

Beginnings of a “gene cloud” definition in hepatocellular carcinoma

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Comment on: Huang W, Chen Z, Shang X, *et al.* Sox12, a direct target of FoxQ1, promotes hepatocellular carcinoma metastasis through up-regulating Twist1 and FGFBP1. *Hepatology* 2015;61:1920-33.

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Hepatocellular carcinoma (HCC) is a major worldwide health burden with over 700,000 cases diagnosed annually (1). Proven risk factors include Hepatitis B and Hepatitis C infections, alcoholic liver disease and, more recently, non-alcoholic fatty liver disease (2,3). HCC is the major cause of death in patients with cirrhosis (2) and in most countries, the mortality rate nearly equals the incidence rate (4). To date, the definition of adequately sensitive and specific HCC biomarkers and signaling pathways has proven to be extremely complicated, in large part due to this cancer's genetic heterogeneity [both between patients and within individual patients (5,6)] as well as patient heterogeneity depending on the underlying risk factor(s) present and other patient background genetic determinants. As such, the future of improved HCC diagnosis, prognosis and treatment (or most any cancer for that matter) will likely rely on a combination of multiple biomarkers, enhanced imaging technologies and accurate clinical assessment of the patient (2,7).

Limin Xia's group report in this issue of *Chinese Clinical Oncology (CCO)* that Sox12, a transcription factor containing the SRY (sex determining region Y) related high mobility group box DNA binding domain, positively correlates with human HCCs that display aggressive clinical characteristics, including poor overall survival and higher recurrence rates post-surgical resection (8). Importantly, they demonstrate upstream (FoxQ1) and downstream (Twist1 and FGFBP1) effectors in Sox12-associated HCCs and thus begin to identify a “gene cloud” for HCCs with a poor prognosis.

I define a gene cloud as a group of genes that work

together to realize a particular biological process, such as a biochemical pathway or a gene signaling network. For example, the Wnt/ β -catenin signaling pathway involves a number of genes (c-Myc, Cyclin D1, Frizzled, Sox1, etc.) that can be thought of as comprising a “cloud”. Which genes are active or inactive in the cloud will determine the cloud's function, i.e., differentiation versus proliferation versus homeostasis (9,10). Clouds driving processes such as proliferation, EMT activation and dedifferentiation will differ between normal cells, premalignant cells, cancer cell tissues of origin, cancer subtypes (e.g., benign versus malignant) and even between different tumor nodules within the same patient. Our current understanding of gene ontology is vexed by the fact that most any given gene's function is entirely contextual: the same gene can have one particular function in a given cell type or disease state and an entirely different function in another. The great challenge of biology today is to comprehensively understand how each gene functions depending on its interaction with other genes, the cell differentiation environment and extracellular milieu. The “cloud” concept attempts to incorporate the contextuality of gene function beyond our currently simple gene ontology lists.

So it is important to define entire gene clouds to learn how each individual gene is functioning relative to the remaining gene cloud members. The size of a cloud will depend on the complexity of the process. For example, a “simple” biologic process such as initiation of cell proliferation may involve hundreds of genes whereas a complicated process such as malignant cancer potential

may involve thousands of genes. Xia's group has begun to scratch the surface of understanding an "HCC metastasis gene cloud" in demonstrating the synergy of Sox12/Twist1, Sox12/FGFBP1 and Sox12/FoxQ1 co-expression in more biologically aggressive tumors. Clearly, a single gene or even two genes together do not tell the whole story. The task of completely defining an entire gene cloud even in the simplest of biological processes is protean, but Xia and colleagues are on the right path.

HCC recurrence is known to be associated with many clinical factors, especially vascular invasion, tumor grade, tumor size/burden and, more often than not, Alpha Fetoprotein levels. Sox12 overexpression correlates with tumor encapsulation loss, microvascular invasion and higher TNM staging as per Xia's investigations, but how is Sox12 actually functioning? From what is known from other Sox gene family members in their regulation of specification and differentiation in various cell types (11), Sox12 may simply enable metastatic potential in HCC by enacting or participating in a dedifferentiation program. But might Sox12 be more specifically involved in cell growth deregulation or vascular invasion? Existing data and materials are in hand to address these questions and hopefully shed more light on Sox12's exact function in hepatocellular carcinogenesis (12).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

- Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;379:1245-55.
- Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014;63:844-55.
- White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol* 2012;10:1342-1359.e2.
- Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. *Hepat Med* 2012;4:19-37.
- Barry CT, D'Souza M, McCall M, et al. Micro RNA expression profiles as adjunctive data to assess the risk of hepatocellular carcinoma recurrence after liver transplantation. *Am J Transplant* 2012;12:428-37.
- Xie QY, Almudevar A, Whitney-Miller CL, et al. A microRNA biomarker of hepatocellular carcinoma recurrence following liver transplantation accounting for within-patient heterogeneity. *BMC Med Genomics* 2016;9:18.
- Schütte K, Schulz C, Link A, et al. Current biomarkers for hepatocellular carcinoma: Surveillance, diagnosis and prediction of prognosis. *World J Hepatol* 2015;7:139-49.
- Huang W, Chen Z, Shang X, et al. Sox12, a direct target of FoxQ1, promotes hepatocellular carcinoma metastasis through up-regulating Twist1 and FGFBP1. *Hepatology* 2015;61:1920-33.
- Kim M, Lee HC, Tsedensodnom O, et al. Functional interaction between Wnt3 and Frizzled-7 leads to activation of the Wnt/beta-catenin signaling pathway in hepatocellular carcinoma cells. *J Hepatol* 2008;48:780-91.
- Tsao CM, Yan MD, Shih YL, et al. SOX1 functions as a tumor suppressor by antagonizing the WNT/ β -catenin signaling pathway in hepatocellular carcinoma. *Hepatology* 2012;56:2277-87.
- Kamachi Y, Kondoh H. Sox proteins: regulators of cell fate specification and differentiation. *Development* 2013;140:4129-44.
- Chuang KH, Whitney-Miller CL, Chu CY, et al. MicroRNA-494 is a master epigenetic regulator of multiple invasion-suppressor microRNAs by targeting ten eleven translocation 1 in invasive human hepatocellular carcinoma tumors. *Hepatology* 2015;62:466-80.

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