Hepatocellular carcinoma (HCC) is the most common type of liver cancer [1], and it accounts for the third leading cause of cancer-related mortality in the world [2]. Even though it is widely believed that the occurrence of HCC is closely related to liver cirrhosis and viral hepatitis infection [3], there is an increasing body of evidence which reveals that HCC is associated with insulin resistance (IR) and type 2 diabetes mellitus (DM). Firstly, DM is an independent risk factor for HCC as shown by meta-analysis reports [4]. Secondly, the development of HCC is positively associated with DM duration. Thirdly, DM shows synergistic effects with other risk factors for HCC occurrence. Fourthly, diabetic patients have a significantly high rate of HCC recurrence after liver transplantation [5]. Also, it is reported that HCC patients with DM have an increased 1-year mortality compared to HCC patients without DM [6].

IR can result in hyperinsulinemia, a condition characterized by an excess level of circulating insulin relative to blood glucose level [7]. In the context of IR or hyperinsulinemia, insulin-like growth factor 1 (IGF-1) appears to be a most causative factor for promoting DM related HCC mediated by its role in proliferation and inhibition of apoptosis [8]. Hung CH and others demonstrated that in the presence of IR or hyperinsulinemia, excess insulin competes for the binding to IGF-binding proteins (IGFBP), leading to the increased levels of free serum IGF-1 [9-11]. The free serum IGF-1 then binds to the IGF-1 receptor (IGF1R), resulting in mitosis and cell proliferation [12]. Consistent with the demonstration mentioned above, exogenous insulin or second-
generation sulphonylurea increase the free serum IGF-1 concentration, and the use of these agents is reported to increase HCC risk for the patients with liver cirrhosis [13, 14]. Also, the overexpression of IGF-1 and its immediate downstream target insulin receptor substrate-1 (IRS-1) has been reported in liver cancer [15]. Interestingly, the expression of the IGF1R can be induced by ROS in both mRNA and protein level, and ROS is one of the significances in IR-related chronic liver diseases [16]. On the other hand, IGF1R antagonist picropodophyllin (PPP) induces the apoptosis in human HCC selectively [17]. In summary, IGF-1 signaling plays a central role in IR-related HCC.

As a master metabolic regulator and energy sensor, AMP-activated protein kinase (AMPK) is tightly regulated in liver [18]. Altered levels of AMPK activity are linked to many human cancers, including HCC, but the exact linkage between AMPK activity and its significance in HCC has not yet been found. Zheng L and colleagues showed that the level of phosphor-AMPK (Thr 172) was significantly reduced in both human primary and cultured HCC cells, and they further showed that low phospho-AMPK was an independent prognostic factor for HCC recurrence [19]. As a result, metformin which specifically activates AMPK is reported to decrease the HCC risk for the diabetic patients with either liver cirrhosis or HCC [20]. The therapeutic effect of metformin on HCC has been partially revealed. NF-κB and IL-6/STAT 3 signaling pathways are inhibited by metformin-mediated AMPK activation and the interference to these pathways lead to cell cycle arrest, senescence and apoptosis in HCC [21]. Similar to metformin treatment, the other AMPK signaling activator, 5-aminoimidazole-4-carboxamide-1-h-D-ribofuranoside (AICAR) is also shown to suppress the proliferation of HCC both in vitro and in vivo [22].

Even though both IGF-1 and AMPK signaling pathways are fundamental in HCC, the
potential linkage between two phenomena has been overlooked. Moreover, the reason AMPK is down-regulated is unknown. However, there is a growing body of evidence which shows that these two pathways are interrelated in liver diseases and other organisms. For example, AMPK activity can be directly modulated by NAD+ dependent protein deacetylase SIRT-1. The extent of phosphorylation on AMPK Thr 172 can be enhanced by SIRT-1[23]. However, Tran D and et. al demonstrated that prolonged IGF-1 signaling inhibited SIRT-1’s deacetylase activity[24]. Troncoso R and colleagues showed that IGF-1 treatment could reduce the phosphorylation level of AMPK in cardiomyocyte [24]. Moreover, it also has been reported that insulin/IGF-1 can inhibit AMPK Thr 172 phosphorylation through protein kinase B/Akt complex in the periphery nervous system [25]. Conclusively, IGF-1 signaling pathway can directly down-regulate AMPK activity status, so as to negatively affect the entire AMPK pathway. On the other hand, however, IGF-1 can modulate the activity of AMPK indirectly. One significant evidence is the transcription factor Forkhead box protein (FOXO). AMPK enhances FOXO’s transcriptional activity by phosphorylation [26]. On the contrary, IGF-1/Akt pathway phosphorylates and sequestrates FOXO out from the nucleus to cytoplasm, and thus inhibits its transcriptional activity. AMPK can activate TSC1/TSC2 complex by phosphorylation, which in turns inhibits mTORC1 [27]. On the contrary, Miyazaki M and et al. demonstrated that IGF-1 signaling can translocate TSC1/TSC2 complex to the cytosol and thus diminish the AMPK-mediated TSC1/TSC2 inhibition on mTORC1 [28]. Besides, ERK, as one of the most important downstream targets of IGF-1 signaling pathway, is found to inhibit AMPK phosphorylation, given that the application of ERK inhibitor can significantly reverse the inhibition of AMPK in cardiac fibroblast [29]. As a consequence,
we infer that IGF-1 mediated pathways may inhibit AMPK signaling by multiple dimensions.

In summary, we hypothesize that in the IR related HCC, IGF-1 signaling pathway inhibits AMPK signal cascade either directly or indirectly and thus promotes HCC occurrence. Due to the inhibitory link between IGF-1 and AMPK signaling, we further hypothesize that specific IGF-1 antagonist and AMPK agonist may have a significant synergistic effect. Therefore, we think that the application of PPP together with metformin will have greater efficacy in treating human HCC.

Reference