Hesperetin is a potential therapy for metastatic renal cell carcinoma

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Abstract

Renal cell carcinoma is the most frequent and lethal malignant tumor of kidney in adults. Current therapeutic strategies have not satisfactory effect against metastatic renal cell carcinoma. Previous research indicated hesperetin had antineoplastic activity through a variety of molecular mechanisms. However, the effect of hesperetin on metastatic renal cell carcinoma through glycolysis inhibition has not been reported before. It comes up a possibility that hesperetin is a potential therapy for metastatic renal cell carcinoma, and glycolysis inhibition might be its potential mechanism.

Key words: Hesperetin; Metastatic renal cell carcinoma; Glycolysis.

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Background

Renal cell carcinoma (RCC) is a common malignant tumor in urinary system. It was estimated that there were 65150 new cases of RCC and 13680 deaths in the United States in 2013[1]. About one-third of patients have metastatic disease at presentation, a median survival of 7 to 11 months, and 5 year survival of 10% [2]. The treatment of metastatic RCC is still a challenge for urologists, as it is resistant to traditional chemotherapy and radiotherapy [3]. Immunotherapy with interferon-alpha or interleukin-2 was a frequently used strategy in the past decades. However, only 25-30% responses rate was reported according to previous studies and serious adverse effects had been observed in patient's undergone immunotherapy. Several targeted drugs have been used as first line treatment for metastatic RCC, and results of clinical research demonstrated that they were signify-cantly better than immunotherapy [4]. Howe-ver, side effects such as fatigue and diarrhea occurred in nearly 30% of patients and laboratory abnormalities were observed in 42% of patients [5], and long-term clinical benefit need to be further observed. In addition, the cost of targeted treatment is an important issue in many developing countries as well.

Hesperetin is a flavanone found in citrus

fruits such as oranges and grapefruits. It has previously been reported to decrease lipid levels and to decrease secretion of free fatty acids [6, 7]. Most recent studies indicated that hesperetin had antineoplastic activity on prostate cancer, breast cancer, colon cancer and carcinoid cancer [8-11]. The antineoplastic effect of hesperetin to these cancers occurs through a variety of molecular me-chanisms. However, the application of hespe-retin on metastatic RCC has not been reported.

Hypothesis

Most cancer cells depend primarily on glycolysis for their energy production and show increased glycolysis known as "Warburg effect" [12]. For many cancers, the specificity and sensitivity of FDG-PET to identify primary and metastatic lesions is near 90%, which is based on increased glucose uptake of cancer cells [13]. The results of a published study showed that metastatic RCC could be diagnosed with FDG-PET, and PET positive lesions were associated with prognosis [14]. Hesperetin is known to decrease basal glucose uptake in U937 mononuclear cells, although the mechanism is largely unknown [15]. Based on these findings, we hypothesized that hesperetin could be used to treat metastatic RCC mainly through inhibition of the glycolysis.

Discussion

Cancer cells have high rates of glycolysis partly due to overexpression of glucose transporters [16]. RCC specimens revealed a highly significant increase in the expression of glucose-transporter 1 (GLUT-1) compared to the corresponding normal kidney tissue [17]. Specifically targeting glucose uptake through GLUT1 could selectively kill RCCs [18]. It has been shown that hesperetin suppresses glucose uptake by down regulation of GLUT1 in breast cancer cells [9]. Similarly, hesperetin might reduce the glucose uptake via regulation of GLUT1 expression, and then inhibit proliferation of RCC.

A key regulator of glycolytic response is the transcription factor hypoxia-inducible factor-1α(HIF1α). For example, in renal cell carcinoma cell line RCC4, which has constitutive high HIF1α level because of VHL mutation, introducing VHL in the cell line could restore normal HIF1α and greatly reduce aerobic glucose consumption rates [19]. A cross talk between the NF-kB pathway and the HIF pathway has been documented extensively in protein level. In pulmonary artery smooth muscle cells, expression of the NF-kB enhanced HIF-1αmRNA levels, whereas blocking of NF-kB attenuated HIF-1αmRNA induction by hypoxia [20]. Considering hesperetin could suppress NF-kB and related gene expressions in rats kidneys [21]. It is possible that hesperetin could down regulate HIF-1α by decreasing NF-kB expression in RCC.

Upregulated glycolysis often results in increased intratumoral lactate concentrations which is associated with metastasis in some cancers [22]. Furthermore, overexpression of GLUT1 is associated with invasion in human cancers [23]. These facts make it possible that hesperetin decrease the incidence of metastasis and inhibits metastatic lesion through down regulation of glycolysis and GLUT1 expression.

Signal transducers and activators of transcripttion (STAT) mediate the signaling downstream of cytokine and growth factor receptors, and play a role in cancer [24]. STAT3 induces aerobic glycolysis in STAT3 dependent tumor cell lines. Inhibition of STAT3 tyrosine phosphorylation in tumor cell lines down regulates glycolysis prior to leading to growth arrest and cell death [25]. In renal tumors, over stimulation of STAT3 was observed and was probably responsible for the cell proliferation induced by cytokine inerleukin-6 (IL-6) [26].

A research on animal model of arthritis revealed hesperetin suppressed the level of IL-6 in serum and expression of IL-6 mRNA in synovium, and then decreased mRNA expression of JAK2 and STAT3 as well as protein expression [27]. These findings suggest that hesperetin might down regulate glycolysis through suppression of IL-6-JAK2-STAT3 signaling pathway, which should result in tumor cells death.

It has been reported that glycolytic inhibition can improve response to conventional chemotherapy and radiation [33]. Hesperetin might significantly improve therapeutic effect based on current treatment strategies by glycollytic inhibition. Concentration and accumulation in target tissues are another important issue for an ideal drug, biochemical analysis demonstrated that concentration of hesperetin was high in kidney tissue which was obtained from rats fed on hesperetin diet [34].

Conclusion

Although a few researches revealed that citrus flavonoids had chemopreventive effects such as antioxidant suppression of carcinogenesis, apoptosis and cell cycle regulation [35], the effectiveness of hesperetin for metastatic RCC teatment remains unclear. This hypothesis showed that hesperetin might inhibit glycolysis by several possible molecular mechanisms, which suggest hesperetin was hoped to be a promising drug for metastatic renal cell carcinoma.

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