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 gastroin-

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testinal 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-g; 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; NSAIDs = nonsteroidal anti-inflammatory drugs; PDGF-β = platelet derived growth factor β; PEL = primary effusion lymphoma; PGE2 = prostaglandin E2; PI3-K = Phosphatidylinositide 3-kinase; ROS = reactive oxygen species; SDF-1 = stromal cell-derived factor-1; STAT-1α = Signal transducer and activator of transcription 1-alpha; TGF-b = 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.[1] Inflammation is a physiological mechanism evolved for wound healing and therefore is counterintuitive 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.[1] 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.[1-8] Chronic persistent inflammation is believed to play an important role in the pathogenesis of 15% of all malignancies.[1-5] 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.[1,7,8]

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.[6,9-11] Viruses are obligate intracellular parasites and use host proteins for genome replication and production of progeny.[12] 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, immunesuppressive, and antiapoptotic niche that persistent inflammation provides.[11] 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.

COX-2 AND CANCERS

COX or prostaglandin-endoperoxide synthase catalyzes the conversion of arachidonic acid (AA) into prostaglandin H2, which is further converted into the proinflammatory lipid metabolites such as PGE2, PGI2, PGF2, and thromboxane-2 by specific enzymes and play crucial roles in diverse physiological functions such as platelet aggregation, inhibition of gastrointestinal (GI) acid secretion, regulation of glomerular function, and labor.[13] The COX-1 isoform has a constitutively active promoter whereas COX-2 has an inducible promoter activated by stress, growth factors, cytokines, and infections.[13] Numerous studies have demonstrated the induction of COX-2 and associated inflammatory pathways in the pathogenesis of several cancers such as colorectal, prostate, lung and breast cancers, as well as several hematological malignancies including chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas (NHLs), and multiple myeloma.[5,14-18] In recent years, COX-2 has been investigated as a potent chemotherapeutic target due to the