FEATURED NEW INVESTIGATOR

Lipoxins exert antiangiogenic and anti-inflammatory effects on Kaposi's sarcoma cells

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Lipoxin A4 (LXA4) is an endogenously produced host molecule with anti-inflammatory resolution effects. Previous studies demonstrated it to be involved in anti–vascular endothelial growth factor (VEGF)-mediated angiogenesis and in a possible anticancer role via interaction with its receptor, lipoxin A 4 receptor (ALXR). Here, we examined the effects of LXA4 and its epimer 15-epi–LXA4 in inhibiting proinflammatory and angiogenic functions in a human Kaposi's sarcoma tumor–derived cell line (KS-IMM). KS-IMM cells expressed increased levels of inflammatory cyclooxygenase 2 (COX-2) and 5-lipoxygenase (5-LO) pathway enzymes when compared with human microvascular dermal endothelial cells (HMVEC-d). KS-IMM cells secreted high levels of prostaglandin E2 (PGE2) and chemotactic leukotriene B4 (LTB4). Treatment with LXA4 or 15-epi–LXA4 effectively reduced the levels of COX-2, 5-LO proteins, and secretion of PGE2 and LTB4 in KS-IMM cells. LXA4 or 15-epi–LXA4 treatment also decreased secretion of proinflammatory interleukin 6 (IL-6) and IL-8 cytokines but induced the secretion of anti-inflammatory IL-10. LXA4 treatment reduced the phosphorylation of VEGF receptor (VEGFR) and ephrin family receptor tyrosine kinases. LXA4 treatment effectively induced dephosphorylation of multiple cellular kinases such as Focal Adhesion Kinase, Protein kinase B, nuclear factor kappa-light-chain-enhancer of activated B cells, and Extracellular signal-regulated kinases (ERK)1/2, and reduced angiogenic factor VEGF-C secretion in KS cells. LX treatment drastically induced the Src-homology 2 domain-containing phosphatase tyrosine (Y542) phosphatase and reduced VEGFR-2 phosphorylation at sites Y1059, Y1175, and Y1212. Treatment of KS-IMM cells with LXA4 resulted in selective localization of VEGFR-2 in nonlipid raft (non-LR) and ALXR to LR fractions. These results demonstrated that LXA4 or 15-epi–LXA4 induce anti-inflammatory and antiangiogenic effects in KS cells and suggest that treatment with LXs is an attractive novel strategy against KS. (Translational Research 2015;166:111–133)

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Abbreviations: IL-8 = interleukin 8; IL-10 = interleukin 10; LTB4 = leukotriene B4; LXA4 = lipoxin A4; PGE2 = prostaglandin E2; VEGF = vascular endothelial growth factor

AT A GLANCE COMMENTARY

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Background

Lipoxins (LXs) are anti-inflammatory, proresolving, and short-lived bioactive lipids. The anti-inflammatory activity of LXs is extremely effective because of high potency, high bioavailability, low half maximal inhibitory concentration, and safety, with minimal unwanted adverse effects. LXs have not been studied in Kaposi's sarcoma (KS) and warrant attention.

Translational Significance

KS is an inflammation-linked endothelial malignancy. We hypothesized that regulation of inflammatory and angiogenic vascular endothelial growth factor–vascular endothelial growth factor receptor cascade is one of the putative therapeutic strategies to control KS pathogenesis. We show that KS overexpresses inflammatory and angiogenic cascades, and targeting these pathways by LXs provide a new avenue of treatment against malignancies associated with KS-associated herpesvirus.

INTRODUCTION

Inflammation and angiogenesis are the key early events in tumor progression and metastasis. Therefore, the development of new, powerful, and safer anti-inflammatory and antiangiogenic strategies contributes to future cancer therapies. The host inflammatory response in the form of redness, swelling, and pain is a physiological mechanism meant to protect against and help remove damage from invading pathogens. The initiation of host response leads to an immunologic cascade consisting of polymorphonuclear neutrophils, monocytes, and macrophages that work cooperatively to bring the host and the inflamed area back to homeostasis.[1] Molecules such as tumor necrosis factor α, monocyte chemotactic protein 1, interleukin 6 (IL-6), and 5-lipoxygenase (5-LO) metabolite leukotriene B4 (LTB4) function to attract neutrophils and macrophages to the damaged area. To repair the damaged area, the immune response relies on the eventual activation of fibroblasts and endothelial cells, which further activate proinflammatory enzymes such as cyclooxygenase 2 (COX-2) and its metabolite prostaglandin E2 (PGE2) and IL-8.[2-5] Acute inflammation, if left unchecked, can eventually progress to a chronic state, which may lead to uncontrolled cell proliferation and cancer.

One of the hallmarks of cancer and tumor growth in general is the increased angiogenic potential of the tumor cells. Angiogenesis is controlled primarily by vascular endothelial growth factor (VEGF) and its receptor subtypes VEGFR-1 (Flt-1), VEGFR-2 (Kinase Insert Domain Receptor or Flk-1), and VEGFR-3 (Flt-4). The VEGF-related polypeptide family is made up of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor.[6] VEGF-A mainly mediates angiogenesis by binding to VEGFR-1 and VEGFR-2. VEGFR-3 is activated by VEGF-C to induce lymphangiogenesis; however, VEGF-C can also bind VEGFR-2 and induce angiogenesis.[7] Aberrant angiogenesis is a feature of uncontrolled inflammation and cell proliferation, which can be found in various cancers including colorectal, breast, lung, head and neck, and Kaposi's sarcoma (KS).[6]

KS is a highly vascularized tumor associated with infection of KS-associated herpesvirus (KSHV), which develops commonly in 15%–30% of cases during the course of acquired immunodeficiency syndrome (AIDS).[8-10] The pathology of KS commonly includes the invasion of mucocutaneous sites; however, lymph nodes and visceral organs, most notably the respiratory and gastrointestinal tracts, may also be infiltrated.[11] The use of highly active antiretroviral therapy has drastically reduced the incidence and burden of KS tumors in patients with AIDS-KS in the Western hemisphere but the risk for KS recurrence because of therapeutic immune suppression continues to pose a grave issue in patients where highly active antiretroviral therapy is discontinued. KS is the leading tumor contributing to the morbidity and mortality in the areas of sub-Saharan Africa where a high endemic KSHV infection rate overlaps with poorly treated human immunodeficiency virus infection. KS is characterized by abnormal neoangiogenesis, inflammation, and proliferation of KS spindle cells, which are transformed and reprogrammed endothelial cells.[12] A KS lesion typically consists of clusters of spindle-shaped cells that are considered to be the tumor cells of the lesion; inflammatory infiltrating cells, fibroblasts, smooth muscle cells, and intense neoangiogenesis leading to a dense and poorly organized capillary network, are also recruited by the host response. Basic fibroblast growth factor, VEGF, and platelet-derived growth factor (PDGF-B) are angiogenic molecules in vivo and have been suggested as contributing factors in KS angiogenesis.[12-17] KS is classified as a chronic inflammation-associated malignancy and is