Obesity and renal cancer
Role of adipokines in the tumor-immune system conflict

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Introduction

The incidence of obesity and obesity-associated disorders have been steadily increasing over the past few decades in developed and developing countries, making it one of the most serious health problems worldwide. Several morbidities have been etiologically associated with obesity, including Type 2 diabetes and cardiovascular diseases. Recently, an epidemiological link between obesity and the prevalence of a variety of cancers, including breast, endometrial, esophageal, gastric, colorectal, gallbladder, pancreatic, hepatic, renal, and bladder tumors, has been established.

Renal cell carcinoma (RCC) accounts for approximately 3% of all cancers in adults in several western countries, and its incidence has been rising over the last few decades.1 Although several potential risk factors have been recognized, including tobacco smoking,2 hypertension,3 and a familial history of kidney cancer, the etiology of RCC is still largely undefined. Several studies worldwide have demonstrated the influence of body mass index (BMI), i.e., weight in kg/(height(m))2 on renal carcinogenesis.4 RCC is the third cancer most robustly associated with increased BMI after endometrial and esophageal tumors. One of the most rigorous meta-analysis studies performed to date revealed a strong association between overweight and RCC.5 Forty percent of RCC cases in USA and 30% in Europe are indeed associated with excessive body weight. The risk for the development of RCC has been directly correlated with increased weight in a dose-response manner, with an estimated increase of 24% for men and 34% for women for every 5 kg/m2 increase in BMI, leading to a 4% increased risk of developing RCC.5 This said, limited information is available on the variation in the risk of obese patients to develop RCC of different histological type, stage or grade, or stratified on other potential risk factors. However, it appears that clear cell RCC (ccRCC) is the histological subtype of RCC that is the most strongly associated with obesity,6,7 and for which perinephric fat invasion is a significant predictor of poor disease outcome.8 Paradoxically, obesity appears to be associated with an improved survival of cancer patients as well as with relatively poor symptomatic or local tumors, as it was documented recently by several studies. Yet, the rate of postoperative complications increases with BMI.9,10 Here, we review how a dysfunctional adipose tissue (AT) interferes with oncogenesis and may modulate anticancer immune responses.

Dysfunctional Adipose Tissue and Tumor Development

The adipose tissue (AT) is the most prevalent tissue in the human body. It is commonly found in the subcutaneous connective tissue and also surrounds various organs including the kidneys. In humans and most animal models, the development of obesity leads not only to increased fat depots in classical...
anatomical locations, but also to significant deposits of lipids within and around other tissues and organs, a phenomenon known as ectopic fat storage. The AT becomes increasingly dysfunctional upon weight gain. The altered physiological state of the expanding fat pads may affect carcinogenesis and impact on the progression of established renal tumors, modulating the tumor microenvironment (Fig. 1).

Adipokines dysregulation and RCC
The AT is not only a long-term energy storage organ, but also a major endocrine gland, being responsible for biosynthesis and secretion of a large number of hormones and cytokines, commonly referred to as adipokines. AT dysfunction results in altered circulating levels of adipokines, an alteration that may be directly involved in obesity-related tumorigenesis. Here, we discuss 2 adipokines, leptin (LEP) and adiponectin, which are among the proteins most specifically produced by adipocytes and are linked to RCC by both epidemiological and preclinical data.

LEP (also known as Ob; molecular weight = 16 kDa; 167 amino acids) is a small non glycosylated protein structurally similar to interleukin (IL)-6, IL-12, IL-15, prolactin, the growth hormone and granulocyte colony-stimulating factor (G-CSF).\textsuperscript{11} LEP exclusively binds to its receptor (LEPR, also known ObR), with ObR being the predominant isoform responsible for the biological actions of LEP. ObRB activates indeed the Janus kinase/signal transducer and activator of transcription (JAK/STAT3) signaling pathway, which in turn stimulates phosphoinositide-3-kinase (PI3K) to promote proliferation, migration and angiogenesis.\textsuperscript{12}

Accumulating evidence supports the idea that LEP is the link between obesity and the increased incidence of various cancers.\textsuperscript{3,13} The ObR is highly expressed on multiple malignant cells, including those of mammary, pancreatic, esophageal, gastric, and colorectal origin, as compared with their normal counterparts (in which the receptor is expressed at very low levels or not at all).\textsuperscript{14} Data from animal studies reinforced the hypothesis that LEP can contribute to cancer growth. Thus, the progeny of LEP-signaling (ob/ob or db/db) mice crossed with MTTV-TGF\textsubscript{α} mice (which are prone to undergo spontaneous mammary carcinogenesis) do not develop mammary tumors.\textsuperscript{15,16} Several carcinogenic actions have been attributed to LEP, including the modulation of cell cycle-regulatory proteins as cyclin D1 and G, cyclin-dependent kinase 2 (CDK2), cyclin-dependent kinase inhibitor 1A (CDKN1A, best known as p21\textsuperscript{CIP1}), CDKN1B (best known as p27\textsuperscript{KIP1}), and CDKN2A (best known as p16\textsuperscript{INK4A}) and transforming growth factor\textsubscript{β}1 (TGF\textsubscript{β}1), resulting in the acceleration of cancer cell growth.\textsuperscript{17,18} LEP also sustains angiogenesis. For instance, human MCF7 and MDA-MB-231
breast carcinoma cells exposed to LEP secrete increased levels of vascular endothelial growth factor (VEGF) and are more invasive than their untreated counterparts. Finally, LEP signaling not only induces the expression of the anti-apoptotic proteins BCL-2 and survivin, but also limits the activity of caspases.

The circulating levels of LEP in RCC patients have been the primary focus of numerous epidemiological studies highlighting the strong correlation between elevated LEP concentrations and increased risk of RCC. The LEPR is expressed in the renal tissue as well as in RCC cell lines, supporting a role for LEP signaling in RCC carcinogenesis. Interestingly, increased circulating levels of LEP and the overexpression of LEPRs are both associated with the invasion and progression in human RCC. Finally, Li and colleagues have recently demonstrated that LEP stimulates cell proliferation and promotes the invasion and migration capabilities of RCC Caki2 cells upon the activation of both extracellular signal-regulated kinase (ERK) and JAK/STAT3 signaling pathways.

Adiponectin is normally produced by the AT, almost exclusively by mature adipocytes, and is an abundant circulating protein. Structurally, adiponectin is a polypeptide of 247 amino acids bearing an N-terminal collagen-like domain and a C-terminal globular domain. The globular domain shares significant homology with the subunits of the complement factor Clq. So far, 2 adiponectin receptors have been shown to share some homology with G protein-coupled receptors, namely, adiponectin receptor 1 (ADIPOR1) and ADIPOR2, and one to belong to the cadherin protein family, i.e., cadherin 13 (CDH13).

The study of the link between adiponectin and increased risk of oncogenesis or tumor progression led to the understanding that LEP and adiponectin always have antagonist properties. Several mechanisms underlying the anticarcinogenic effects of adiponectin have been described. Wang and colleagues showed that adiponectin significantly attenuates the proliferation of breast cancer cells by reducing the expression of cyclin D1. Experiments in nude mice demonstrated that both the supplementation of recombinant adiponectin and the adenovirus-mediated overexpression of this adipokine modulate the glycogen synthase kinase-3β (GSK3β)/β-catenin signaling pathway and substantially reduce the growth of MDA-MB-231 breast cancer cells in vivo. Adiponectin has also anti-angiogenic effects as it inhibits the proliferation and migration of endothelial cells.

**Figure 2.** Characteristics of the adipose tissue in leanness and obesity and their impact on the tumor microenvironment. The secretion of pro-inflammatory cytokines by adipocytes favor the expansion of tumor-infiltrating macrophages and limit immunocompetence.
Additional in vitro studies revealed that adiponectin is able to limit cell growth and stimulate apoptosis by inhibiting the activation of nuclear factor-κB (NF-κB), resulting in the downregulation of BCL-2 expression. Finally, adiponectin can interfere with cancer progression by exerting anti-inflammatory effects through the inhibition of TNFα. Adiponectin-deficient mice manifest indeed increased levels of the TNFα-coding mRNA in the AT and higher TNFα concentrations in the plasma as compared with wild-type mice.

Several studies have demonstrated that adiponectin levels are reduced in RCC patients, and also that adiponectin levels inversely correlate with tumor size. Furthermore, a reduction in levels of ADIPOR2 has been associated with an increased metastatic potential.34 The protective effects of adiponectin on tumorigenesis may be mediated by the downstream effectors of ADIPOR1 and ADIPOR2, including the AMP-activated protein kinase (AMPK) and c-Jun N-terminal kinase 1 (JNK1), both of which can limit cell proliferation, trigger apoptosis and inhibit inflammation. Although adiponectin is downregulated in dysfunctional AT, LEP is upregulated in the very same adipocytes, suggesting that a functional crosstalk between these 2 adipokines may impact oncogenesis and tumor progression. The effects of the dysfunctional AT in obesity and their link to tumorigenesis are summarized in Figure 2.

**Obesity associated inflammation**

Obesity is associated with the secretion of high amounts of pro-inflammatory cytokines, which generate a low-grade chronic inflammatory state. Paradoxically, inflammation is associated with both tumor suppression and tumor progression. Inflammation is indeed required for the host immune system to kill cancer cells, yet chronic inflammation has been shown to promote cancer progression. Thus, the chronic inflammatory state sustained by adipocytes may modulate the host immunosurveillance and therefore exert a direct impact on both the local tumor microenvironment and on distant tumor cells (through the systemic effects of endocrine signals). This state of chronic inflammation is due (at least in part) to the accumulation of immune cells into the dysfunctional AT, macrophages constituting a large fraction among them. Moreover, the expanding AT produces high levels of pro-inflammatory cytokines, including TNFα, IL-6, IL-1β and chemokine (C-C motif) ligand 2 (CCL2, best known as MCP1), and high levels of acute phase reactants, i.e., proteins that are released into the circulation in response to local inflammatory processes such as serum amyloid A (SAA), retinol binding protein 4, plasma (RBP4), and C-reactive protein (CRP). Finally, adipocytes can support chronic inflammation by expressing or producing a multitude of additional proteins such as intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), chemokine C-X-C motif ligand 10 (CXCL10), IL-8, IL-10, and multiple adipokines.

Inflammatory responses play a decisive role at different stages of tumor development, including initiation, progression, malignant conversion, invasion, and metastasis. Markers of inflammation are associated with an increased risk of recurrence upon RCC surgical resection. Inflammatory cytokines are detected in the plasma of RCC patients and are associated with poor prognosis. In line with this notion, the treatment of RCC cells with IL-6 and IL-8 enhances their invasive potential. Interestingly, RCCs are not highly infiltrated by macrophages. This implies that the pro-inflammatory cytokines detected in RCC patients may be generated by the expanded AT, acting as an important initiator of oncogenesis.

**Adipose tissue angiogenesis and hypoxia**

The hypertrophic expansion of the AT that accompanies obesity can trigger local hypoxia, which is one of the most prominent microenvironmental stimuli for the metastatic dissemination of previously localized tumors. The master regulator of oxygen homeostasis is hypoxia-inducible factor 1α (HIF-1α). The levels of HIF-1α are increased in the AT of obese patients while its expression is reduced upon surgery-induced weight loss. HIF-1α stimulates inflammation and angiogenesis by deregulating the production of TNFα, VEGF, and angiopoietin. The dysfunctional AT can also enhance angiogenesis by secreting cytokines with angiogenic activities such as LEP, TNFα, IL-6, IL-8, VEGF, and hepatocyte growth factor (HGF), as well as by producing limited amounts of anti-angiogenic proteins such as adiponectin. Kleinman et al. showed that the exposure of RCC cells to adiponectin inhibits the secretion of VEGF, matrix metallopeptidase (MMP)2 and MMP9, resulting in the suppression of their invasive and migratory capacities. ccRCC is well known for its intense vascularity and high expression levels of angiogenic factors. HIF-1α plays an important role in ccRCC originating from alterations of von Hippel–Lindau tumor suppressor, E3 ubiquitin protein ligase (VHL), an important onco- genetic event driving the development of 75% of ccRCC. An altered balance between pro- and anti-angiogenesis mediators may contribute to the increased risk of metastatic disease in obese subjects with RCC. This may have implications for the use of anti-angiogenic agents in RCC patients. Indeed, Ladoire et al. have recently shown that an expansion of visceral fat is associated with poor clinical outcome in RCC patients treated with anti-angiogenic agents.

**Adipose tissue and mesenchymal stromal cells**

The human AT is an important source of mesenchymal stromal cells (MSCs). These cells substantially affect the tumor biology due to their ability to accumulate within the tumor stroma and to exert multiple regulatory functions in the tumor microenvironment. AT-derived MSCs share a number of key characteristics with bone marrow-derived MSCs. MSCs promote the proliferation of endothelial cells and the formation of new blood vessels, the survival and migration of malignant cells, as well as the so-called epithelial-to-mesenchymal transition (EMT). The accumulation of AT-derived MSCs to neoplastic lesions has been demonstrated by several studies. These cells which expand in obese individuals, may be mobilized in response to tumor-derived signals to sustain angiogenesis, hence contributing to disease progression.

**Adipose tissue and the EMT transition**

Over the past decade, accumulating evidence has shown that epithelial cancer cells can convert themselves into migratory mesenchymal cells. This phenotypic and behavioral shift, known as the EMT, might explain how epithelial cancer cells escape their...
anatomical location and migrate to form micrometastases in distant tissues. During the EMT, cancer cells lose epithelial characteristics, including polarization and the engagement in specialized cell-to-cell contacts, and acquire a migratory behavior. All murine and human cancer cells co-cultured with mature adipocytes exhibit increased invasive capacities in vitro and in vivo. In RCC, the AT may promote the EMT via multiple factors, including TNFα. The treatment of RCC cell lines with TNFα increases the expression of MMP9 and vimentin while downregulating cell-to-cell adhesion proteins such as E-cadherin, thus increasing their invasiveness and metastatic potential.

### Adipose tissue as a source of energy for cancer cells

The expanded AT constitutes not only a microenvironment that is favorable for oncogenesis as it produces and secretes pro-inflammatory cytokines, but also as an energy source driving the survival and proliferation of malignant cells (which generally exhibit a very intense metabolic activity). Interestingly, Nieman et al. have shown that adipocytes are able to directly transfer lipids to co-cultured ovarian cancer cells, promoting their growth in vitro and in vivo. In this setting, adipocytes manifested high levels of lipolysis while malignant cells mainly engaged in β-oxidation, suggesting that the former can act as an energy source for the latter. This mechanism may not be limited to the ovarian cancer setting, and may provide a rationale for the growth of malignant cells that form metastasis in the abdomen or other adipocyte-rich environments, including RCC cells.

### Effects of Adipokines on Immune Cells and Antitumor Immunity

By altering the immune infiltrate and by secreting pro-inflammatory cytokines, the dysfunctional AT is known to modulate immunocompetence in humans. Several studies have found that obesity impairs natural killer (NK) cell-dependent immunity.

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**Figure 3.** Specific impact of obesity on the proliferation of clear cell renal cell carcinoma and the characteristics of its microenvironment. HIF1α, hypoxia-inducible factor 1α; IL, interleukin; IL15 r, IL-15 receptor; KIR, killer-cell immunoglobulin-like receptor; mb, membrane-bound; NK, natural killer; ObR, obesity (leptin) receptor; RCC, renal cell carcinoma; s, soluble; VHL, von Hippel-Lindau tumor suppressor; E3 ubiquitin protein ligase.
NK cell activation is altered in obese rats, a functional defect that can be reversed by transferring them into lean animals. LEP differentially affects the functions of human NK cells. A short-term exposure to LEP has indeed a stimulatory effect, while long-term administration significantly impairs key NK-cell functions such as their cytotoxic potential, their ability to secrete cytokines, their proliferative potential, suggesting that LEP may increase the risk of RCC in obese people by inhibiting NK cell-dependent antitumor responses. The AT may also interfere with the functions of NK cells via adiponectin. Adiponectin has indeed been shown to suppress the ability of IL-2 to promote NK-cell cytotoxicity, interferon γ (IFNγ) production, as well as the IFNγ-inducible expression of TNFα-related apoptosis inducing ligand (TRAIL) and FAS ligand (FASL).

Adipokines can also modulate adaptive immune responses. LEP favors the secretion of pro-inflammatory cytokines such as TNFα and IL-6 by macrophages, stimulate the accumulation of IFNγ-producing T<sub>1</sub> polarized cells, and interestingly persuades dendritic cells (DCs), major antigen-presenting cells, to drive a T<sub>1</sub> response. In addition, LEP promotes the survival of T cells by modulating the expression of apoptotic proteins that inhibit stress-induced apoptosis. Finally, LEP modulates adaptive immune response by acting on regulatory T cells (Tregs). Freshly isolated human Tregs constitutively express high amounts of LEP and LEPR. Interestingly, LEP neutralization has been shown to reverse the anergic state of Tregs in some settings. This is consistent with the enhanced proliferation of Tregs observed in ob/ob or db/db mice. Although LEP seems to exert positive effects on adaptive T-cell responses, its specific activity on T cells targeting tumor-associated antigens is not known. Moreover, its ability to stimulate the secretion of pro-inflammatory cytokines may lead to the activation of immunosuppressive myeloid-derived suppressor cells or immunosuppressive CD8<sup>+</sup> T cell subsets leading therefore to tumor progression.

Also adiponectin interferes with adaptive immune responses, but the precise underlying mechanisms have not been precisely elucidated. Adiponectin promotes the synthesis of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (ILRA) by human monocytes, macrophages and DCs while it suppresses the production of IFNγ and TNFα by lipopolysaccharide (LPS)-stimulated human macrophages. Tsang et al. reported that adiponectin downregulates the expression of co-stimulatory molecules while increasing that inhibitory ones on DCs, resulting in the accumulation of CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> Tregs. Conversely, adiponectin can mediate a pro-inflammatory effects by stimulating the secretion IL-12 and IL-6. Recently, Jung et al. have reported that adiponectin activates DCs, resulting in the elicitation of T<sub>1</sub> and T<sub>17</sub> responses.

In Figure 3, we depict how the alterations of obesity-associated AT may interfere with the immune cells that infiltrate ccRCC, taking into account their particular immunological features. Renal tumors express tumor-associated antigens that induce limited T-cell activation in vivo and the tumor-infiltrating lymphocytes that recognize self antigen are driven into anergy by the expression of inhibitory NK receptors. Conversely, NK cells participate in the immune response against RCC in a peculiar manner: (1) the percentage of NK cells infiltrating RCCs allow for subgrouping independently of the tumor-node-metastasis (TNM) classification; (2) cytokine-activated NK cells efficiently lyse RCC cell lines; (3) the loss-of-function of VHL results in the reduced expression of MHC class I molecules, hence favoring the activation of NK cells; and (4) the expression of IL-15 on the membrane of RCC cells modulates the survival of NK cells and probably maintains activated NK cells within neoplastic lesions. Taken together, these observations call for additional studies to understand the role of adipokines in the RCC microenvironment.

Conclusions

Despite substantial advances in the treatment of localized RCC, disease recurrence and metastasis remain the primary cause of cancer-related mortality in this setting. It becomes now increasingly clear that metabolic changes ensuing an altered energy status and the secretion of endocrine factors facilitate oncogenesis. Malignant lesions need to escape the immune system and to rely on an abundant energy source to grow and form metastases. The hypertrophic expansion of the AT in the course of obesity can provide such an energy source and also modulate antitumor immune response. Progress in understanding the pivotal role of the AT in the tumor-immune system conflict is crucial for identifying early changes in the tumor microenvironment that contribute to malignant progression and could provide a rationale for the development of novel anticaner therapies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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