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Editorial

Hormonal control of the metabolic machinery of hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most fatal malignancies worldwide. It is an aggressive cancer with low cure rate, frequent metastasis, and highly resistant to conventional chemotherapies. Better knowledge regarding the molecular and metabolic alterations in HCC will be instrumental to the development of novel therapeutic interventions against HCC. In the August 2015 issue of *Hepatology*, Nie *et al.* reports an important molecular pathway that contributes to the Warburg Effect in HCC. They have beautifully demonstrated that the loss of a component of a hormonal system, the mineralocorticoid receptor (MR), reprogrammed the metabolic machinery of HCC cells to aerobic glycolysis through the miR-338-3p-PKL/R axis. The implication could be that in addition to drugs that directly target the metabolic enzymes in cancer cells, more translational efforts could be focused on the development of drugs that involve the activation of the MR-aldosterone system or other hormonal systems to target the Warburg effect.

Keywords: Mineralocorticoid receptor (MR); aerobic glycolysis; miR-338-3p-PKL/R axis

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Hepatocellular carcinoma (HCC) remains one of the most fatal malignancies worldwide. High death rate in HCC is mostly attributed to the lack of curative therapy and late symptom presentation. Only a minority of HCC patients are eligible for surgical resection or liver transplantation due to poor liver functions or presence of metastasis. Furthermore, HCC has a high recurrence rate and is highly resistant to conventional chemotherapies. So far, there is only one FDA-approved targeted therapy for advanced HCC patients, but its effect is only modest (1). Better knowledge regarding the molecular and metabolic alterations in HCC will be instrumental to the development of novel therapeutic interventions against HCC.

Warburg effect and hepatocellular carcinoma (HCC)

Liver is a center that coordinates the major metabolic events in our body. During the development of HCC, in the cancer cells, the normal hepatocytic functions are lost, accompanied by the acquisition of new metabolic traits that support the increased nutrient requirement for HCC cells. HCC cells prefer to metabolize glucose by glycolysis over oxidative phosphorylation to produce energy even in the presence of O_2, a cancer hallmark which is also named the Warburg Effect (2). Although less energy efficient, this metabolic shift maximizes the production of anti-oxidants and building blocks for rapid cell division (3). In the August 2015 issue of *Hepatology*, an elegant article by Nie *et al.* reports an important molecular pathway that contributes to the Warburg Effect in HCC (4). Nie *et al.* demonstrated that down-regulation of the mineralocorticoid receptor (MR) in HCC led to down-regulation of its transcriptional target, miR-338-3p, which resulted in the up-regulation of pyruvate kinase (PK) L/R and subsequently increased glycolysis (4). PK is a glycolytic enzyme which catalyzes the last step of glycolysis, transferring a phosphate group from ADP to phosphoenolpyruvate forming pyruvate and ATP. As pyruvate diverges into glycolysis and TCA cycle, PK determines the metabolic flux into glycolysis and

oxidative phosphorylation. PK has 4 isoforms which are derived from 2 genes, the *PKL* and *PKM*. The *PKL* gene produces the PKL and PKR isoforms, the transcriptions of which are initiated from two different tissue-specific promoters. The *PKM* gene produces PKM1 and PKM2 by alternative splicing and resulting in a 9th and 10th exon-containing PKM isoforms. PKL is highly expressed in liver and kidney. PKR is highly expressed in red blood cells. PKM1 is highly expressed in muscle, brain, and bladder. PKM2 is particularly abundant in cancer cells. PKM2, a less active isoform as compared to PKM1, favors tumor growth as PKM2 channels glucose intermediates from the TCA cycle to glycolysis (5,6). Most studies in the field compare the biochemical and oncogenic properties of PKM2 and PKM1 without taking into account of the PKL and PKR isoforms. Nie *et al.* beautifully showed that PKL/R isoforms enhanced the glycolytic flux of HCC cells and promoted the Warburg Effect (4). The deregulation of PKL is particularly important in the context of HCC and liver, as PKL is highly expressed in liver but not in other tissues. Of note, this study did not distinguish the roles of PKL and PKR. Our previous study showed that PKR expression was barely detectable in HCC and normal liver tissues (7), suggesting that effects observed by Nie *et al.* should be mediated mostly by PKL but not PKR. A long-standing question as to why cells of different tissue contexts express and require different PK isoforms is yet to be addressed.

MiRNAs and pyruvate kinase (PK)

As PKL/R and PKM1/2 isoforms are derived from *PKL* and *PKM* genes, respectively, PKL/R and PKM1/2 share different 3' untranslated regions (3'UTR). 3'UTR is recognized and bound by the miRNAs with complementary seed sequences, mediating degradation of the target mRNAs or translational repression (8). Therefore, PKL/R and PKM1/2 are regulated by different sets of microRNAs (miRNAs). Mounting evidence has documented those miRNAs that interfere with the 3'UTR of PKM1/2. MiR-122, miR-let-7a, and miR-29b have been shown to directly interact and suppress PKM2 expression in various cancer models (7,9,10). PKM2 is known to be a transcriptional target of c-myc (11). MiR-290/371 cluster represses a transcriptional repressor of c-myc, Mdb2, thereby promoting c-myc-induced PKM2 expression and glycolysis in embryonic stem cells (11). While most studies tilt to reveal the miRNA regulation on PKM2, Nie *et al.* provides the first report to establish the link between miRNA and PKL/R (4). In HCC cells, Nie *et al.* showed that miR-338-3p suppressed PKL/R and confirmed that miR-338-3p inhibited glycolytic flux (4). They also demonstrated that miR-338-3p and PKL/R expression levels were inversely correlated in human HCC samples (4). Intriguingly, they showed that miR-338-3p expression was controlled by a transcription factor, MR in human HCC (4).

Mineralocorticoid receptor (MR) system in liver

MR is also known as the aldosterone receptor as it is activated by its ligand, aldosterone, a steroid hormone produced by the adrenal gland. The MR-aldosterone system is particularly important to the kidney (12). Upon stimulation by aldosterone, MRs of the renal cells are translocated into the nucleus and bind to promoters of genes to activate their transcription to promote sodium and water retention and reduce potassium concentration in the blood, thereby increasing blood pressure. When blood flow in the kidney is decreased, renal cells produce renin which converts the angiotensinogen which is generated by the liver to angiotensin I and subsequently angiotensin II. Angiotensin II in turn stimulates renal cells to secrete aldosterone. The renin-angiotensin-aldosterone system is mainly regulated by the kidney and liver and plays an essential role in blood pressure maintenance. Increasing evidence has shown that MR expression is not restricted to renal cells but in different types of cells in the central nervous system, heart, blood vessels, sweat glands, brown adipose tissue, and colon (13). Nie *et al.* documented that MR could be detected in normal liver and was under-expressed in around 80% of HCC cases (4). This important clinical observation suggests that there may be some unknown functions of MR in the liver and HCC patients might have impairment in the renin-angiotensin-aldosterone system.

Taken altogether, Nie *et al.* have beautifully disclosed that the loss of a component of a hormonal system, the MR, reprogrammed the metabolic machinery of HCC cells to aerobic glycolysis through the miR-338-3p-PKL/R axis (4). In the coming future, in addition to drugs that directly target the metabolic enzymes in cancer cells, more translational efforts should be focused on the development of drugs that involve the activation of the MR-aldosterone system or other hormonal systems to target the Warburg Effect.

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Footnote

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Comment on: Nie H, Li J, Yang XM, *et al*. Mineralocorticoid receptor suppresses cancer progression and the Warburg effect by modulating the miR-338-3p-PKLR axis in hepatocellular carcinoma. Hepatology 2015;62:1145-59.

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