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Cyclooxygenase-2-prostaglandin E2-eicosanoid receptor inflammatory axis: a key player in Kaposi’s sarcoma-associated herpes virus associated malignancies

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The role of cyclooxygenase-2 (COX-2), its lipid metabolite prostaglandin E2 (PGE2), and Eicosanoid (EP) receptors (EP; 1-4) underlying the proinflammatory mechanistic aspects of Burkitt’s lymphoma, nasopharyngeal carcinoma, cervical cancer, prostate cancer, colon cancer, and Kaposi’s sarcoma (KS) is an active area of investigation. The tumorigenic potential of COX-2 and PGE2 through EP receptors forms the mechanistic context underlying the chemotherapeutic potential of nonsteroidal anti-inflammatory drugs (NSAIDs). Although role of the COX-2 is described in several viral associated malignancies, the biological significance of the COX-2/PGE2/EP receptor inflammatory axis is extensively studied only in Kaposi’s sarcoma-associated herpes virus (KSHV/HHV-8) associated malignancies such as KS, a multifocal endothelial cell tumor and primary effusion lymphoma (PEL), a B cell-proliferative disorder. The purpose of this review is to summarize the salient findings delineating the molecular mechanisms downstream of COX-2 involving PGE2 secretion and its autocrine and paracrine interactions with EP receptors (EP1-4), COX-2/PGE2/EP receptor signaling regulating KSHV pathogenesis and latency. KSHV infection induces COX-2, PGE2 secretion, and EP receptor activation. The resulting signal cascades modulate the expression of KSHV latency genes (latency associated nuclear antigen-1 [LANA-1] and viral-Fas (TNFRSF6)-associated via death domain like interferon converting enzyme-like inhibitory protein [vFLIP]). vFLIP was also shown to be crucial for the maintenance of COX-2 activation. The mutually interdependent interactions between viral proteins (LANA-1/vFLIP) and COX-2/PGE2/EP receptors was shown to play key roles in the biological mechanisms involved in KS and PEL pathogenesis such as blockage of apoptosis, cell cycle regulation, transformation, proliferation, angiogenesis, adhesion, invasion, and immune-suppression. Understanding the COX-2/PGE2/EP axis is very important to develop new safer and specific therapeutic modalities for KS and PEL. In addition to COX-2 being a therapeutic target, EP receptors represent ideal targets for pharmacologic agents as PGE2 analogues and their blockers/antagonists possess antineoplastic activity, without the reported gastrointestinal toxicities.
testicular and cardiovascular toxicity observed with few a NSAIDs. (Translational Research 2013;162:77–92)

Abbreviations: cIAP-1 = Cellular inhibitor of apoptosis protein-1; COX-2 = cyclooxygenase-2; CREB = cAMP response element-binding; C-X-C motif = chemokine; EBV = Epstein-Barr virus; ERK = Extracellular signal-regulated kinase; FAK = focal adhesion kinase; HTLV = human lymphotropic virus; ID4 = Inhibitor of DNA binding 4; IFN-γ = Interferon-gamma; KS = Kaposi’s sarcoma; KSHV = Kaposi’s sarcoma associated-herpes virus; LANA-1 = latency associated nuclear antigen; LMO2 = LIM domain only 2; LRMP = lymphoid restricted membrane protein; MnSOD2 = manganese superoxide dismutase; MYC = v-myc myelocytomatosis viral oncogene homolog; NFAT = nuclear factor of activated T cells; NSAIDs = nonsteroid anti-inflammatory drugs; PEG2 = nonsteroidal anti-inflammatory drugs; PI3-K = platelet derived growth factor beta; PEL = primary effusion lymphoma; PGE2 = prostaglandin E2; PI3-K = Phosphatidylinositol 3-kinase; ROS = reactive oxygen species; SDF-1 = stromal cell-derived factor-1; STAT-1α = Signal transducer and activator of transcription 1-alpha; TGF-β = Transforming growth factor beta; TLR5 = Toll-like receptor 5; VCAM-1 = vascular-cell adhesion molecules; VEGF = vascular endothelial growth factor; XCR4 = receptor 4; X-IAP = X-linked inhibitor of apoptosis protein

In the 19th century, Rudolf Virchow first proposed a potential link between inflammation and cancer based on his observations on the presence of leukocytes in tumors. Inflammation is a physiological mechanism evolved for wound healing and therefore is counter-intuitive to consider it to be oncogenic. Nevertheless, inflammation is a ‘double-edged sword’ with a pathologic edge that can promote various aspects of tumorigenesis deregulated such as cell proliferation, migration, angiogenesis, and apoptosis. Within the last decade, a multitude of studies demonstrating the a) abundance of inflammatory cells such as macrophages and fibroblasts in cancer biopsies, b) the role of proinflammatory molecules such as cyclooxygenase-2 (COX-2), prostaglandin E2, leukotrienes, transforming growth factor beta (TGF-β), hypoxia inducible factor-1 alpha, vascular endothelial growth factor (VEGF), nitric oxide synthase, nitric oxide, reactive oxygen species (ROS), cytokines and chemokines in the pathogenesis of several cancers, and the tumorigenic nurturing properties of the proinflammatory tumor microenvironment strongly indicates that inflammation plays a pathogenic role in several cancers. Chronic persistent inflammation is believed to play an important role in the pathogenesis of 15% of all malignancies. Depending on the type and stage of cancer, the physiological to pathologic switch of inflammation is triggered by various factors such as genomic instability, epigenetic changes, somatic mutations, tumor suppressor and oncogene mediated carcinogenesis, chronic persistent infections, and environmental stressors such as pollutants.

The role of tumor viruses in chronic persistent inflammation associated carcinogenesis is demonstrated in several malignancies such as Kaposi’s sarcoma associated-herpes virus (KSHV/HHV-8) in Kaposi’s sarcoma (KS) and primary effusion lymphoma (PEL), Epstein-Barr virus (EBV) in Burkitt’s lymphoma and nasopharyngeal carcinoma, human papillomavirus (HPV) in cervical cancer, hepatitis B (HBV) and hepatitis C viruses (HCV) in hepatocellular cancer, and human T-lymphotropic virus (HTLV) in T-cell leukemia. Viruses are obligate intracellular parasites and use host proteins for genome replication and production of progeny. Piracy of inflammatory mechanisms is a recurring theme in the story of infections by KSHV, EBV, HCV, HPV, HBV, and HTLV because of the proliferative, angiogenic, immune-suppressive, and antiapoptotic niche that persistent inflammation provides. The purpose of this review is to highlight the salient findings demonstrating how KSHV uses the pivotal COX-2/PGE2/EP receptor mediated inflammatory axis for its survival and pathogenesis and, therefore, plays a crucial role in KSHV-associated malignancies.
well-studied anticancer properties of nonsteroid anti-inflammatory drugs (NSAIDs). The major lipid metabolite of COX-2 implicated in tumorigenesis is PGE2. PGE2 is an autocrine and paracrine lipid signal inducer with a circulating half-life of approximately 30 seconds and normal plasma levels varying from 3-15 pg/mL. PGE2 exerts its effects through the 7-transmembrane rhodopsin family of G protein coupled (GPCR) eicosanoid (EP) receptors, namely, EP1, EP2, EP3, and EP4 (EP 1-4) that initiate signal transduction through Calcium (Ca2+), Cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and Phosphatidylinositol 3-kinase (PI3K). EP receptor induction has been associated with several oncogenic pathways including Src, PI3K, PKC, NFκB, Ras/Raf, ERK, VEGF, AKT/PI3K, PPAR, and interleukin (IL)-10/DAF and, therefore, forms the mechanistic context underlying the diverse aspects of COX-2 mediated tumorigenesis. Recent years, the link between EP receptors and tumorigenesis had also revealed the possibility of using highly specific EP receptor antagonists such as SC-51322 (EP1 antagonist), AH6809 (EP2 antagonist), and AH23848 (EP4 antagonist) as anticancer drugs.

**VIRAL INFECTIONS AND COX-2**

Infections by several viruses have been shown to regulate COX-2 expression and PGE2 production such as HBV in hepatocytes, HCV in Huh-7 cells, human herpesvirus 6 (HHV-6) in monocytes, human cytomegalovirus (CMV) in Peripheral blood mononuclear cells (PBMCs), smooth muscle cells, and fibroblasts, murine gammaherpesvirus 68 (MHV-68) in NIH 3T3 cells, HIV in monocytes, HTLV-1 in PBMCs, influenza virus in PBMCs, enterovirus 71 in human neuroblastoma cells, dengue virus in dendritic cells, Severe acute respiratory syndrome (SARS)-associated coronavirus in 293T cells, Theiler’s murine encephalomyelitis virus in astrocytes, encephalomyocarditis virus in macrophages, coxsackie virus B3 in monocytes, respiratory syncytial virus in macrophages and dendritic cells, and canine distemper virus in monocytes. COX-2/PGE2 has been implicated in a multitude of viral mechanisms such as genome replication (HBV), CMV, HTLV, gene expression (MHV-68), transmission (HTLV), cell tropism (rhesus CMV), cell invasion (CMV), T cell regulation (HIV), and even has identified a viral homologue of COX-2 in rhesus CMV revealing the significance of COX-2 in the evolution of inflammation mediated viral pathogenesis. Among the herpes viruses, studies using COX inhibitors have shown the role of COX-2/PGE2 pathways for replication and successful lytic cycle in HSV, CMV, HHV-6, and MHV-68. However, the role of the extensive molecular framework underlying the COX-2/PGE2/EP receptor inflammatory axis in herpes viral latency is described only in KSHV associated malignancies such as KS and PEL.

**KSHV ASSOCIATED DISEASES**

KSHV/HHV-8 is grouped in the γ-2 herpes virus family and is the etiologic agent underlying KS, PEL, and multicentric Castleman’s disease. Like other herpes viruses, the KSHV life cycle is characterized by 2 phases, the latent and the lytic cycles. After infection, KSHV enters the latency phase, where the virus remains evasive by transforming the infected cell into a stable reservoir. The lytic cycle results in the replication of the viral genome and production of new viral progeny. Both life cycles are associated with distinct viral proteins. Gene expression profiles of KS, PEL, and multicentric Castleman’s disease biopsies have shown that the majority of tumor cells express latency transcripts with 1%-3% of tumor cells undergoing the lytic cycle at a given time point and both stages of the life cycle are implicated in the pathogenesis of KSHV associated diseases. Although, there are no specific treatments targeting KSHV associated diseases, highly active antiretroviral therapy (HAART) and consequent immune reconstitution is demonstrated to be beneficial in treating AIDS-KS.

**KS.** Epidemiologically, KS is classified into 4 subgroups: (1) classical KS as described by Moritz Kaposi in elderly men of Mediterranean origin in 1872, endemic KS in sub-Saharan Africa, (3) epidemic KS in AIDS patients, where KS forms the most common AIDS associated malignancy, and (4) transplant defining KS. Pathologically, KS is a multifocal angio proliferative tumor of vascular nature characterized by extravascular erythrocytes, spindle shaped cells of endothelial origin, inflammatory cells such as monocytes, fibroblasts, neutrophils, and lymphocytes interspersed between narrow, irregular angulated slits within a proinflammatory and angiogenic microenvironment. Fatality by KS is often due to systemic spread into the respiratory system, gastrointestinal tract, lymph nodes, and other organs.

**PEL.** PEL is a rare, yet aggressive form of B cell lymphoma that accounts for 2%-4% of all AIDS associated NHLs with a prognosis of less than 6 months. PEL is characterized by primary lymphomatous aggregations within the major body cavities such as the pleura, pericardium, and the
Pathologically, PEL cells show varying phenotypes, such as immunoblastic, plasmablastic, and anaplastic, and are proposed to lie between the pro-B cell and plasma cell lineage.\textsuperscript{66,67,69,71,77} PEL cells are characterized by B cells transformed by persistent KSHV infection and consists of multiple copies (in the order of 50-150 copies/cell) of episomal KSHV genomes with the latent viral gene expression pattern involving latency associated nuclear antigen (LANA)-1, viral homologues of host proteins cyclin (vCyclin) and FLICE-inhibitory protein (Viral-FLICE-inhibitory protein [vFLIP]), a pre-microRNA transcript encoding viral microRNAs, as well as vIRF3/K10.5/LANA-2 and a homologue of IL-6 (vIL-6) is also expressed in some PEL cells.\textsuperscript{66,67,69,71,77} PEL cells express a variety of cell surface markers from different stages of B cell development such as the activation markers CD30, CD38, and CD71 and several plasma cell markers including CD138, VS38c, and MUM-1/IRF4 but are devoid of the B cell markers CD19 and CD20.\textsuperset{66,67,69,71,77}

**KSHV LATENCY, INFLAMMATION, AND COX-2**

KSHV latency is proposed to be a symphony of well-orchestrated interactions between viral and host proteins leading to the transformation of infected cells for viral survival through successful genome replication and immune evasion.\textsuperset{70,78-81} The host and viral protein interactions initially established by KSHV infection for survival through the establishment and maintenance of latency progress pathologically as KS and PEL under conditions of persistent selective pressures such as AIDS related or transplant associated immune suppression.\textsuperset{70,79-81} The decrease in the incidence of KS post-HAART therapy in AIDS patients is suggestive of this scenario.\textsuperset{70-72} The host mechanisms underlying the establishment and maintenance of KSHV infection and KSHV associated malignancies include cell signaling, anti-apoptosis, angiogenesis, immune modulation, and cell proliferation mediated by cytokines, growth factors, and inflammatory molecules.\textsuperset{70,79-81} Thus, identification of molecules used by the KSHV latency program will enable us to delineate the pathogenesis of KS and PEL as well.

Studies by Naranatt et al (2004)\textsuperset{82} and Sharma-Walia et al (2006)\textsuperset{61} first indicated the induction of COX-2 during \textit{de novo} KSHV infection of human microvascular dermal endothelial (HMVEC-d) cells Studies by introduced a novel idea regarding the functional significance of COX-2/PGE2 within the context of the KSHV latency program. KSHV infection induced COX-2/PGE2 and PGE2 supplementation reversed the COX-1/COX-2 inhibitor mediated downregulation of latency gene LANA-1. Therefore, the studies for the first time generated a hypothesis that KSHV infection induced COX-2/PGE2 is crucial for establishment and maintenance of latency.\textsuperset{61} Considering the oncogenic potency of COX-2 through the activation of inflammatory mechanisms, the proinflammatory mechanisms underlying KS and PEL pathogenesis, and the well characterized roles of COX-2 in other viral tumors such as Burkitt’s lymphoma and cervical cancer, the study by Sharma-Walia et al (2006)\textsuperset{61} also raised several important questions as follows. (1) What are the different biological mechanisms regulated by COX-2 in KS? (2) What are the mechanisms underlying sustained COX-2 activation in the KSHV latency program? (3) How does COX-2/PGE2 regulate the KSHV latency program? (4) What is the role of COX-2 in PEL? (5) Do NSAIDs and EP receptor antagonists hold chemotherapeutic potential in treating KS and PEL? (6) Does simultaneous blockade of COX-2 and EP receptors provide synergistic anticancer effects?

**INDUCTION OF COX-2 AND EP RECEPTORS BY KSHV**

Several gene array studies have demonstrated the induction of COX-2 in a multitude of malignant and pre-malignant human cancer lesions with progressive increase in expression as the stage of the cancer advances.\textsuperset{83} We demonstrated CD31-COX-2 double stained spindle shaped cells in tissue microarray of human KS sections (eye orbit, tonsil, mouth, and small bowel) (Sharma-Walia et al 2010).\textsuperset{59} Similarly, abundant expression of mPGES, PGE2, and EP1-4 was observed in human KS biopsies (George Paul et al 2010).\textsuperset{62} Collectively, these findings corroborate with earlier in vitro observations\textsuperset{61,82} and is the first detailed investigation of COX-2 and EP receptors in human KS and is the first detailed investigation of COX-2 and EP receptors in human KS biopsies. There are several possible mechanisms underlying COX-2/PGE2/EP receptor induction in KS lesions such as persistent KSHV infection, persistent chronic inflammation, and pathologic stress from chronic persistent infection and inflammation in KS patients.

The association of COX-2 and cancer is attributed to its inducible promoter activated by stress, infection, and inflammation.\textsuperset{13,24} The role of infection mediated signaling in COX-2 induction is demonstrated by several viruses such as CMV (ROS, cAMP/nuclear factor of activated T cells [NFAT]), HBV (Ca$^{2+}$/ROS, cAMP/NFAT), HCV (Ca$^{2+}$/ROS), encephalomyocarditis virus (EMCV) (NFκB/MAFK/c-Jun N-terminal Kinases/p38), Enterovirus 71 (NFκB/AP-1/PAK/cAMP/Src/EGFR/p300/cAMP response element-
binding (CREB)), SARS (NFκB/CEBP), and Dengue virus (NFκB/AP-1). We examined whether similar molecular mechanisms were at work in the induction of COX-2 in KS and demonstrated that de novo KSHV infection and exogenous PGE2 upregulates COX-2 promoter activity through Src, PI3K, PKC, focal adhesion kinase, JNK, p38, cAMP, PKA, and NFκB. Promoter analysis using COX-2 promoter deletion constructs and mutation reporter constructs identified transcription factors CREB and NFAT cells downstream of the signal cascades synergistically modulating COX-2 promoter activity. A multitude of similar pathways are also activated by early KSHV binding and infection such as PI3K-PKC-ζ-MEK-ERK, Src-PI3K-RhoGTPase, RhoA-GTP-Diaphenous-2 microtubules, NFκB, FAK, VEGF, and lipid rafts indicating that KSHV entry associated signal transduction events and infection-induced PGE2 secretion work in concert to activate the COX-2 promoter. However, the presence of strong COX-2 expression in KS lesions strongly suggests the existence of viral mechanisms that sustain COX-2 expression post establishment of KSHV latency.

COX-2 induction has been demonstrated by other viral proteins as well such as Tax protein (HTLV-1), gp120 (HIV), HBx (HBV), and CoV N-protein (SARS virus). KSHV latency protein vFLIP and lytic proteins KSHV G protein-coupled receptor, a constitutively active lytic phase protein with significant homology to the human IL-8 receptor, and K15 are the viral proteins proposed to be important for KS pathogenesis, such as immune modulators (TNF-α, IFN-γ, IFN-α, Stromal cell-derived factor-1, growth regulated oncogene, Regulated on activation, normal T cell expressed and secreted), cyto- kines (IL-8, IL-1β, IL-1α, α, ILs-2/-3/-8/-P40/-16), chemokines (MCP-2, MCP-3, TARC, MIP-1α, ENA-78, 1-309, MIF, GCP-2, MIP-3α, -β, eotaxins -2/-3, -5, IP-10, NAP-2, CK-β3-1), growth and angiogenic factors (VEGF-A/C, PDGF-BB, M-CSF, G-CSF, GM-CSF, angiogenin, oncostatin M, thrombopoietin, SCF, insulin-like growth factor-binding protein (-2, -3, and -4), BDNF, PIGF, HGF, osteoprotegerin, NT-3, NT-4), and anti-inflammatory cytokines (IL-4, IL-13, and IL-15) and MMPs like MMP-1, -2, -3, -9, and -19. The combined effect of these molecules contributes to the different aspects of KS pathogenesis such as neovascularization, angiogenesis, maintenance of KSHV latency, and metastasis whereas the mechanisms underlying the sustained activation of these molecules is still an active area of investigation. Considering the well-established roles of COX-2 in the progression of several cancers, Sharma-Walia et al (2010) characterized the role of COX-2 in KSHV pathogenesis related processes such as secretion of GFs, ICs, AFs, and ICAMs in endothelial cells. In de novo infected HMVEC-d cells, key molecules proposed to be important for KS pathogenesis, such as immune modulators (TNF-α, IFN-γ, Stromal cell-derived factor-1, growth regulated oncogene, Regulated on activation, normal T cell expressed and secreted), cytokines (IL-8, IL-1β, IL-1α, α, ILs-2/-3/-8/-P40/-16), chemokines (MCP-2, MCP-3, TARC, MIP-1α, ENA-78, 1-309, MIF, GCP-2, MIP-3α, -β, eotaxins -2/-3, -5, IP-10, NAP-2, CK-β3-1), growth and angiogenic factors (VEGF-A/C, PDGF-BB, M-CSF, G-CSF, GM-CSF, angiogenin, oncostatin M, thrombopoietin, SCF, insulin-like growth factor-binding protein (-2, -3, and -4), BDNF, PIGF, HGF, osteoprotegerin, NT-3, NT-4), and anti-inflammatory cytokines (IL-4, IL-13, and IL-15) and MMP-1, -2, -3, -9, and -10, were downregulated by the pharmacologic (NS-398, indomethacin) and small interfering RNA based inhibition of COX-2. Therefore, the work by George Paul et al (2010) and George Paul et al (2013) is strongly suggestive of their role in KS pathogenesis. Further work is required to characterize the signaling and transcriptional mechanisms underlying the induction of EP receptor expression.

**BIOLOGICAL MECHANISMS REGULATED BY COX-2 IN KS**

The pathogenesis of KS lesions consisting of spindle shaped endothelial cells, neovascular structures, and inflammatory cells is profoundly influenced by growth factors (GFs), proinflammatory cytokines (ICs), angiogenic factors (AFs) such as basic and acidic fibroblast growth factor (bFGF, aFGF), IL-1α and IL-1β, granulocyte-macrophage colony stimulating factor (GM-CSF), platelet derived growth factor β (PDGF-β), VEGF, interferon-γ (IFN-γ), IL-6, tumor necrosis factor-α (TNF-α), angiopoietin-2, angiogenin, heme oxygenase-1, TGF-β, adhesion molecules like intercellular/vascular-cell adhesion molecules (ICAM-1 and VCAM-1), and matrix metalloproteinases (MMPs) like MMP-1, -2, -3, -9, and -19. The combined effect of these molecules contributes to the different aspects of KS pathogenesis such as neovascularization, angiogenesis, maintenance of KSHV latency, and metastasis whereas the mechanisms underlying the sustained activation of these molecules is still an active area of investigation. Considering the well-established roles of COX-2 in the progression of several cancers, Sharma-Walia et al (2010) characterized the role of COX-2 in KSHV pathogenesis related processes such as secretion of GFs, ICs, AFs, and ICAMs in endothelial cells. In de novo infected HMVEC-d cells, key molecules proposed to be important for KS pathogenesis, such as immune modulators (TNF-α, IFN-γ, Stromal cell-derived factor-1, growth regulated oncogene, Regulated on activation, normal T cell expressed and secreted), cytokines (IL-8, IL-1β, IL-1α, α, ILs-2/-3/-8/-P40/-16), chemokines (MCP-2, MCP-3, TARC, MIP-1α, ENA-78, 1-309, MIF, GCP-2, MIP-3α, -β, eotaxins -2/-3, -5, IP-10, NAP-2, CK-β3-1), growth and angiogenic factors (VEGF-A/C, PDGF-BB, M-CSF, G-CSF, GM-CSF, angiogenin, oncostatin M, thrombopoietin, SCF, insulin-like growth factor-binding protein (-2, -3, and -4), BDNF, PIGF, HGF, osteoprotegerin, NT-3, NT-4), and anti-inflammatory cytokines (IL-4, IL-13, and IL-15) and MMP-1, -2, -3, -9, and -10, were downregulated by the pharmacologic (NS-398, indomethacin) and small interfering RNA based inhibition of COX-2. Therefore, the work by George Paul et al (2010) and George Paul et al (2013) is strongly suggestive of their role in KS pathogenesis. Further work is required to characterize the signaling and transcriptional mechanisms underlying the induction of EP receptor expression.
response (IFN-γ, SDF-1, GRO, RANTES), chemotaxis of immune cells (SDF-1 and IL-8), inflammasome activation (IL-1β), and cell migration and metastasis (MMP-1, -9, 10, and SDF-1).59 Further characterization of the biological significance of COX-2 in KSHV infected cells has demonstrated that pharmacological and small interfering RNA based inhibition of COX-2 downregulated the (1) formation of intricate in vitro capillary tubes and (2) cell adhesion and cell invasion capability of HMVEC-d cells.59 We64 have added an additional dimension to these observations by demonstrating that COX-2 inhibition could downregulate vFLIP mediated pathogenic mechanisms such as (1) expression of immune cell regulators and recruiters such as chemokines (CXCL-5 and CXCL-6), cytokines (IL-6 and IL-8), C-C ligand related molecules (CCL-2, CCL-5, CCL-20, MCP-1, RANTES-2, and MIP-3x), (2) expression of cell adhesion molecules ICAM-1, VCAM-1, and E-selectin and metalloproteinase MMP-10, (3) induction of actin cytoskeleton modulators FAK, Src, AKT, and Rac1GTPase, (4) ROS regulation through mitochondrial antioxidant enzyme manganese superoxide dismutase (MnSOD2), (5) endothelial-mesenchymal transitions (EMT) by downregulating EMT specific master regulator genes (snail, twist, slug, and laminin-γ1) and upregulating E-cadherin, and (6) anoikis resistance and anchorage resistant colony formation by upregulating proapoptotic proteins BIM and DR5.64

**REGULATION OF KSHV LATENCY BY EP RECEPTORS**

PGE2 and EP receptors are proposed to be the tumorigenic workhorses of COX-2.5 EP receptors are GPCRs and have been well-characterized in the pathogenesis of a multitude of cancers such as melanoma, breast cancer, and colon cancer by contributing to proliferation, immunosuppression, angiogenesis, invasion and blocking apoptosis through the activation of Src kinase, cAMP/CREB, PI3K/Akt, Ras/Raf, ERK-1/2, NFκB, EGFR, PPARβ/δ, and GSK-3β/β-catenin pathways.22-24 The role of Src kinase, PI3K, Akt, ERK, and NFκB during the early events of KSHV infection and establishment of latency is well-characterized.84-86,89,98 Collectively, studies by Sharma-Walia et al (2010; 2012)59,64 demonstrated that pathways downstream to COX-2 when activated by viral and nonviral mechanisms or both participate in enriching the tumor microenvironment and consequently various pathologic processes underlying KS such as endothelial transformation, neovascularization, and metastasis.59,64 However, pathways downstream of COX-2 resulting in the activation of Src, cAMP, PI3K, Akt, Ras/Raf, ERK, NFκB, EGFR, and GSK-3β/β-catenin pathways, which form the first line of signal transducers in a molecular avalanche eventually resulting in the induction of ICs, GFs, AFs, and MMPs, is still an active area of investigation. We62 identified the involvement of EP receptors in the induction of various signaling molecules downstream of COX-2 in KSHV latency program. Specifically, the EP1 receptor was implicated in the activation of Ca2+, PI3K, and NF-κB, the EP2 receptor in PI3K, PKCζ/λ, and NFκB activation and the EP4 receptor in PI3K, PKCζ/λ, ERK 1, ERK 2, and NF-κB activation in long-term-infected cells.62

EP1, EP2, and EP4 antagonists could also downregulate the expression of major KSHV latency gene LANA-1 by inhibiting the induction of Ca2+, phosphorylation of Src, PI3K, PKCζ/λ, and NFκB signaling.62 The signal molecules that regulate the COX-2 promoter and PGE2 induced LANA-1 promoter activity were found to be similar to the EP receptor mediated signal transduction pathways in latently infected endothelial cells and COX-2 gene expression and PGE2 secretion was also significantly downregulated by the pharmacologic inhibition of EP2 and EP4 receptors.62 These observations implicate for the first time the role of EP receptors in any form of herpesvirus latency and, thus, substantiating the earlier observations by Sharma-Walia et al (2006)61 and elucidated signal transduction network through EP receptors, initiated by KSHV infection mediated COX-2 activation and PGE2 secretion.62 PGE2 in the tumor microenvironment activates EP receptor mediated signal cascades in a paracrine and autocrine fashion that exert its effects on LANA-1 and COX-2 expression.62 Consequently, a self-sustained positive feedback loop networking the KSHV protein LANA-1 to the proinflammatory pathways regulated by COX-2/PGE2/EP receptors is created by viral infection. Recent work by Dupuy et al (2012) further substantiates the role of EP receptors in KS pathogenesis by reporting the use of PGE2 inhibitors as an attractive approach to treat aggressive KS, as they could restore activation and survival of tumoricidal NK cells.99 These studies provided strong evidence that downmodulation of NKG2D is mediated by inflammatory PGE2, known to be released by KS cells, and also showed that PGE2 acts by preventing IL-15-mediated activation of NK cells.99 The role of EP receptors in the induction of several KSHV associated signal networks and consequently various pathogenic mechanisms is indicative of how KSHV subverts the COX-2/PGE2/EP receptor mediated protumorigenic signal pathways to sustain viral and host gene expression.62 However, these studies also demonstrated that neither chemical inhibitors (NS-398 and indomethacin) nor si-COX-2 could completely abolish the induction of ICs, GFs, MMPs, and AFs indicating the presence of
ROLE OF COX-2 IN KSHV ASSOCIATED B CELL NEOPLASIA (PEL)

PEL is comprised of B cells transformed by KSHV latent infection. Studies have proposed the cumulative interdependent vitality of the expression of KSHV latency genes, the proinflammatory environment, and the manipulation of canonical anticancer host defense machinery, such as p53 and p21, in the metamorphosis of PEL neoplasia. The mechanistic role of COX-2 in hematological malignancies and KSHV latency program in endothelial model systems is well established.59-62,64 The study by Paul et al (2011) for the first time delineated the role of COX-2 in PEL pathogenesis using the COX-2 inhibitor nimesulide. Nimesulide downregulated KSHV latency genes vFLIP and LANA-1 and induced G1 cell cycle arrest and apoptosis through the activation of the p53/p21 tumor suppressor pathway and downregulation of cell survival kinases p-Akt1/2 and p-GSK-3B, and angiogenic factor VEGF-C in PEL cells. LANA-1 is a multifunctional protein and a major marker for KSHV latency.70,102 The diverse roles of LANA-1 in KSHV latency include maintenance of viral episomes, host gene manipulation through the recruitment of chromatin binding proteins, cell cycle regulation and blockade of apoptosis by down-regulating p53 and Rb. vFLIP is one of the key KSHV latent proteins; it performs multiple functions such as IL-8 and IL-6 upregulation, induction of NFκB, spindling of infected endothelial cells, and modulation of cell proliferation, and immune evasion. PEL consists of transformed B cells with in vitro clonogenic properties attributed to a multitude of molecules. A key observation by Paul et al (2011) is the inhibition of the colony formation capacity of PEL cells by nimesulide because it encapsulates the pathologic consequence of COX-2 inhibition mediated latency blockade, G1 arrest, and apoptosis induction in PEL cells. Nimesulide mediated proliferation arrest, alteration in cell cycle profile, and apoptosis in PEL cells could be related to the downregulation of KSHV latency proteins LANA-1 and vFLIP resulting in the blockade of virus induced prosurvival mechanisms in PEL. However, considering the oncogenic potential of COX-2/PGE2/EP receptors in other cancer systems that are also important for PEL pathogenesis, the antigrowth effects of nimesulide could also be due to the drug’s effects on these pathways as well as independent of viral proteins.

CHEMOTHERAPEUTIC POTENTIAL OF NSAIDS IN TREATING PEL

NSAIDs consist of COX-1/COX-2 inhibitors such as aspirin, indomethacin, and diclofenac and COX-2 specific inhibitors such as nimesulide and the COXIB (ceclocoxib, rofecoxib, valdecoxib, and lumiracoxib) family. COX-2 specific drugs such as COXIBs have gained popularity and notoriety in the last 2 decades because of their potent antiinflammatory and analgesic effects and numerous trials strongly suggesting an increase in cardiovascular events from the chronic use of rofecoxib and celecoxib, respectively. From a chemotherapeutic perspective after considering the severe side effects of existing anti-PEL drug regimens, which provide no specific cure for PEL, the goal should be to identify a drug with potent anti-KSHV and anticancer activity with the least side effects. Several lines of work are currently underway to develop anti-PEL therapies based on PEL pathogenesis such as the proapoptotic agents bortezomib and azidothyimidine, antiangiogenic vasodilator antibiotic rapamycin, p53 activator nutlin-3a, antiviral compounds cidofovir and IFN-α, reactive oxygen species hydrogen peroxide, activation of unfolded protein response, and KSHV latency gene blocking agents glycyrrhizic acid, and small RNA transcripts. The well-established tumorigenic potential of COX-2/PGE2/EP receptor pathway, the availability of well-characterized EP receptor antagonists and Food and Drug Administration-approved COX-2 inhibitors with known anticancer effects, the demonstration of COX-2/PGE2/EP receptors in KSHV latency and the correlation between COX-2 expression and poor NHL prognosis provided an excellent context to examine the chemotherapeutic potential of NSAIDs in treating PEL by Paul et al (2011). The study by Paul et al (2010) and work by George Paul et al (2013) examined the chemotherapeutic potential of nimesulide and celecoxib against PEL and several NHL cell lines, respectively. Nimesulide is a well-characterized COX-2 inhibitor with known anticancer properties and is already prescribed to approximately 500 million people in 50 different countries since its introduction in 1985. Celecoxib was introduced in 1998, and several lines of work have strongly suggested the anticancer effects of both nimesulide and celecoxib. Celecoxib’s anticancer effect is proposed to be due to COX-2 inhibition and non-COX dependent antigrowth effects. Nimesulide could induce significant proliferation arrest on a multitude of KSHV+/EBV- (BC-3, KSHV-BJAB), KSHV-/EBV+ (Akata/EBV+, LCL, Raji), KSHV+/EBV+ (JSC-1), and KSHV-/EBV- (Loukes, Ramos, Akata/EBV-).
NHL cell lines with selective potency against KSHV+/EBV- cell lines suggesting that the proliferation arrest induced by nimesulide on all NHL cell lines tested is not due to the generalized antiproliferative effects of NSAIDs on tumor cell lines. In the work by Paul et al. (2013), celecoxib had significant antiproliferative effects on KSHV+/EBV- (BCBL-1 and BC-3), KSHV+/EBV+ (Akata/EBV+), KSHV+/EBV+ (JSC-1), and KSHV-/EBV- (BJAB) cell lines.

The chemotherapeutic potential of EP receptor antagonists in any NHLs is still unexamined. The study by Paul et al. (2013) investigated the anticancer effects of EP receptor blockade on various NHL cell lines. The study demonstrates for the first time the anticancer effects of SC-51322 (EP1 antagonist), AH6809 (EP2 antagonist), and GW 627368X (EP4 antagonist) on NHL cell lines. EP1 and EP4 receptor antagonist had significant antiproliferative effects on KSHV+/EBV- (BCBL-1 and BC-3), KSHV+/EBV+ (Akata/EBV+), KSHV+/EBV+ (JSC-1), and KSHV-/EBV- (BJAB) cell lines. EP1 and EP4 antagonists also induced apoptosis in BCBL-1, Akata/EBV+, and Akata/EBV- cells but not in BJAB cells.

An intriguing idea proposed by the studies by Paul et al. (2010) and current work (Paul et al. 2013) is the multimodal anticancer and anti-KSHV effects of COX-2 inhibition on the PEL cell lines. The specificity of the ‘knock-out’ punch of nimesulide on PEL cells might be due to the additive antiviral (blockade of KSHV latency genes LANA-1 and vFLIP), anti-inflammatory/antisurvival properties (downregulation of VEGF-C, AKT 1/2, and GSK-3β), anti-PEL specific properties (downregulation of syndecan-1, VDR, and aquaporin-3) as well as anticancer (induction of G1 arrest and apoptosis) properties (Paul et al. 2011).

**COMBINATIONAL BLOCKADE OF COX-2 AND EP RECEPTORS**

Previous work examining the role of COX-2 mediated tumorigenesis has proposed the combination of lower doses of COX-2 inhibitors with EP receptor antagonists to reduce the adverse effects of NSAIDs such as GI and cardiovascular toxicities. However, potential synergistic anticancer effects of combinational blockade of COX-2 and EP receptors are still unexamined. The current study by Paul et al. (2013) demonstrates that combining 1.0 μM each of celecoxib, SC-51322 (EP1 antagonist) and GW 627368X (EP4 antagonist) can potentiate the proapoptotic effect of celecoxib on KSHV+/EBV- and KSHV-/EBV+ cells. This strongly suggests the chemotherapeutic potential of a novel paradigm based on concurrent inhibition of COX-2 and EP receptors to obtain potent additive anticancer effects. The study shows that simultaneous inhibition of COX-2 and EP1/EP4 receptors modulates several classes of genes proposed to be important for KSHV and EBV associated lymphoma pathogenesis including tumor suppressors, and genes belonging to lymphoma survival, cell cycle arrest, cell adhesion, apoptosis, PI3K/Akt signaling, and epigenetic regulation. Furthermore, the study also shows the activation of several host genes proposed to be downregulated by either KSHV/EBV infection or respective viral proteins such as chemokine (C-X-C motif) receptor 4 (CXCR4), LIM domain only 2 (LMO2), v-myc myelocytomatosis viral oncogene homolog (MYC), Toll-like receptor 5 (TLR5), inhibitor of DNA binding 4 (ID4), TGF-β1, antigen identified by monoclonal antibody Ki-67 (MKI67), ATM, lymphoid-restricted membrane protein (LRMP), TP53, membrane metallo-endopeptidase (MME), TIMP3, MLH1, CDH1, DLC1, CDKN1C, glutathione S-transferase pi 1 (GSTP1), HIC1, and RASSF1. Overall, the study by Paul et al. (2010) and Paul et al. (2013) propose that the anticancer effects of concurrent targeting of COX-2 and EP1/EP4 receptor is due to the simultaneous inhibition of viral and nonviral mediated tumorigenic mechanisms acting at multiple levels.

**CONCLUSIONS AND FUTURE STUDIES**

A key aspect of chronic inflammation and oncogenesis attributable to inflammation is the sustenance of the driving factors such as COX-2 activity, PGE2 secretion, and PGE2 mediated functional autocrine and paracrine signaling. An interesting finding in the study by George Paul et al. (2010) is the downregulation of COX-2 gene expression and PGE2 secretion by EP2 and EP4 antagonists indicating a positive feedback loop mediated through EP2 and EP4 receptor signaling that simultaneously regulates LANA-1 and COX-2 expression. Mechanistically, the stability of the COX-2 messenger RNA (mRNA) transcript has been shown to be mediated by p38/MK2 dependent signaling acting on the ARE sequences in the 3' UTR region of the COX-2 mRNA. Interestingly, the KSHV protein kaposin B is also shown to stabilize mRNA transcripts with 3'UTR ARE sequences through p38/MK2 signaling. Further studies are critical to fully understand this pathway, such as examining the effect of EP receptor antagonism on the gene expression of Kaposin B, cytokine and p38/MK2 activation, and COX-2 protein levels. Multiple promoters (Lti, Ltc, Ltd) have been identified in the KSHV latency locus and account for the transcripts of LANA-1, vFLIP, vCyclin, viral microRNAs, and Kapo-
Fig 1. Model summarizing the role of the cyclooxygenase-2 (COX-2)/Prostaglandin E2/Eicosanoid receptor pathway in Kaposi’s sarcoma (KS) and primary effusion lymphoma (PEL) pathogenesis. During the early stages of Kaposi’s sarcoma-associated herpes virus (KSHV) infection of target cells, KSHV binds to the cell surface receptors via its envelope glycoproteins, and by using multiple overlapping pathways, the virus enters the host cell.98,193 KSHV interactions with receptors, while binding and entering the target cell, induces a variety of overlapping cell signaling cascades (Extracellular signal-regulated kinase, Phosphatidylinositide 3-kinase, Rho family of GTPases, Focal adhesion kinase, Src, nuclear factor kappa-light-chain-enhancer of activated B cells, and protein kinase C) and transcription factors (c-Fos, c-Jun, c-Myc, and Signal transducer and activator of transcription 1-alpha) early during infection.59,84-90,92,193-198 KSHV infection via the induction of signal pathways also reprograms and modulates various host cell genes,82 and one of these molecules is the angiogenic stress response gene COX-2.61,82 KSHV infection induced COX-2 led to the secretion of its inflammatory metabolite PGE2.61 A variety of transcription factors (NF-κB, NFAT, NF-IL-6/cEBP, AP-1, and CRE) can stimulate COX-2 expression. KSHV entry associated signal cascades involving FAK, Src, JNK, and p38 activate transcription factors NFAT and Cyclic adenosine monophosphate response element-binding CREB, which stimulate COX-2 gene expression and PGE2 secretion.60 PGE2 exerts its effect through the family of 7-transmembrane G-protein-coupled rhodopsin-type EP (1-4) receptors, which along with COX-2 and PGE2 were detected in human KS lesions.59,62 Besides manipulating host genes, KSHV establishes latency in the host cell as observed by increased expression of its viral latent genes latency associated nuclear antigen (LANA)-1 and vFLIP. PGE2 in the microenvironment of the infected cell functions in paracrine and autocrine fashion to augment its goal to establish and maintain the expression of viral latency protein LANA-1 through Ca2+, Src, PI3K, NK-κB, and ERK1/2 mediated signal cascades.62 EP receptor antagonists downregulate LANA-1 expression through inhibition of Ca2+, p-Src, p-PI3K, p-PKCζ/δ, and p-NF-κB while exogenous PGE2 and EP receptor agonists induced the LANA-1 promoter by activating transcription factors (yin-yang), Specificity Protein 1, octamer transcription factor-1, CCAAT-enhancer-binding proteins, and c-Jun.62 Collectively, our studies demonstrate that KSHV has pirated the proinflammatory PGE2 and its receptors for maintaining its latency in the host cell. Conversely, viral latency protein vFLIP mediated signaling sustains COX-2 expression and PGE2 secretion.64 KSHV oncogenic protein vFLIP induces COX-2/PGE2 to enhance its transforming ability (anchorage independent colony formation), metastatic potential (matrix metalloproteinase (MMP)-10), and inflammatory phenotype (inflammatory cytokines: monocyte chemotactic protein-1, RANTES, GRO-α/β, interleukin 8, and interleukin 6; inflammation-related adhesion molecules: ICAM-1, VCAM-1; and chemokines: CXCL-6 and CXCL-5), and to promote anoikis resistance and prolong infected cell survival (cell survival genes: Cellular
activate other latency promoters as well. Elucidating such mechanisms, if any, would provide a comprehensive perspective on how KSHV utilizes PGE2 and EP receptors for regulating latency.

Studies with LANA-1 promoter deletion constructs identified a PGE2 response region in the KSHV latency locus.62 The KSHV latency locus is known to be regulated by Sp1, C/EBP, c-Jun, Oct-1, and Oct-6.22,187 The transcription factors (TFs) that are potentially stimulated by PGE2 and the EP receptor such as Sp1, C/EBP, c-Jun, Oct-1, and Oct-6 within the minimal region of the LANA-1 promoter activity, there are several transcription factors that could be potentially stimulated by PGE2 and the EP receptor such as Sp1, C/EBP, c-Jun, Oct-1, and Oct-6.22,187 The functional significance of these TFs in inducing the LANA-1 promoter, their specific binding sites, and influence of PGE2 and EP receptors over these TFs remains to be determined. Key concept introduced by George Paul et al (2010)62 is the role of the EP1 receptor in inducing Ca 2+ signaling in the KSHV latency program. The study had identified a specific type of calcium signal induced by EP1 receptor in long-term-infected cells leading to several questions such as the effect of calcium signaling and the transcription factors activated by calcium signaling.

One of the most intriguing findings of the study by Paul et al (2011)63 was the downregulation of syndecan-1, VDR, and AQP3 expression by nimesulide in PEL cells. Syndecan-1/CD138, VDR, and AQP3 are uniquely over-expressed in PEL cell lines unlike other NHLs.69,188 The role of transmembrane proteoglycan syndecan-1 in cell migration through Rac-1/PKCα signaling and the significance of syndecan secretion in proteoglycan signaling are key aspects of oncogenesis.189 VDR is the natural receptor for 1α25-dihydroxyvitamin D3.190 Induction of VDR with chromatin remodeling and is also proposed to increase the risk of esophageal squamous, prostate, and pancreatic cancers by the activation of osteopontin and Ran-GTPase.190 AQP3 is a channel protein involved with the transportation of water and glycerol, and ATP generation.191 In lung adenocarcinoma, colorectal cancer, and squamous cell carcinoma, AQP3 has been proposed to play a role in promoting cell migration through actin depolymerization and ATP generation.192 The link between COX-2 and the expression of syndecan-1, AQP3, and VDR within the context of PEL raises several important questions such as the role of proteoglycan mediated signaling, chromatin remodeling, and ATP metabolism in PEL and how COX-2 might be contributing to PEL pathogenesis through such a novel signal network.

Overall, the studies reviewed here provide a glimpse of the molecular framework underlying the angiogenic stress response proinflammatory protein COX-2, its famous lipid metabolite PGE2, and EP receptors in the establishment and maintenance of KSHV latency and, therefore, implicated COX-2 inhibitors and EP receptor antagonists as potent chemotherapeutic modalities in treating KSHV related lymphomas (Fig 1). Thus, the studies add a novel paradigm in the pathogenesis of KSHV associated diseases and raise several questions that could expand our understanding of the role of chronic persistent inflammation in KS and PEL.

Currently, NHLs are the fifth most common cancer in the United States and account for 5% of all cancers with an annual incidence increasing by 1%-2%.126,192 Keeping in mind the ultimate aim of cancer treatment is to inhibit the growth of precancerous and cancerous cells without affecting the normal cells, could the studies reviewed here suggest the antiproliferative effects of COX-2 inhibitors and EP receptor antagonists against various NHL cell lines? The data emanating
from our in vitro studies is valuable, informative, and requires further examination (ongoing studies) using an in vitro angiogenic model and an in vivo nude mice model to further validate COX-2, PGE2 inhibitors, and EP receptor antagonists as novel therapeutics to target latent KSHV infection, viral pathogenesis, and associated diseases; KS and PEL.

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