals who were negative [60]. In summary, the upregulation of MMPs by EBV plays a significant role in EBV-triggered metastasis.

Figure 1: Schematic model of deregulation of MMPs by EBV virus

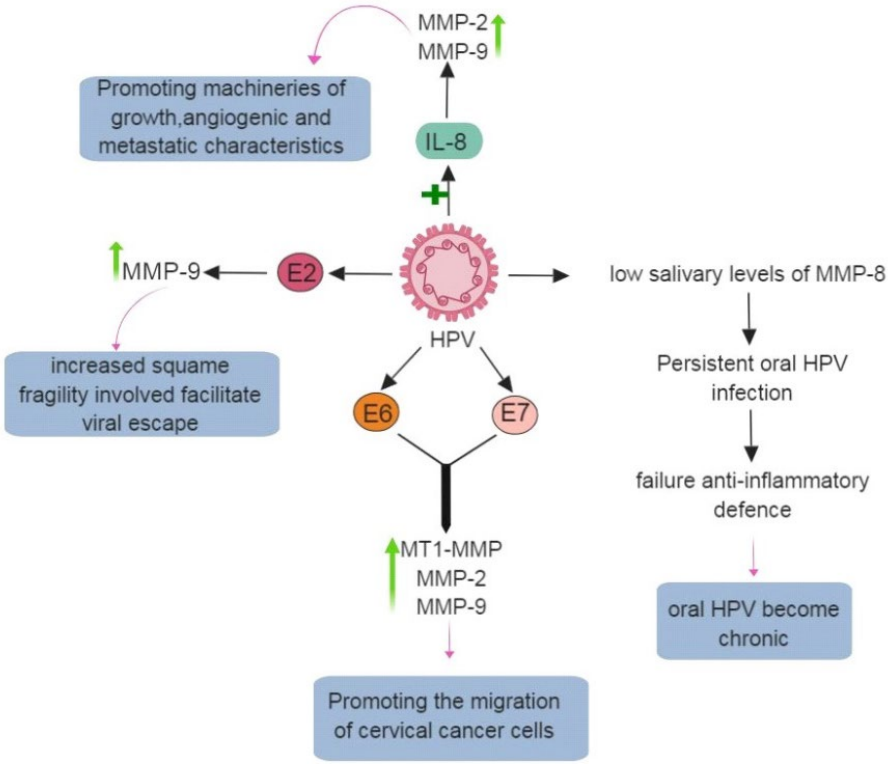


Human papillomavirus

Human papillomaviruses (HPVs), namely double-stranded DNA viruses, are recognized as one of the main agents that relate to the progression of numerous cancers such as head and neck, cervix, vagina, vulva, anal and penile carcinomas [61]. Continuing infection with high-risk human papillomavirus (HPV) types, especially HPV type 16 or 18, is essential for the development of a cancer precursor lesion and invasive cervical cancer, which is identified through deregulated and high-level expression of HPV early genes (E6 and E7) [62]. The high-risk HPV E6 and E7 oncoproteins result in transformation by a disruption in the activity of cellular tumor suppressor proteins p53 and RB, respectively, and several cellular proteins [63,64]. Induction of MT1-MMP expression in HaCaT cells, an immortalized human keratinocyte line, by the E7 protein of high-risk HPV types 16 and 8 contributes to cellular proliferation, angiogenesis, and, malignant progression, for the invasion of HPV-positive tumor cells [65]. In human keratinocytes and organotypic skin cultures, HPV8 E2 protein overexpresses the expression of MMP-9 by direct activation of its promoter, resulting in increased squamous fragility involved in facilitating viral escape [66]. A recent study demonstrated that HPV-16 E6/E7 oncoproteins cause upregulation of MT1-MMP, MMP-2, and MMP-9 to promote cervical cancer cells [67]. Previous studies reported that HPV 16 infection might lead to lung tumor cells through increasing in interleukin-17 (IL-17) expression. IL-17 along with its downstream signaling mediator, interleukin-8 (IL-8), play an efficient role in tumor angiogenesis and metastasis by modulation of various pro-angiogenic factors [68]. Induction of IL-8 by HPV upregulates the expression of MMP-2 and MMP-9 in lung adenocarcinoma that correlated with progressive

mechanisms of growth, and metastatic and angiogenic characteristics [69]. HPV-16 E6/E7 overexpressed the expression of MT1-MMP and MMP-2, which are correlated with increased cell invasion in cervical cancer [70]. According to recent research (Haukioja), low salivary levels of MMP-8 are due to continued oral HPV infection, which appears like a failure of the anti-inflammatory defense of the oral mucosa to allow an incident oral HPV infection to become a chronic infection [71]. Common skin extract immunoblots and zymographic analysis revealed increased expression of MMP-9, MMP-13, and MT1-MMP in HPV8-positive mice rather than HPV8-negative mice, which are involved in the development of HPV8-induced cutaneous tumors (Figure 2) [72]. Singh et al. have shown that SNPs -1306CC (rs243865: C>T) in the promoter of the MMP2 gene, enhanced transcription and enzymatic activity of the MMP-2 gene is associated with the incidence possibility of cervical cancer. A significant relationship between the −1306CC genotype and HPV infection in increasing the risk of cervical cancer was observed [73].

Figure 2: Schematic model of deregulation of MMPs by HPV virus

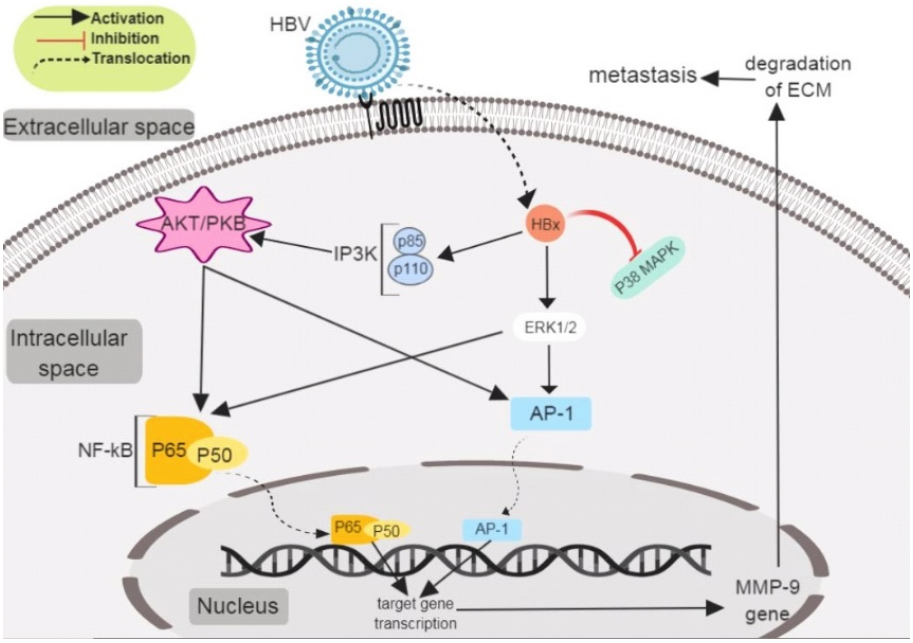


HBV

Chronic hepatitis B (CHB), an important agent responsible for liver cirrhosis and hepatocellular carcinoma, is among the primary health problems of the world [74,75]. HBV transactivator protein (HBx) enables the invasive capacity of the virus, which is mediated by increased the expression of membrane-type one matrix metalloproteinase (MT1-MMP) that subsequently activates matrix metalloproteinase-2. HBx is able to induce both MT1-MMP expression and cell invasion through dependence on cyclooxygenase-2 (COX-2) activity. Furthermore, HBx increases COX-2 expression through the activation of COX-2 gene promoter transcription in a nuclear factor of an activated T-cell-dependent (NF-AT–dependent) manner. These data indicated the capacity of HBx to augment tumor cell invasion by a mechanism consisting of MT1-MMP and COX-2 upregulation and led to new insights into HBx protein mechanism of action, its involvement in tumor metastasis and hepatocellular carcinoma resulting from intrahepatic metastasis to HBx protein expression following establishment of tumor [76]. HBx protein plays a crucial role in the progression of hepatocellular carcinoma (HCC). HBx is often the only HBV protein that would be detected in hepatic tumor cells, which enhances tumor cell invasion and metastasis. HBx, by inducing the PI-3K/AKT and ERK pathways except for the P38 MAPK pathway, leads to the activation of NF-kB and AP-1 transcription factors. HBx triggers the translocation of NF-kB and AP-1 into the nucleus, leading to increasing MMP-9 expression. Thus, HBx modulates the transcriptional function of MMP-9 that is essential to the incursion and metastasis of tumors through PI-3 K/AKT and

ERK pathways. These findings suggest that HBx could induce MMP-9 and, in turn, in the invasion and metastasis of cancer, by activating ERK and PI-3K signaling pathways (Figure 3) [77].

Figure 3: Molecular mechanism of HBX-activated MMP-9 expression. HBx induces PI-3K/AKT and ERK pathways but not the p38 MAPK pathway. This process leads to the stimulation of NF-kB and AP-1 transcription factors. Translocation of NF-kB and AP-1 activated by HBx into the nucleus leads to an increase of MMP-9 expression. Therefore, HBx via regulation of transcriptional activation of MMP-9, plays an important role in the invasion and metastasis of tumors via PI-3K/AKT and ERK pathways

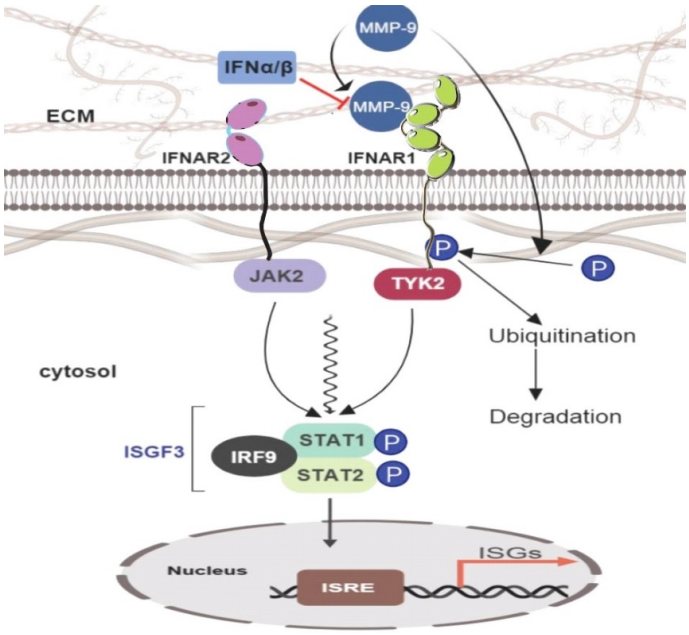


Genes that were defined to be modulated in the presence of HBx include those genes involved in signal transduction, cell cycle, cytokine production, metabolism, apoptosis, cell adhesion, and oncogenesis. The functions of other less-defined genes also were affected. Transactivation by HBx upregulates the translation, transcription, and release of matrix metalloproteinase-3 (MMP-3), which manifests as a cell migratory phenotype. This effect of HBx was suppressed in the presence of an MMP-3-specific peptide inhibitor. HBx applies selective control of transcription in hepatoma cells as well as inducing cell migration via activation of MMP-3. Therefore, by upregulation of MMPs, HBx increases the invasion of tumor cells and the destruction of the extracellular matrix that is reported to increased cell migration [78]. The progression of tumors tightly depends on a permissive microenvironment that is highly correlated with the destiny of tumor cells. The normal structure of ECM is of high importance in the modulation of cell growth. For invasiveness, cancer cells must overwhelm the mechanical barriers caused by the ECM. It has been demonstrated which conformational changes in the ECM by MMPs have a noticeable role in the mobility and spread of tumor cells, resulting in invasion and metastasis. The activation of MMP induced by HBx signifies a role of HBx protein in the development of HCC metastasis. However, HBx is demonstrated to relieve transcriptional stimulation activity, it is not defined in what way HBx induces the expression of MT1-MMP [79,80]. HBV replication is assisted by MMP-9 through repression of IFN/JAK/STAT signaling as well as IFNAR1 function. Thus, these outcomes have discovered a novel role for MMP-9 in viral replication, revealing a new mechanism by which HBV escapes host immunity to maintain persistent infection. Indeed, there is a positive feedback loop between the injection of HBV and the production of MMP-9. Firstly, HBV activates MMP-9 production in PBMCs and macrophages. Subsequently, HBV replication would be facilitated by MMP-9 through repressing IFN/JAK/STAT signaling, interacting with IFNAR1 to prevent its binding to IFN-α and promoting the ubiquitination phosphorylation, degradation of IFNAR1 and ISRE, subcellular distribution, and interferon-stimulated response element. Thus, MMP-9 would benefit HBV by blocking innate immunity to launch or maintain chronic infection (Figure 4) [81].

In hepatitis B infection, apoptosis of liver cells that is induced by varying degrees of inflammation plays an essential role in the outcome of CHB [82]. The MMP-9 expression level is directly related to TNF-α and IL-6. Because IL-6 and TNF-α can

regulate MMP-9 activity in a concentration- and time-dependent mode, overexpression of MMP-9 can degrade ECM to destroy the basement membrane and lead to disorganized and loose tissue structures, leading to further penetration of TNF-α and IL-6. These factors can interact with each other and create a vicious cycle, resulting in pathological changes in the liver. In conclusion, the MMP-9 level is increased remarkably in patients with varying degrees of CHB, it would be important in the pathological progress of the liver, and it has a close correlation with inflammation, which can provide a theoretical basis for clinical treatment [83].

Figure 4: MMP-9 assists HBV replication by suppressing IFN/JAK/STAT signaling and IFNAR1. Indeed, HBV induces MMP-9 in infected patients and in HBV-stimulated leukocytes. Then, MMP-9 comforts HBV replication through repressing IFN/JAK/STAT signaling, interacting with IFNAR1 to block its binding to IFN-α, and promoting the phosphorylation, ubiquitination, subcellular distribution, and degradation of IFNAR1

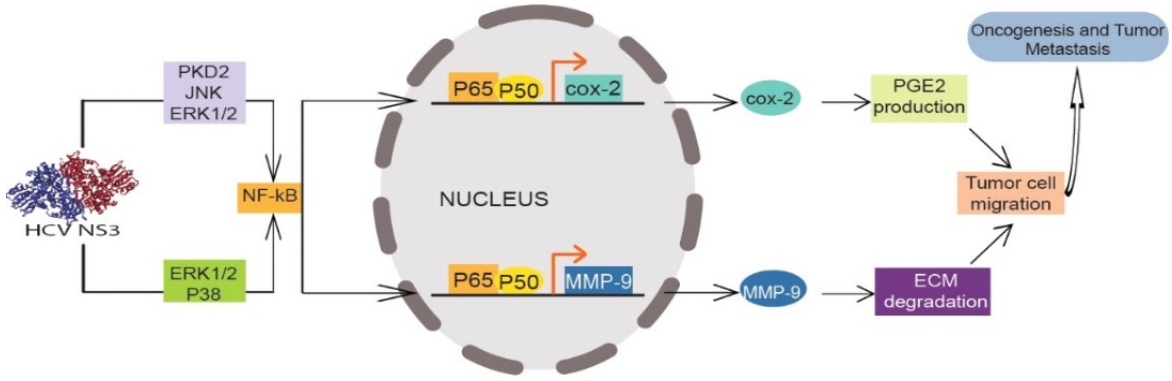


HCV

Hepatic inflammation, cirrhosis, developing liver fibrosis, and hepatocellular carcinoma (HCC) are common problems in HCV patients [84,85]. In the liver, the main reason for fibrogenesis is pathological repletion of the extracellular matrix (ECM), which leads to an imbalance in the rate of enhanced matrix synthesis to reduce the degradation of connective tissue proteins that can be controlled by matrix metalloproteinases (MMPs). Recent studies showed that increasing levels of hepatic gelatinases, including MMP-9, and MMP-2, are related to the progression of HCC and the fibrotic index of chronic HCV patients [86,87]. The disparity between matrix metalloproteinases (MMPs) and tissue suppressors of matrix metalloproteinases (TIMPs) is remarked to be a significant index of degradation of the extracellular matrix. MMPs are members of gene families that can degrade collagen and play an essential role in the natural mechanism of tissue repair in pathological states, including liver fibrosis. Thus, an increase of the MMP-1/TIMP-1 ratio by IFN treatment can relieve liver fibrosis of chronic hepatitis C that demonstrates the anti-fibro genetic effect of IFN on the factors modulating hepatic fibrosis [88]. During chronic liver harm, activated hepatic stellate cells (HSC) turned backward into myofibroblast-like cells and proliferated. This stage is an important factor in the creation of fibrosis and subsequent cirrhosis [89]. HSCs are considered important sources of fibrillar as well as nonfibrillar collagens of the liver, matrix-degrading proteases (MMPs), and their specific blockers (TIMPs). Briefly, recent studies on patients with chronic hepatitis C reported important variations in hepatic TIMP and MMP expression. It is likely that TIMP expression was affected via the inflammatory conditions of the disease, which can reflect the effects of the disease. Promoted fibrosis enhances the expression of MMP-7 and MMP-2 and provides a condition for the destruction assessment of connective tissue [86]. The primary activity in the biosynthesis of different prostaglandins (PG) and thromboxanes catalyzes via cyclooxygenases [90,91]. There are two cyclooxygenases (COX) isoforms: COX-1 is basically expressed in several cell types and is the main factor in the homeostatic activity of PG, while COX-2 is triggered by different proinflammatory stimuli, including lipopolysaccharide (LPS) and cytokines [92-94]. COX-2 is involved in fibrogenesis, inflammation, and carcinogenesis [95-97]. Therefore, different researchers reported that

increased COX-2 expression and PG production might be associated with liver dysfunction and tumorigenesis in various animal models [98-100], in addition to fibrosis and hepatocellular carcinoma (HCC) among humans [101,102]. HCV core and NS5A proteins, both alone and in association with the impact of endotoxin and proinflammatory cytokines, are capable of regulating the expression of COX-2 and MMP-9 genes through chronic HCV infection. Therefore, this mechanism may be considered evidence for this process that chronic HCV infection may result in liver fibrosis. Thus, it seems reasonable that much PGs generated in hepatocytes via the correlated effect of HCV proteins in addition to inflammatory factors may affect neighboring liver cells by autocrine and/or paracrine pathways, therefore participating in hepatocarcino-genesis [103]. The E2 envelope glycoprotein of the hepatitis C virus (HCV) is an important modulator of HCV interaction with cell surface receptors. E2 interacts with an extracellular loop of human CD81; it's a receptor expressed on various cell types such as hepatocytes and B-cells. CD81 on the cell surface is expressed in human hepatic stellate cells (HSC) at a high level, Matrix metalloproteinase-2 (MMP-2; gelatinase A), an important enzyme responsible for the degradation of the normal hepatic extracellular matrix, upregulates subsequently after binding E2 toCD81. Furthermore, E2/CD81 interaction in human HSC causes an increasing amount of MMP-2 via increasing the binding activity of activator protein-2/DNA via ERK/MAPK phosphorylation. Increased degradation of the hepatic extracellular matrix in HCV-concentrated regions may be associated with inflammatory as well as parenchymal damage [104]. HCV replication may be regulated by signal cascades, cellular factors, and viral proteins [105-108]. The HCV nonstructural protein 3 (NS3) has a serine protease required for the synthesis of viral protein and helicase activity needed for viral replication [109,110]. NS3 also is a major protein in modulating cell proliferation, indicating its role in carcinogenesis [111,112]. HCV NS3 protein facilitates tumor cell invasion in two ways. Firstly, NS3 induces several signaling pathways like protein kinase D2 (PKD2), JNK, and ERK1/2 to modulate the transcription factor NF-κB, and subsequently, it regulates the expression of COX-2 [113], and COX-2, in turn, activates MMP-9 expression. Secondly, NS3 induces the ERK1/2–p38 signal pathway to modulate the activity of NF-κB, which triggers the translocation of NF-κB to the nucleus and binding of NF-κB to MMP-9 promoter, which consequently upregulates MMP-9 expression. MMP-9 (an important enzyme in degrading the extracellular matrix), and COX-2 (the main enzyme in prostaglandin E2 production) exert key roles in tumor invasion and tumorigenesis. Therefore, NS3 enhanced tumor cell metastasis by MMP-9 and COX-2, leading to tumorigenesis (Figure 5) [114]. The MMP2, MMP9, and TNF-α levels have an effective increase in chronic HCV patients. However, no considerable correlation has been reported in the levels of MMPs and TNF-α between fibrotic and cirrhotic cases. In consequence, MMP2, MMP9, and TNF-α revealed high reproduction capacity in distinct patients afflicted with liver fibrosis (F1–F4) compared to the control group. In contrast, MMP9, MMP2, and TNF-α were not distinguishable factors for liver fibrosis in patients with chronic HCV. Therefore it is likely that they would be used as prognostic markers for liver fibrosis [115].

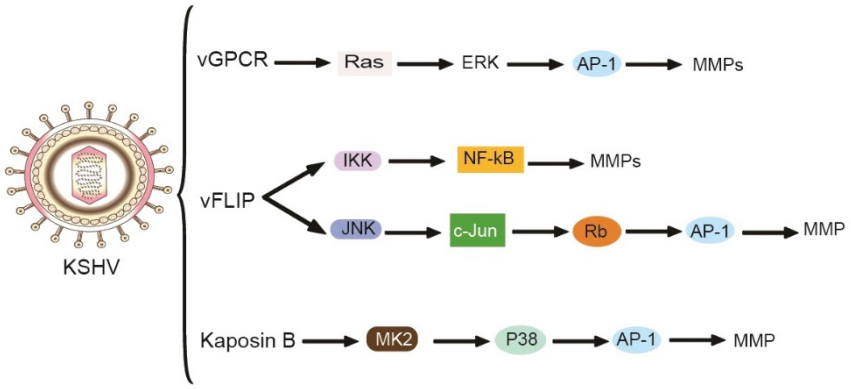
Figure 5: The mechanism of hepatoma cell invasion by HCV NS3 protein. First, NS3 activates multiple signaling components such as protein kinase D2 (PKD2), JNK, and ERK1/2 to regulate the activity of transcription factor NF-κB, which in turn regulates the expression of COX-2, and then COX-2 activates MMP-9 expression. Second, NS3 activates ERK1/2–p38 signaling pathway to regulate NF-κB activity, stimulates the translocation of NF-κB from the cytosol to the nucleus and the binding of NF-κB to the MMP-9 promoter, and thus activate MMP-9 expression.Thus, NS3 enhances tumor cell migration through COX-2 and MMP-9, resulting in oncogenesis or tumorigenesis



KSHV

Human herpesvirus-8 (HHV-8) or Kaposi sarcoma-associated herpesvirus (HHV-8 /KSHV) is a ds DNA virus with 165 kb in length. The HHV-8 life cycle consists of two states, lytic replication, and a latent phase. After primary infection, HHV-8 uses the cellular machinery of the host for replication and is subsequently observed in a latent phase as an episome. Like all herpesviruses, the B lymphocyte is the primary source of HHV-8 latency. The second sites for viral latency are endothelial cells, but these cells are the first infected cells in Kaposi sarcoma (KS). During latency, HHV-8 can regulate host cellular signaling pathways by different cellular mechanisms. Latent proteins, which include viral Cyclin a (v-Cyclin), LANA, kaposin, viral FLICE inhibitory protein (v-FLIP), and several miRNAs contribute to the pathogenesis of malignancies associated with HHV-8 [116]. HHV-8 has been identified in a Kaposi sarcoma lesion in an AIDS patient in 1994. This virus was reported to be associated with many B cell lymphoproliferative disorders (LPDs) such as posttransplant and germinotropic LPDs, multicentric Castleman disease (MCD), as well as primary effusion lymphoma (PEL) [117]. MMPs possibly associate with the mechanism of invasive KS growth and can be a proper target for effective therapeutic measures [118]. Developing KS lesional cells express gelatinases (MMP-2, MMP-9), stromelysin-1 (MMP-3), matrilysin (MMP-7), and collagenase (MMP-1, MMP-13) [119]. Cheng F. et al. demonstrated KSHV induces endothelial-to-mesenchymal transition (EMT). EMT was triggered by the viral proteins vGPCR and vFLIP via activation of the Notch pathway, which leads to a gain of membrane-type-1 matrix metalloproteinase (MT1-MMP) (Figure 6) [120]. The transcription factor PROX1 expression was recently investigated in KS. PROX1 binds the MMP14 promoter to repress its transcription. PROX1 negatively regulates MMP14 in normal tissues. Silvia Gramolelli et al. revealed that infection of lymphatic endothelial cells (LECs) with KSHV decreases PROX1 expression [121].

Figure 6: Schematic model of deregulation of MMPs by KSHV virus

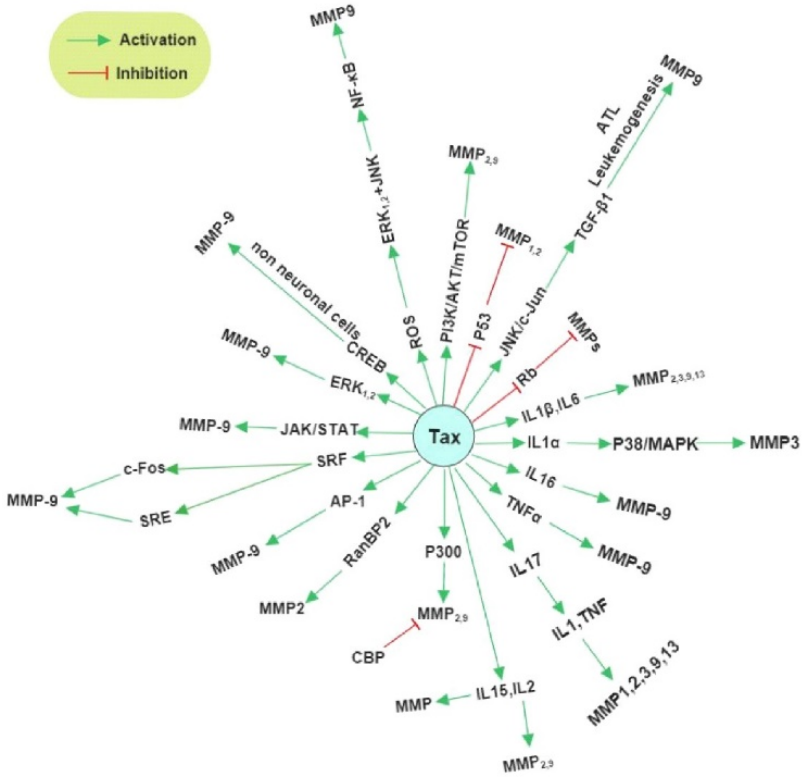


Human T-cell lymphotropic virus type I (HTLV-I)

HTLV1 is a member of the retroviridae family, which is an etiologic factor of Adult T-cell Leukemia (ATL).ATL is a malignancy responsible for the extremely aggressive proliferation of CD4+ cells with no known cure [122]. ATL commonly originates from an infection that is acquired in early life [123]. Also, besides ATL, other manifestations of infiltrated T-cells, matrix metalloproteinases (MMPs), and cytokines of viral infection are Sjogren syndrome with an inflammatory appearance and HAM/TSP associated with neurological symptoms and incomplete paralysis of limbs [124-126]. The 3' end of the genome (pX region) encodes some specific genes, including Rex, Tax, p12, p13, p30, and HTLV-1 bZIP factor (HBZ) [127,128]. HTLV-1 encodes two important genes, basic leucine zipper factor (HBZ), and tax, that are recognized to exert key roles in the infectivity of HTLV-1, survival, and growth of leukemic cells. Unlike HTLV-1 tax, HBZ escapes the antiviral response and is not detectable via the immune system. HTLV-1 provirus pX region encodes HBZ protein and in contrast to Tax, expressed in 100% of ATLL cells [123,129,130]. Although the proliferation of T cells is increased by HBZ, its function is interestingly antagonist to many tumorigenic activities of tax, such as activation of classical signaling pathways such as NFAT, AP-1, CREB, and NF-κB. Tax Repression through HBZ provides a condition for HTLV-1 to develop ATL by evading the immune system [123,131]. Tax may interact with cellular factors including AP-1, CBP/p300, CREB/ATF, and NF-κB. Both HTLV-1-replication and T-cell proliferation are generally enhanced by activating of IκB kinase (IKK)-NF-κB that is stimulated by viral Tax oncoproteins. Viral transactivator Tax is a presumed E3 ubiquitin ligase that is unitedly related with UbcH7, UhcH5c, and UbcH2 and is responsible for direct activation of IKK via binding to the NEMO subunit [132,133]. Bazarbachi et al. proved the interaction of HTLV-I-transformed cells in relation

to endothelial cells triggers the gelatinase activity of MMP-9 and MMP-2 in endothelial cells and decreases the tissue blocker of MMP. In a study by Szymocha et al. on infected astrocytes (T cells) with HTLV-1, contact with T cells is the factor that the astrocyte obtains a typical phenotype of gliosis and causes the release of proinflammatory cytokines (i.e. IL-1 α, IL-6, TNF-α) and matrix metalloproteinases (MMP-3, MMP-9). The high expression of MMPs and their endogenous suppressors (TIMP-3 and TIMP-1) cause MMP/TIMP imbalance. It changes the extracellular matrix [134]. Giraudon et al. showed cytokines secreted by infected glial cells with HTLV-1 are responsible for increasing the expression of TIMP-3, and MMP-3, MMP-9, while MMP-2, TIMP-1, and TIMP-2 remained stable (Figure 7) [135].

Figure 7: The demographic characteristics of the nurses (average score and standard deviation of nurses' clinical competence and moral reasoning)



MATRIX METALLOPROTEINASE INHIBITORS

Nowadays, MMPS targeting suppression of the activity of MMPs in the extracellular matrix as a novel anticancer strategy could be reconsidered. TIMPs, which are natural inhibitors of MMPs, at first, were the compounds to be developed for medical research. Hypothetically, TIMPs with potent inhibitory activity specifically can suppress the function of some MMPs which could lead to a useful therapeutic effect. However, their clinical application is still hampered by the absence of an efficient gene delivery style that has restricted the clinical use of this method [136]. Nevertheless, the progress of several types of natural synthetic suppressors of MMPs has been completely adopted and broadly investigated in clinical trials and researched in various cancers during the past decade (Table 3). Generally, synthetic suppressors of MMPs divide into three distinct pharmacologic groups including collagen non-peptidomimetics and peptidomimetics, tetracycline derivatives, and bisphosphonates [137].

THE RELATION BETWEEN INHIBITING OF MAJOR SIGNALING PATHWAYS BY MMP INHIBITORS AND ONCOVIRUSES

As previously mentioned, in HBV infection, HBx controls the transcription induction of MMP-9 which plays a key role in migration as well as metastasis of the tumor via PI-3 K/AKT and ERK pathways. Therefore, these data show that HBx plays a major role in inducing MMP-9 and, in turn, in the invasion and metastasis of cancer via activating ERK and PI-3K signaling pathways [77]. On the other hand, all the findings of one study already implied that 3-azidoWA suppresses 3-azidoWA-mediated MMP-2 expression through the attenuation of internal phospho-ERK as well as phospho-Akt expression in a dose-dependent condition that may have a significant role in the prevention of mouse angiogenesis as a natural inhibitor [138].

Table 3: An overview of the mechanisms deregulation MMPs by oncoviruses

Virus	Viral Factor	Number MMP	Mechanism/Effect	References
EBV	LMP1	MMP-9	Enhanced MMP-9 expression through induction of the MMP9 promoter by recruitment transcription factors AP-1, Sp-1, and NF-kappa B on MMP-9 promoter	[42]
	LMP1	MMP-1, MMP3	Upregulated MMP-1 and MMP-3 expression in NPC tumors	[45]
		MMP-9	Upregulated MMP-9 expression correlation with lymph nodes metastasis and clinical stage	[44]
	Zta	MMP-9, MMP-3	Overexpressed MMP-9 and MMP-3 expression in epithelial cells derived from NPC tumor	[48]
	EBNA3C	MMP-9	The interaction between EBNA3C and Nm23-H1 upregulated expression of MMP-9	[53]
	LMP2A	MMP-9	Upregulated MMP-9 expression by activation of extracellular signal-regulated kinase (ERK)-1/2 and a downstream transcription factor Fra-1	[56]
	Zta		Zta protein also up-regulated TIMP-1 gene expression in EBV-infected B cells and EBV-immortalized LCLs	[49]
HPV	E7	MT-1 MMP	E7 protein of the high-risk HPV types 16 and 8 lead to the induction of MT-1 MMP in in HaCaT cells	[65]
	E2	MMP-9	Increases the expression of MMP-9 in human keratinocytes and organotypic skin cultures	[66]
	E6/E7	MT1-MMP, MMP-2 and MMP-9	Upregulated expression of MT1-MMP, MMP-2 and MMP-9 in cervical cancer	[67]
		MMP-2, MMP-9	Up-Regulates MMP-2 and MMP-9 Expression and Activity by Inducing Interleukin-8 in Lung Adenocarcinomas	[69]
		MMP-8	Persistent oral HPV infection was associated with a low salivary MMP-8 concentration	[71]
		MMP-2, MMP-9, MMP-13 and MT1-MMP	Increased expression of MMP-9, MMP-13 and MT1-MMP in HPV8-positive mice than HPV8-negative animals	[72]
		MMP-2	A significant relationship was observed between the −1306C>T functional polymorphism in MMP-2 gene and HPV infection in increasing the cervical cancer risk	[73]
HBV	HBX	MT1-MMP, MMP-2	Up-regulated MT1-MMP expression by cyclooxygenase-2 (COX-2) activity and activates MMP-2	[76]
	HBX	MMP-9	Increased expression and regulate the transcriptional activaton of MMP-9 by activation of ERK and PI-3K signal pathways	[77]
	HBX	MMP-3	Up-regulated thetranscription,translationandsecretionofMMP-3	[78]
HCV	CORE AND NS5A	MMP-9	Up-regulated expression of MMP-9 with the synergistic effect of endotoxin and proinflammatory cytokines during chronic HCV infection	[103]
	E2	MMP-2	Up-regulation of MMP-2 by interaction between E2 and CD81and E2/CD81 interaction induced the up-regulation of MMP-2 by increasing activator protein-2/DNA binding activity via ERK/MAPK phosphorylation	[104]
	NS3	MMP-9	Activates MMP-9 expression by activates PKD2, JNK, and ERK1/2 to regulate NF-κB which regulates COX-2 expression , finally cox-2 activates mmp-9 expression Activates ERK1/2–p38 signal pathway to regulate NF-κB activity, stimulates the translocation of NF-κB from cytosol to the nucleus and the binding of NF-κB to the MMP-9 promoter	[114]
KSHV	vGPCR and vFLIP	MT1-MMP	Increases of MT-MMP by induced EMT through activation of Notch pathway, leading to gain of MT1-MMP	[120]
		MMP-14	KSHV reduced prox-1 expression(Prox-1 binds to MMP14 promoter and represses its transcription),therefore prevents the repression of MMP-14 by prox-1 and induces mmp-14 expression	[121]
HTLV-1	TAX	MMP-2 MMP-9	Induces the gelatinase activity of MMP-9 and MMP-2 in endothelial cells and downregulates the tissue inhibitor of MMP	[134]
		MMP-9 MMP-3	Increases expression of MMP-9 and MMP-3 bysecreted proinflammatory cytokines (IL-1alpha, IL-6, TNF-alpha) by infected glial cells with HTLV-1	[134, 135]

Moreover, the results of a study by LU et al. provide molecules for the molecular signaling basis of the effects of newly synthesized quinazolinone MJ-29 on the inhibition of metastasis and invasion that could be beneficial as a therapeutic strategy to treat human oral cancer [139]. Accordingly, it can be concluded that 3-azidoWA and MJ-29 as natural MMP-9 inhibitors may have a more effective inhibitory ability on HBV, and HCV-related cancers by attenuating the internal phospho-ERK and phospho-Akt protein expression, which led to the repression of ERK and PI-3K signal pathways.

Other natural compounds such as curcumol via activation of JNK1/2, Akt, and nuclear translocation of NF-κB p65 [140], as well as magnolol through the inhibition of TNF-α by suppressing NF-κB binding activity [141], both caused the reduction of MMP-9 expression in MDA-MB-231 cells, breast cancer cell metastasis, and human urinary bladder cancer 5637 cells, respectively. Meanwhile, there is a possibility that these natural inhibitors can also modulate MMP-9 protein expression through multiple signaling pathways such as JNK, Akt, and TNF-α in HCV-related cancers. Antcin-H, a pure compound that is isolated from A.cinnamomea, can downregulate MMPs through inhibition of the FAK-ERK-C/EBP-/β/c-Fos-MMP-7 pathway, especially MMP-7 expression in renal cancer cell [142] (Table 4).

Table 4: Natural and synthetic inhibitors of MMPs in inhibiting targets of major signaling pathways in various types of cancer

Inhibitor	Class	Selectivity	Type of cancer studied	Inhibiting targets of major signaling pathways	Reference
Batimastat	Peptidomimetic	Broad spectrum	malignant ascites and malignant pleural effusion		[33]
Marimastat	Peptidomimetic	Broad spectrum	Breast cancer, small cell lung cancer, on-small cell lung cancer		[33]
BB-2516	Peptidomimetic	Broad spectrum	Head and neck squamous cell carcinoma (HNSCC)	through interference with autocrine loops in EGFR/c-erbB signaling pathways	[143]
BAY 12-9566	Nonpeptidomimetic inhibitor	MMP-2, MMP -3	advanced ovarian cancer, Breast cancer		[167]
AG3340	Nonpeptidomimetic inhibitor	MMP-2, MMP -3	non-small cell lung cancer		[168]
BMS-275291	Nonpeptidomimetic inhibitor	MMP-2, MMP -9	Non-small-cell lung cancer, prostate cancer, colorectal cancer, Breast cancer		[169, 170]
CGS 27023A	Small molecule	Broad spectrum	Advanced solid cancer		[33]
Col-3 (metastat)	Chemically modified tetracycline	MMP-2, MMP -9	Soft-tissue sarcoma, AIDS-related Kaposi's sarcoma, high-grade gliomas		[171, 172]
Prinomastat	Small molecule	Broad spectrum	Non-small cell lung cancer, , prostate cancer		[136]
Tanomastat	Small molecule	MMP-2, MMP-3, MMP-9	Ovarian cancer, adenocarcinoma of the pancreas, non-small cell lung cancer		[136]
Doxycycline	Tetracycline derivative	Broad spectrum	polycystic ovarian cancer		[136]
SB-3CT	Small molecule	MMP-2, MMP-9	T-cell lymphoma and prostate cancer models		[173]
ND-322	Small molecule	MMP-2/MT1-MMP	melanoma		[174]
curcumol	Major active components in the essential oil of RhizomaCurcumae	MMP-9	Breast cancer cell metastasis	via JNK1/2 and Akt(Ser473)-dependent NFκB signaling pathways	[140]
3 -azidoWA	derivative of Withaferin A	MMP-2	human cervical HeLa and prostate PC-3 cells	concomitant marked reduction in pAkt and pERK signaling by modulating extracellular par-4	[138]
MJ-29	2-phenyl6-pyrrolidinyl-4-quinazolinone derivatives	MMP-2/9	Oral squamous cell carcinoma	Down-regulation of MAPK and AKT Signaling	[139]
antcin-H	pure compound isolated from A. cinnamomea	MMP-7	Renal Cancer Cell	Partly through Inactivation of FAK-ERK-C/EBP-/β/c-Fos-MMP-7 Pathways	[142]
magnolol	the main constituent of Magnoliaceae	MMP-9	human urinary bladder cancer 5637 cells	Inhibition TNF-α-induced MMP-9 expression by suppressing NF-κB binding activities	[141]

The presence of MMP-inhibitory effects in virus-related cancers is still unknown. It has been determined that BB-2516, among all synthetic inhibitors, decreases the protein expression of a broad spectrum of MMPs by interfering with autocrine loops of EGFR/c-erbB signaling pathway in head and neck squamous cell carcinoma (HNSCC) [143]. However, more studies are necessary to understand the connections between MMP inhibitors and these signaling pathways in oncovirus-related cancers, making it especially important to examine how the relationships are.

CONCLUSIONS

In summary, matrix metalloproteinases as cellular proteases play the main role in biological processes as well as pathological conditions, including tissue repair, wound healing, developmental morphogenesis, inflammatory diseases, and tumor progression. Oncoviruses, in many cases, promote tumor progression through multiple mechanisms that affect the expression of these cell proteases. As oncoviruses upregulate the expression of MMPs genes through direct (via DNA binding) as well as indirect interactions (via activating PI-3K/AKT, ERK/MAPK, IFN/JAK/STAT, JNK, NF-κB signaling pathways or immune response), causing escape from the immune system and play a key role in cell proliferation, migration, angiogenesis, EMT, invasion, metastatic features, and subsequent tumor progression. Today, several compounds have been studied as matrix metalloproteinase inhibitors. Various studies have shown that these inhibitors activate the immune system and suppress tumor progression by inhibiting signaling pathways activated by viruses. With these interpretations, these cell proteases may be used as biomarkers to detect different stages of the development of oncovirus-related tumors, soon followed by inhibitors of these proteases in the treatment of viral tumors.

Conflict of interest

The authors report no conflicts of interest.

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Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of the Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1399.520).

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