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FGL2/PROTHROMBINASE CONTRIBUTES TO HCC TUMOR GROWTH AND ANGIOGENESIS THROUGH THE MAPK PATHWAY

Y. Liu, Q. Zeng, J. Wang, X. li, X. Wang, D. Yang, X. Luo, **Q. Ning***
*Department of Infectious Disease, Tongji Hospital of Tongji Medical College, University of Science and Technology, Wuhan, China. *qning@tjh.tjmu.edu.cn*

Fibrinogen-like protein 2(fgl2) /prothrombinase has been identified as a procoagulant protein which directly generates thrombin from prothrombin without activation of the conventional coagulation cascade. Fgl2 has been found to be overexpressed in a number of human malignant tumors including human hepatocellular carcinoma(HCC), however, its functional role in malignancy remain largely unexplored. To define the role of tumor cell-associated fgl2 in tumor growth and tumor angiogenesis, we established a fgl2 stably knock down HCCLM6 cell line, a highly aggressive HCC derived cell line in which fgl2 expression was found upregulated in response to tumor necrosis factor-α(TNF-α) stimulation in a dose-dependent manner. Consequently, fgl2 depletion in HCCLM6 cells led to a delayed tumor growth and vascularization of HCC xenografts in nude mice. These changes were associated with decreased phosphorylation of extracellular signal-regulated kinases (ERK) but not p38 mitogen-activated protein kinase (p38-MAPK) in vivo. In vitro, fgl2 depleted HCCLM6 cells exhibit decreased proliferation and pro-angiogenic factors expression following TNF-αstimulation, associated with a higher susceptibility to TNF-αinduced apoptosis. One mechanism underlying this phenomenon that we discovered is that endogenous fgl2 enhanced TNF-αinduced MAPK pathway activation in HCCLM6 cells through both thrombin dependent and independent manner. However, exogenous recombinant fgl2 was found to induce phosphorylation of ERK and p38-MAPK only in thrombin dependent manner. Collectively, our data suggest that fgl2 expression in tumor is regulated by inflammatory cytokines, and that it contributes to tumor growth and tumor angiogenesis through thrombin dependent and independent activation of MAPK pathway.

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