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Review article

Interleukin-6 as an emerging regulator of renal cell cancer

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Abstract

Background: Our knowledge on the molecular basis of kidney cancer metastasisis still relatively low. About 25-30% of patients suffering from clear cell renal cell carcinoma (ccRCC)present metastatic disease at the time of primary diagnosis. Only 10% of patients diagnosed with stage IV disease survive 5 years and 20-50% of patients diagnosed with localized tumor develop metastases within 3 years. High mortality of patients with this cancer is associated with a large potential for metastasis and resistance to oncologic treatments such as chemo- and radiotherapy. Literature data based on studies conducted on other types of cancers suggest that in metastatic ccRCC, the complex of interleukin-6 (IL-6) and its soluble receptor (sIL-6R; complex IL-6/sIL-6R) and the signal transduction pathway (gp130/STAT3) might play a key role in this process.

Purpose: Therefore, in this review we focus on the role of IL-6 and its signaling pathways as a factor for development and spread of RCC. Analyzing the molecular basis of cancer spreading will enable the development of prognostic tests, evaluate individual predisposition for metastasis, and produce drugs that target metastases. As the development of effective systemic treatments evolve from advancements in molecular biology, continued studies directed at understanding the genetic and molecular complexities of this disease are critical to improve RCC treatment options.

Keywords: Renal cancer; Interleukin-6; Metastasis

1. Introduction

Up to 85% of kidney tumors are malignant, and more than 75% of those malignancies are of the clear cell renal cell carcinoma (ccRCC) subtype. The disease is characterized by a lack of early warning symptoms, diverse clinical manifestations, and resistance to radiation and chemotherapy. ccRCC is also characterized by a high metastatic potential. In 25% to 30% of patients with ccRCC, metastases are already present at diagnosis. Only 10% of patients diagnosed with metastatic disease survive for 5 years, but 60% of patients with localized disease survive for 5 years [1,2]. Surgical intervention is the primary treatment for localized RCC, but when performed alone, it has limited benefit in patients with aggressive disease [3]. In addition, traditional cytotoxic chemotherapy and immunotherapy have failed to demonstrate a clear benefit in patients in the adjuvant setting [4]. Furthermore, our understanding of the molecular basis for metastatic seeding and how RCC cells communicate is still incomplete [5].

Oncogenic transformation induces the development of cancer per se and also promotes the generation of an inflammatory microenvironment within/around the tumor and also systemic inflammation [6]. Cytokines are one of the molecules that favor inflammatory reactions. Lack of response in patients and regression of the disease after immune-based treatments demonstrates that ccRCC is an immunodependent tumor [7]. However, the administration of interleukin-2 (IL-2) and interferon-α (IFN-α) has limited clinical activity in the treatment of metastatic RCC. High doses of IL-2 have durable responses in a small number of carefully selected patients, and IFN-α treatment has resulted in a low response rate and short progression-free survival (PFS) [8–10]. Further studies investigated effects of other

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cytokines on RCC cell proliferation and tumor progression. Cytokines are also considered potential new treatment compounds [11,12] and potential molecular diagnostic, predictive, and prognostic markers in RCC [13,14].

2. IL-6 pathophysiology

Human IL-6 was discovered and cloned in 1968 [15]. Because of its various biological functions, IL-6 was also named B-cell stimulatory factor-2 and IFN-β-2 [16]. This pleiotropic cytokine is encoded by a gene located on chromosome 7p21 and consists of 5 exons and 4 introns. The promoter region contains a transcription start site with response elements for (1) activator protein (AP)-1, (2) nuclear factor (NF)-κB, and (3) CCAT/enhancer-binding protein beta (C/EPBβ; formerly NF-IL-6). IL-6 is a glycoprotein composed of 184 amino acids with a molecular weight of 21 to 28 kDa depending on its degree of glycosylation. It has a 4-helix bundle structure made up of 4 long α-helices [17–19]. IL-6 is produced in many tissues and various cell types, including monocytes, macrophages, T and B lymphocytes, neutrophils, fibroblasts, epithelial and endothelial cells, keratinocytes, mesangial cells, adipocytes, chondrocytes, and osteoblasts. Enhanced IL-6 production is observed under stimuli that cause an inflammatory response, such as TNF-α and TNF-β, IL-1, interferons, and bacterial endotoxin and lipopolysaccharide or viral infection [20]. Normal renal cortical tissues and also renal tumors were shown to produce IL-6 (without extra stimulation) [21]. Elevated IL-6 serum levels are observed under pathological conditions such as rheumatoid arthritis, systematic and multiple sclerosis, asthma, Crohn disease, Behçet disease, lupus erythematosus, obstructive sleep apnea, chronic obstructive pulmonary disease, and many types of cancer [22].

IL-6 activates cells via transmembrane receptor (IL-6R) and its soluble form (sIL-6R). The transmembrane receptor —IL-6R—consists of 2 distinct membrane-bound glycoproteins, an 80-kDa cognate receptor subunit (gp80, CD126, and IL-6R) and a 130-kDa signal-transducing element (gp130, CD130, IL-6ST, and IL-6-β). IL-6R is predominantly expressed in hepatocytes, megakaryocytes, and several leukocyte subpopulations (monocytes, neutrophils, T cells, and B cells), which are the primary target cells of IL-6 activity [23]. CD130 is involved in the formation of high-affinity IL-6–binding sites, and its expression is found in almost all organs, including the heart, kidney, spleen, liver, lung, placenta, and brain [24].

The soluble receptor IL-6sR is released from the membrane-bound receptor IL-6 (IL-6R) by ectodomain shedding [25] by the enzymes that belong to the A disintegrin and metalloproteinase (ADAM) gene family of metalloproteases—ADAM-17 and ADAM-10 [26]. The second mechanisms for IL-6sR production is alternative splicing [27]; differential messenger RNA (mRNA) splicing leads to an expression of soluble factors that lack cytoplasmic and membrane-spanning domains of the cell-associated protein [27] and is therefore released (excreted) by the cell.

For signal transduction, IL-6 binds IL-6sR or membrane-bound IL-6R (Fig.1). Subsequently 2 gp130 molecules are recruited. Ligand binding to gp130 leads to activation of the

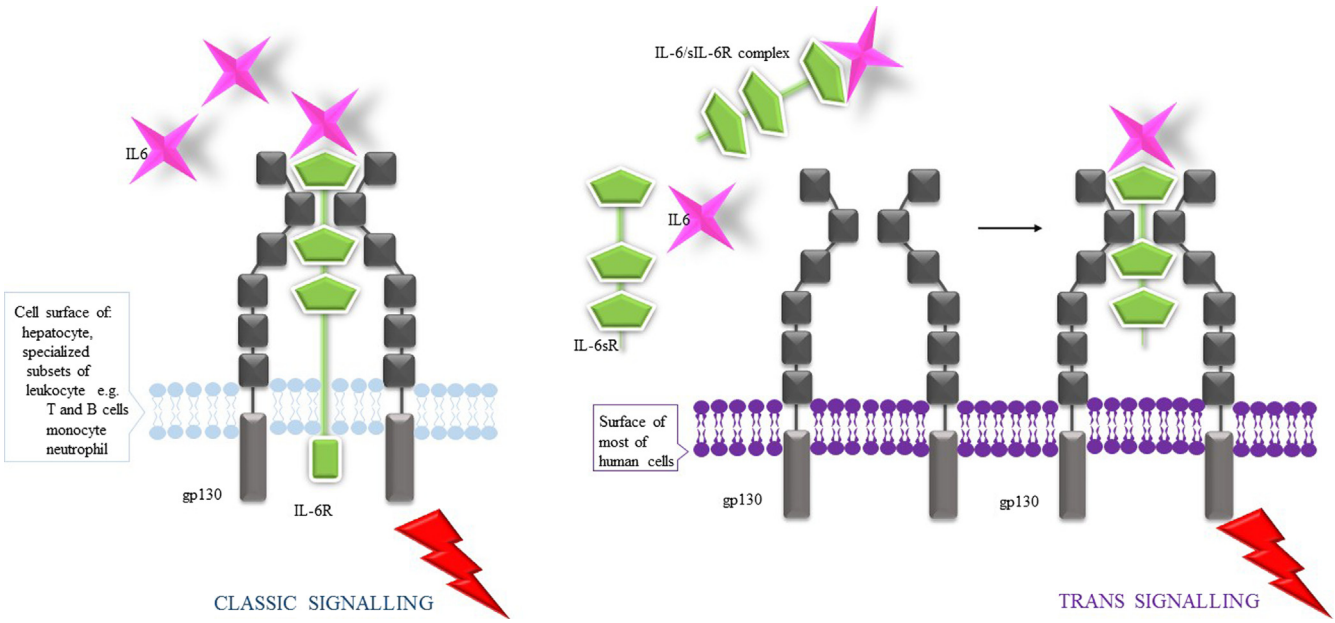

Fig. 1. Interleukin-6 (IL-6) signal transduction. In IL-6 classic signaling, IL-6 binds first to the membrane-bound nonsignaling IL-6R. After recruitment of 2 gp130 molecules, the signaling complex is formed and signal transduction is induced. In IL-6 transsignaling, IL-6 binds to the sIL-6R. The IL-6/sIL-6R complex stimulates cells that do not express IL-6R or cells from which the IL-6R has been shed or that still express the IL-6R. As gp130 is expressed in most human cells, the IL-6/sIL-6R complex is able to affect almost every cell. (Color version of figure is available online.)