Immunoinflammatory Mechanisms in Lung Cancer Development: Is Leptin a Mediator?

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Abstract: This is a short review focusing on leptin immunoinflammatory mechanisms that ultimately may contribute to lung cancer development. We explored the complex and intricate interaction of leptin with immune cells to propose a pathway of inflammation-associated lung cancer development.

Key Words: Immunity, Leptin, Lung cancer, Inflammation.

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IMMUNOINFLAMMATORY RESPONSE AND LUNG CANCER

Immune cells constitute a critical component of host response to cancer,[1] although their role in cancer pathogenesis remains incompletely established. Epidemiological data indicate that chronic inflammation increases the risk of malignant transformation[2] and, therefore, that unresolved host immune reactivity may promote tumor development.[3] In fact, persistent or recurrent immunoinflammatory up-regulation may induce or influence susceptibility to carcinogenesis by some known mechanisms (Fig. 1).[4]

Most lung cancer patients are smokers,[5] and tobacco consumption is a well-established risk factor.[6] A chronic inflammatory state is known to correlate with the decline in lung function among smokers[7,8] and with lung cancer etiopathogenesis.[9] Chronic cigarette smoking retards mucociliary clearance of foreign particulates and secretions that favor a persistent inflammation, whereas the inhaled particles evoke vigorous lung and airway inflammatory responses.[10–12] Initiation of the immunoinflammatory lung response is induced by exposure to inhaled antigenic particles and is followed by an expression pattern of chemokines and cytokines that may be influenced by the individual genetic background.[13,14] This mechanism may predispose a patient to an amplified and longer immune response. The role of chemokines in lung cancer biology has been highlighted in a previous review.[15]

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LEPTIN, INFLAMMATION, AND LUNG CANCER

Investigators have found that a functional polymorphism in the leptin gene (*LEP*-2548 G/A) was associated with increased risk for developing non-small cell lung cancer (odds ratio, 1.97; 95% confidence interval, 1.13–3.43) and to earlier onset of disease, and that carriers of the risk genotype simultaneously smokers had even higher risk for developing cancer of the lung (odds ratio, 4.82; 95% confidence interval, 1.05–22.17).[16] These results support leptin's role in exacerbating existing cigarette smoke-induced lung inflammation that may lead to increased amplitude and duration of reaction, which has a major role in lung cancer pathogenesis.

Leptin is an adipocytokine that has been consistently implicated in lung physiology and pathophysiology. It is involved in fetal lung development and in adult normal lung cells' physiology or malignant proliferation.[17–19] Besides a possible direct effect of leptin in normal and tumor lung cells, most importantly, there is strong evidence of leptin's up-regulatory role in the immunoinflammatory system,[20] supporting its role as a prominent interplay between inflammation and lung cancer (Figure 1). It is now well established that fat depots' function goes beyond structural, metabolic, and heat-insulating properties because of cytokines, growth factors, and hormone production that may prolong the pro-inflammatory microenvironment.

LEPTIN, INNATE IMMUNITY, AND CANCER

Although the immune surveillance hypothesis has received some experimental support, the net effect of inflammation and/or innate immune system activation is stimulation of tumor growth in most cases.[21] Leptin affects both innate and adaptive immunity. In innate immunity, leptin directly and indirectly modulates the activity and function of neutrophils by increasing chemotaxis and production of oxygen radicals,[22] increases phagocytosis by monocytes/macrophages, and activates and promotes macrophage cell chemotaxis.[23] Cumulatively, it was shown that recombinant human leptin administration increased both C-reactive protein and P-selectin,[24] whereas an association was observed between the concentration of VCAM-1 and ICAM-1 and circulating leptin levels.[25,26] These evidences support an indirect role for leptin in chemotaxis and, consequently, in attraction of inflammatory cells through an action in adhesion molecules, further increasing the magnitude of inflammation.

The inflammatory process initiated by infection, cellular damage, tumor cells, reactive oxygen species production,

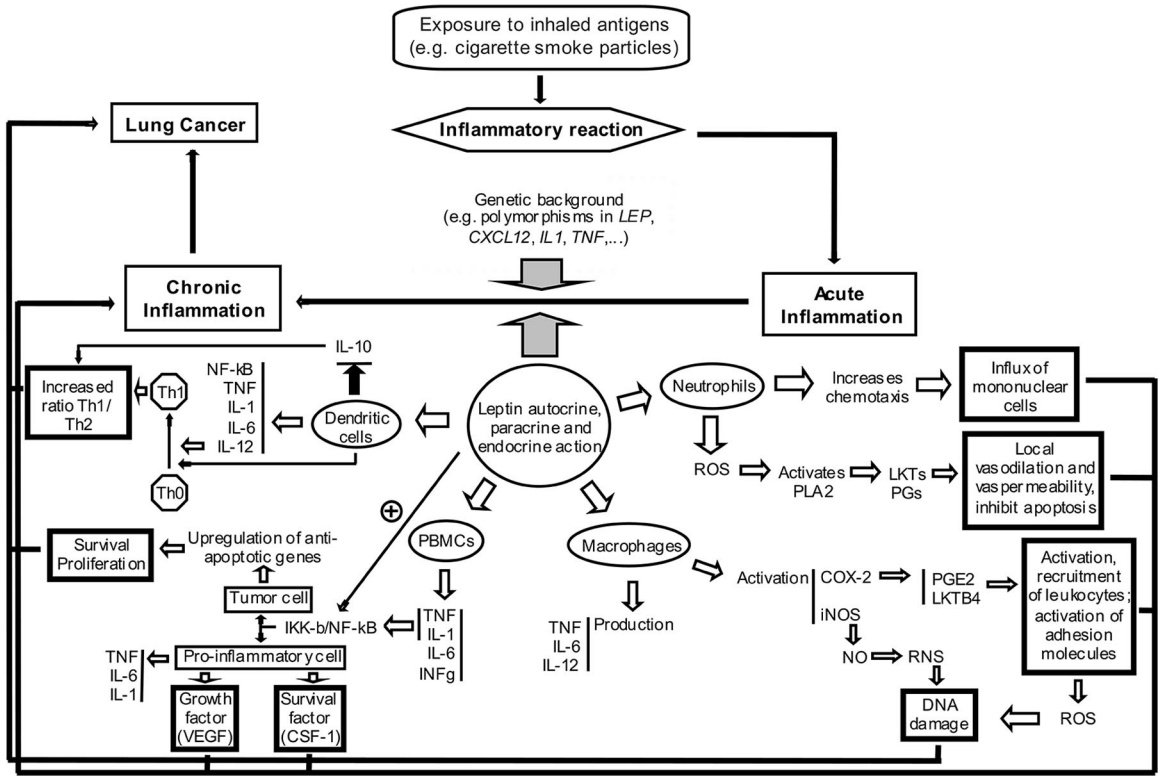

FIGURE 1. Leptin's role in immunoinflamatory-mediated lung cancer development. After exposure to inhaled antigens (e.g., smoke particles) follows acute inflammation that under normal circumstances is self-limited. However, depending on the magnitude and duration of exposure to pro-inflammatory inhaled antigens and on the individual's genetic background (polymorphisms in genes that express pro-inflammatory molecules), the inflammatory reaction may last longer and/or may be increased. Leptin may have a central role in chronic inflammation development and maintenance of chronic inflammation, through autocrine, paracrine, and endocrine mechanisms. There is a broad range of action for leptin in immune cells. Leptin stimulates and activates neutrophils, macrophages, peripheral blood mononuclear cells, dendritic cells, and T cells, whose products, ultimately, may induce chronic inflammation and lung cancer carcinogenesis. Th0 = naive T cell, Th1 = T helper 1, Th2 = T helper 2, NF-κB = nuclear factor κB, TNF = tumor necrosis factor-α, VEGF = vascular endothelial growth factor, PLA2 = phospholipase A2, LKTs = leukotrienes, PGs = prostaglandins, IFNg = interferon-γ, COX-2 = cyclooxygenase 2, iNOS = inducible nitric oxide synthase, NO = nitric oxide, CSF = colony stimulating factor, ROS = reactive oxygen species, RNS = reactive nitrogen species, PBMCs = peripheral blood mononuclear cells.

inhaled particles from tobacco, or environment pollutants stimulates the synthesis of interleukin (IL)-1, IL-6, leptin, and tumor necrosis factor (TNF) by macrophages and stromal and endothelial cells.[27,28] These molecules are partially responsible for the expression of acute-phase inflammatory response elements, such as cyclooxygenase-2, nuclear factor κB, and C-reactive protein,[29] and are associated with the induction of leukocyte recruitment and activating-adhesion molecules, P-selectin, E-selectin, VCAM and ICAM.[28,30] Activated leukocytes produce large quantities of reactive oxygen species that will cause oxidative damage to surrounding cells and enhance risk for inflammation-mediated cytotoxicity and DNA damage in normal cells. The role of leptin in up-regulating reactive oxygen species production through an effect in monocytes or indirectly in endothelial cells by an increase in monocyte-chemoattractant protein 1 is well known.[31,32] Reactive oxygen species derived from inflammation is an important endogenous carcinogenic factor, which is increased by long-term chronic inflammation.

Santos-Alvarez et al.[33] observed a stimulatory effect of leptin on peripheral blood mononuclear cell production of TNF and IL-6. Furthermore, leptin's role in peripheral blood mononuclear cell proliferation and activation is mediated by activation of the leptin receptor in these cells,[34] inducing a pattern of cytokine release compatible with the induction of a T-helper 1 immune response,[35] which is associated with a negative prognostic factor in patients with non-small cell lung cancer. Leptin mediates the up-regulation of dendritic cells' function and survival and decreases production of IL-10, which further contributes further to T-helper 1 immune phenotype.[36] Simultaneously, leptin up-regulates the secretion of IL-1, IL-6, IL-12, TNF, and MIP-1α by dendritic cells.[36]

Activation of the inhibitor of nuclear factor-κB kinase β-dependent nuclear factor-κB molecular pathway is a molecular mechanism that connects inflammation and cancer. Its activation increases tumor growth and progression in different cell types through activation of gene targets of pro-inflammatory cytokines and chemokines, such as TNF, IL-1,

and IL-6.[37] The up-regulation of immunomodulators TNF, IL-1, IL-6, and prostaglandin E_2 through leptin via the nuclear factor-κB pathway[38] further strengthens the up-regulated pro-inflammatory profile in the tumor microenvironment. Furthermore, TNF and IL-1 stimulate leptin production by adipocytes,[39,40] further contributing to prolonged leptin-induced inflammation.

After leptin's stimulatory effect, macrophages also increase the production of the pro-inflammatory enzyme cyclooxygenase 2 and their products leukotriene (LKT) B4 and prostaglandin (PG) E2, and augments inducible nitric oxide synthase (iNOS) activity.[41,42] Production of reactive nitrogen species (RNS) in response to inflammation-induced iNOS overexpression might induce generation and accumulation of additional mutations that drive tumor progression.[43] Several studies support a stimulatory action of leptin in endothelial NOS (eNOS) and inducible NOS (iNOS) activities, which results in increased NO production by adipocitic and endothelial cells.[44,45] Raso et al[42] showed that leptin is a potent synergistic factor that cooperates with IFN-γ to increase the expression of iNOS and cyclooxygenase 2. The cyclooxygenase-2 enzyme up-regulates the production of the vasoactive prostaglandins (PGs) and leukotrienes (LKTs) responsible for increasing the amount of local vasodilation and vasopermeability, and cumulatively, for enhanced inflammation through leukocytes accumulation. The PGs also inhibit apoptosis and stimulate angiogenesis and invasiveness.[46] As a result of chronic inflammation, constant exposure to cyclooxygenase 2-derived prostaglandins may also enhance carcinogenic risk by reducing apoptosis and increasing the likelihood of mutant cell survival and cancer development.

LEPTIN, ADAPTIVE IMMUNITY, AND CANCER

Apparently, T cells may also contribute to tumor growth because, in the progression phase, they are the main source of IL-6,[47] and their overall contribution might depend on the balance between tumor-promoting cytokines, such as IL-6, and tumor-suppressor cytokines, such as IL-10 and TGF-β.[37] Leptin, which increases IL-6 production and decreases IL-10 secretion, provides an interesting clue to the understanding of leptin's association with inflammation and cancer, although much research in inflammatory cancer models is required to clarify this issue.

In adaptive immunity, leptin affects the generation, maturation, and survival of thymic T cells by reducing their rate of apoptosis.[48] Leptin orients naive T-cell proliferation and differentiation to TH1 phenotype[36] and promotes the switch toward TH1 immune responses on memory T cells by increasing IFNγ and TNF secretion and stimulating the production of $IgG_2α$ by B cells.[49] The TH1/TH2 cytokine balance is preserved in normal individuals, but during inflammation, the imbalance in the TH1/TH2 cytokine response overcomes. In patients with non-small cell lung cancer, a high TH1/TH2 ratio in peripheral blood is a negative prognostic factor.[50]

SUMMARY

Recent developments in leptin immunological pathways suggest a previously unappreciated complexity of cancer cell-normal cell-immunoinflammatory cell cross-talk. This interaction found in the inflammatory medium may deregulate and increase the magnitude and duration of inflammation, promoting tumor development. Leptin, a pleiotrophic hormone synthesized mainly by adipocytes, may be an important interplay between immunoinflammatory up-regulation and lung cancer development, warranting further studies in this field.

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