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<th><strong>Title</strong></th>
<th>Hormonal control of the metabolic machinery of hepatocellular carcinoma</th>
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<td><strong>Author(s)</strong></td>
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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 O2, 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, 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-PKLR 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-PKLR axis

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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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Conflicts of Interest: IO Ng is Loke Yew Professor in Pathology. The other authors have no conflicts of interest to declare.


References


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