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Original article

Activation of the kynurenine pathway predicts poor outcome in patients with clear cell renal cell carcinoma

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Abstract

Objective: To investigate the expression of the kynurenine (KYN) pathway components and the prognostic role of the KYN-to-tryptophan ratio (KTR) in a cohort of patients with clear cell renal cell carcinoma (ccRCC).

Materials and methods: The expression of KYN pathway components was investigated by tissue microarray-based immunohistochemistry, indirect immunofluorescence, and confocal microscopy analysis in 100 ccRCC cases and 30 normal renal samples. The role of this pathway in sustaining cancer cell proliferation, migration, and chemoresistance was evaluated. In addition, tryptophan and KYN concentrations and their ratio were measured in serum of 195 patients with ccRCC using a sandwich enzyme-linked immunosorbent assay. The role of KTR as a prognostic factor for ccRCC cancer-specific survival (CSS) and progression-free survival (PFS) was assessed.

Results: Tissue microarray-based immunohistochemistry and indirect immunofluorescence staining showed an increased signal for KYN pathway components in ccRCC. Kaplan-Meier curves showed significant differences in CSS and PFS among groups of patients with high vs. low KTR. In particular, patients with high KTR values had a 5-year survival rate of 76.9% as compared with 92.3% for subjects with low levels ($P < 0.0001$). Similar findings were observed for PFS (72.8% vs. 96.8% at 5 y). At multivariate analysis, KTR was an independent adverse prognostic factor for CSS (hazard ratio $= 1.24$, $P = 0.001$), and PFS (hazard ratio $= 1.14$, $P = 0.001$).

Conclusions: The involvement of the KYN pathway enzymes and catabolites in ccRCC occurs via both immune and nonimmune mechanisms. Our data suggest that KTR could serve as a marker of ccRCC aggressiveness and as a prognostic factor for CSS and PFS. © 2017 Elsevier Inc. All rights reserved.

Keywords: Renal cell carcinoma; Cancer metabolism; Kynurenine; Indoleamine 2,3-dioxygenase; Aryl hydrocarbon receptor

1. Introduction

Renal cell carcinoma (RCC) is one among the most common cancers in the United States, with 63,990 estimated new cases, and 14,400 estimated deaths in 2017 [1].

The pathogenesis of RCC is still poorly understood, although cigarette smoking, obesity, hypertension, diabetes,

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and end-stage renal disease have been recognized as common risk factors [2–4]. In recent years, emerging evidence has confirmed that metabolic reprogramming is a cancer hallmark and has shown that many genes involved in the RCC pathogenesis play an important role in controlling cell metabolism [5–10]. Moreover, RCC is considered an immunogenic tumor on the basis of several observations that demonstrated a significant immune infiltrate in tumor stroma in association with T-cell dysfunction, the incidence of spontaneous regression, and a partial response to immunotherapy [11]. Multi-omics analysis of gene, protein, and metabolite expression profiles of biological specimens has led to the identification of potential biomarkers for early diagnosis, risk assessment, and outcome prediction, although none of these is currently recommended in clinical practice [12–14].

Tryptophan (TRP) is an essential amino acid that is metabolized by 3 main pathways: incorporation into proteins, serotonin production, and the formation of kynurenine (KYN) (Fig. 1A).

The conversion of TRP to KYN is mediated by 2 enzymes: indoleamine 2,3-dioxygenase (IDO1) and tryptophan 2,3-dioxygenase (TDO). Recently, a novel IDO1 paralogue has been discovered, named IDO2, whose role in TRP metabolism and cancer biology remains unclear. IDO1 expression, which is the rate-limiting enzyme for the TRP catabolism, can be induced in response to interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha stimulation.

In the past decade, many studies have shown that activation of this pathway plays an important role in cancer progression, through the action of 2 mechanisms, namely TRP depletion and the accumulation of immunosuppressive metabolites such as KYN [15]. In addition, a part of the protumorigenic role of KYN seems to be mediated by its interaction with the aryl hydrocarbon receptor (AhR) on immune and cancer cells [16].

In this study, we investigated the expression of the KYN pathway components in tissue specimens derived from patients with clear cell RCC (ccRCC), and characterized the IDO1+ circulating and tumor-infiltrating immune cells. We next evaluated the serum levels of TRP, KYN, TNF-α, and IFN-γ, and assessed the prognostic role of the KYN-to-TRP ratio (KTR) for ccRCC cancer-specific survival (CSS) and progression-free survival (PFS). Finally, we explored the possibility to target KYN/AhR axis to decreased cancer cell viability and migration, and increased sensitivity to chemotherapy.

2. Materials and methods

2.1. Metabolite extraction and chromatography/mass spectrometry of TRP and KYN

Primary renal tumor ($n = 40$) and nonneoplastic tissues ($n = 20$) were collected from 40 patients who underwent radical or partial nephrectomy for ccRCC. All tissue

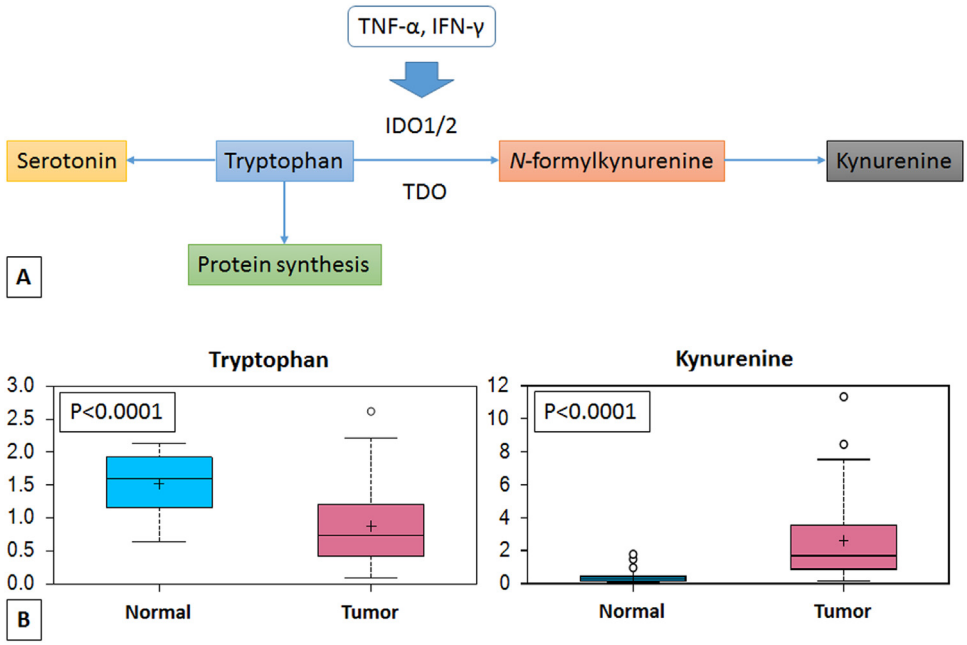

Fig. 1. (A) Tryptophan (TRP) metabolism. TRP is transformed to *N*-formylkynurenine by indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, and tryptophan 2,3-dioxygenase (TDO). *N*-formylkynurenine is then degraded by formamidase to produce kynurenine. Tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) are the most important inducers of IDO1 expression. (B) Human kidney samples were obtained by nephrectomy and metabolites were extracted for metabolite profiling by LC/MS analysis. Tryptophan was reduced, whereas kynurenine was significantly increased in primary ccRCC (tumor) compared to benign kidney tissue (normal). *y*-axis: metabolite relative amount. LC/MS = liquid chromatography/mass spectrometry. (Color version of figure is available online.)

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