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Prognostic role of the expression level of angiogenesis markers in hepatocellular carcinoma by bioinformatics analysis

Miao YD *et al*. Angiogenesis markers in HCC

Abstract

The expression of angiopoietin-1 (ANGPT1), ANGPT2, vascular endothelial growth factor A (VEGFA), VEGFB, VEGFC, VEGFD and placental growth factor (PGF) is significantly higher in tumor samples than in normal samples in unpaired and paired hepatocellular carcinoma samples. ANGPT2, VEGFB, VEGFC, and PGF are primarily involved in regulating the process of the EMT activation pathway; ANGPT1 is primely involved in regulating the process of the RAS/MAPK and receptor tyrosine kinase (RTK) activation pathways; VEGFA is also engaged in the regulation of the RTK activation pathway; and VEGFD is mainly involved in regulating the activation of the tuberous sclerosis protein/mammalian target of rapamycin pathway. There is a prominent difference in overall survival between the groups with high and low expression of ANGPT2, PGF, VEGFA, and VEGFD. DFS was significantly shorter in the high ANGPT2, PGF, and VEGFA groups than in the low ANGPT2, PGF, and VEGFA groups.

Key Words: Hepatocellular carcinoma; Angiogenesis; Marker; Bioinformatics analysis; Pathway

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Core Tip: We found that the expression of angiogenesis markers is significantly higher in tumor tissues than in the normal group, whether in an unpaired or a paired hepatocellular carcinoma sample. These angiogenesis markers are mainly involved in regulating EMT pathway activation, RAS/MAPK and receptor tyrosine kinase pathway activation, and tuberous sclerosis protein/mammalian target of rapamycin pathway activation. In addition, there is a prominent distinction in overall survival between the groups with high and low expression of angiopoietin-2 (ANGPT2), placental growth

factor (*PGF*), vascular endothelial growth factor A (VEGFA), and VEGFD. DFS was significantly shorter in the high ANGPT2, high PGF, and VEGFA groups than in the low ANGPT2, PGF, and VEGFA groups.

TO THE EDITOR

We studied with an interest paper by Choi *et al*[1]. They evaluated plasma level of angiogenesis biomarkers in hepatocellular carcinoma (HCC) patients, then, assessed their roles of forecasting overall survival (OS) and progression-free survival (PFS), indicating that the plasma levels of angiopoietin-2 (ANGPT2) were related to tumor stage, liver function, and cancer invasiveness, demonstrating better accomplishment in predicting OS and PFS than alpha-fetoprotein (AFP), ANGPT1, or vascular endothelial growth factor (VEGF).

We appreciate the authors' unique perspective in exploring the prognostic role of plasma levels of ANGPT1, ANGPT2, and VEGF in HCC. However, there are still some errors in the original text and aspects of confusion for us. For example, the original article's survival curve in Figure 3B should represent the survival curve between the high and low expression subgroups of ANGPT2, which the authors incorrectly labeled as ANGPT1. Second, it is well known that VEGF is a family that includes VEGFA, VEGFB, VEGFC, VEGFD, VEGFE, and placental growth factor (PGF)[2,3], so to which *VEGF* do the authors refer in the text? Usually, VEGF is VEGFA, but the authors should have mentioned it in the text.

Moreover, it might make the results more significant if the authors improve this outcome through demonstrating the differential expression of ANGPT1, ANGPT2, and VEGF in normal tissues and HCC tissues as a whole, for example, the analysis of HCC samples in the Cancer Genome Atlas database using bioinformatics or own data. We found expression of ANGPT1, ANGPT2, VEGFA, VEGFB, VEGFC, VEGFD, and PGF was prominently higher in cancer samples than in corresponding normal samples in both unpaired and paired HCC samples (Figures 1A and 1B). Detailed statistical results are reported in Tables 1 and 2.

In our study, we also found that ANGPT2, VEGFB, VEGFC, and PGF are mainly involved in regulating the EMT activation pathway. ANGPT1 is prominently involved in regulating the process of the RAS/MAPK and receptor tyrosine kinase (RTK) activation pathway; VEGFA is also engaged in the regulation of the RTK activation pathway; and unlike several pathways mentioned above, VEGFD is mainly involved in regulating the activation of the tuberous sclerosis protein/mammalian target of rapamycin pathway (Figure 1C). These results are consistent with those of previously reported studies[4-7]. Our findings could be a supplement to Choi *et al*'s study[1]. In the future, we should explore in depth the roles played through ANGPT1, ANGPT2, and VEGF in the development of HCC.

We agree with Choi *et al*[1], who found that OS was remarkable shorter in high ANGPT2 and high AFP subgroups than in low ANGPT2 and AFP subgroups, respectively, and the differences in OS rates between high and low ANGPT1 subgroups and the high and low VEGF subgroups were not significant. Our study found that OS is prominently shorter in the high ANGPT2 subgroup, high PGF group, high VEGFA and high VEGFD group than in the low ANGPT2, PGF, VEGFA, and VEGFD groups (Figures 2A-D, all $P < 0.05$). However, there is no remarkable distinct in survival time between the groups with high and low expression of ANGPT1, VEGFB, VEGFC, and AFP (Figures 2E-H, all $P > 0.05$). Prognostic data for HCC came from Liu *et al*[8].

In addition, we also analyzed the differences in DFA between the groups with high and low angiogenesis marker expression. We found that DFS was remarkable shorter in the high ANGPT2, PGF, and VEGFA groups than in the low ANGPT2, PGF, and VEGFA groups (Figures 3A-C, all $P < 0.05$). However, there is no obvious distinct in DFS between groups with high and low expression of AFP, ANGPT1, VEGFB, VEGFC, and VEGFD (Figures 3D-H, all $P > 0.05$). Conversely, the above results confirm that the study performed through Choi *et al*[1] is worthy of attention and that our discover could be an addition to their research.

Statistical analysis

We utilized Software: R (version 4.0.3) to finish statistical analysis, dispaly the results. The differential expression analysis of angiogenesis marker between HCC tissues and corresponding normal tissues is performed using the Wilcoxon rank-sum test and showed results by R-package "ggplot2"[9]). Survival analysis was finished through log-rank test and COX regression a. Pathway analysis was using the online database: GSCALite (http://bioinfo.life.hust.edu.cn/web/GSCALite/)[10].

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