

Modularity of the Metabolic Gene Network as a Prognostic Biomarker for Hepatocellular Carcinoma

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Short Abstract — We analyzed the modular expression patterns of metabolism genes for 371 hepatocellular carcinoma samples from the Cancer Genome Atlas. We found that higher modularity significantly correlated with glycolytic phenotype, later tumor stages, higher metastatic potential, and cancer recurrence, all of which contributed to poorer prognosis. Among patients with recurred tumor, we found the correlation of higher modularity with worse prognosis during early to mid-progression. Furthermore, we developed metrics to calculate individual modularity, which was shown to be predictive of cancer recurrence and patients' survival. Our conclusion is that more aggressive HCC tumors had more modular expression patterns of metabolic genes.

Keywords — modularity; metabolism; hepatocellular carcinoma; HCC; HIF-1; AMPK; prognosis

I. BACKGROUND

HEPATOCELLULAR carcinoma (HCC) is a primary malignancy of the liver, and it is the third leading cause of cancer mortality worldwide [1]. We here aimed to analyze cancer-associated gene networks of HCC samples to gain insight into the complex biological systems underlying tumor progression.

We chose the previously identified AMPK and HIF-1 downstream genes to quantify the activities of the two main metabolism phenotypes in HCC, OXPHOS and glycolysis [2]. Modularity was chosen to quantify the modular gene expression patterns. Previous theory developed by Deem predicts that more modular gene expression pattern corresponds to more aggressive tumor [3].

II. RESULTS

There existed a strong anti-correlation between the AMPK activity and HIF-1 activity across all 371 samples. The expression pattern of these genes was highly modular and consisted of two modules, one containing mainly AMPK-downstream genes and the other HIF-1-downstream

genes.

A. Modularity and cancer status

Group modularity calculation showed that the OXPHOS group had the lowest mean modularity and glycolysis group had the highest mean modularity. Survival analysis showed that glycolysis group had the worst survival and OXPHOS had the best survival.

Similarly, samples at stage II-IV had higher modularity than those at stage I. Stage II-IV samples also had worse survival than stage I samples. Samples with higher metastatic potential had higher modularity and worse survival. Samples that recurred in a certain time had higher modularity and worse survival than those did not in the same amount of time. Among patients with recurred tumor, there was correlation of higher modularity with worse prognosis during early to mid-progression, up until about 8 months before recurrence.

B. Individual modularity and prediction

We defined individual modularity and correlated it with probability of no recurrence in 12 months and probability of survival within 24 months. A high value of individual modularity was shown to be predictive of poor prognosis. Individual modularity values of $M > 0.6$ correlated to survival and non-recurrence probabilities less than 0.4.

III. CONCLUSION

Higher modularity of cancer-associated gene network of HCC samples significantly correlated with glycolytic phenotype, later tumor stages, higher metastatic potential, and cancer recurrence, all of which contributed to poorer prognosis. Among patients with recurred tumor, higher modularity correlated with worse prognosis during early to mid-progression. The developed individual modularity was shown to be predictive of cancer recurrence and patients' survival. Our conclusion is that more aggressive HCC tumors had more modular expression patterns of metabolic genes.

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