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Commentary

Hepatocellular carcinoma reduces ATXN7L3 to evade estrogen-dependent growth suppression

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A R T I C L E   I N F O

Annually, more than 800,000 people are diagnosed with primary liver cancer world-wide, with more than 40,000 diagnoses in the United States alone [1]. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, representing 80–90% of all cases of liver cancer [1], and is the fourth most common cause of cancer-related death overall [1]. The risk factors for hepatocellular carcinoma include hepatitis B or C infection, alcoholic liver cirrhosis, non-alcoholic fatty liver disease, and certain toxins such as aflatoxin. HCC is highly invasive, and frequently presents with intrahepatic and remote metastases which significantly complicate treatment. In patients whose malignancy is non-invasive, surgical resection is a first line treatment that can often be curative. As long as the malignancy is localized to the liver, liver transplant remains the definitive treatment option for hepatocellular carcinoma. Several pharmacological options are also available, such as small molecule multikinase inhibitors (eg. Sorafenib, Lenvatinib) and immune checkpoint inhibitors (eg. Nivolumab). Survival across the world varies greatly in correlation with patient access to treatment options and early detection. In low-resource countries such as sub-Saharan Africa, median survival time is only 2.5 months, whereas in more developed countries such as Japan, median survival is 60 months [1]. For hepatocellular carcinoma that has metastasized beyond the liver, the 5-year survival rate is only 5.9% [2]. In a recent report in *EBioMedicine*, Sun et al. [3] examine the molecular mechanisms contributing to liver cancer and uncover specific signaling pathways that contribute to the body's anti-HCC defense effort.

An intriguing opportunity for treatment of liver cancers is to augment signaling pathways suppressing cancer growth. Research into the molecular progression of hepatocellular carcinoma has revealed the importance of estrogen in both primary prevention and inhibition of HCC growth [4]. At first glance, it may seem like low-hanging fruit to provide estrogen to HCC patients. However, the example of liver cirrhosis-driven HCC formation shows the answer is not so simple. The role of estrogen signaling is particularly intriguing because liver cirrhosis is a risk factor for HCC. However, cirrhosis also interferes

with the liver's function of estrogen metabolism, increasing levels of estrogen, which should be protective against HCC. Increases in estrogen due to cirrhosis can be significant. Patients with cirrhosis and other liver diseases exhibit signs of high estrogen, including gynecomastia, due to decreased estrogen metabolism. What can reconcile the protective effects of increased estrogen with the HCC-promoting effects of cirrhosis? Evidence suggests HCCs learn to suppress estrogen-dependent signaling. For example, expression of dysfunctional ERα variants in HCC is associated with worse prognosis [5]. Therefore, it is of particular interest to understand estrogen signaling with the hope of learning how to re-establish estrogen signaling in HCCs.

Sun et al. examine molecular mechanisms of estrogen signaling-mediated suppression of HCC growth, and reveal a very specific set of genes, gene products, and gene regulatory proteins important for this pathway's protective effect against HCC. Analysis of gene expression profiling databases hinted that expression of the Ataxin-7-like 3 (ATXN7L3) gene was strongly correlated with altered gene expression in HCC samples. When they examined HCC samples of patients, they found that levels of ATXN7L3 expression were decreased, and ATXN7L3 levels were negatively correlated with poor clinical outcomes for patients with HCC, indicating the importance of ATXN7L3 in prevention and attenuation of HCC. Sun et al. also found that protein ATXN7L3 is a coactivator for estrogen receptor alpha (ERα). Together, ATXN7L3 and ERα altered patterns of histone ubiquitination at a very specific set of genes. In particular, ATXN7L3 and ERα activated the expression of SMAD7, a known inhibitory factor for the TGF-β signaling pathway. When they expressed ATXN7L3 in a mouse model for HCC, tumor growth was reduced.

A role for ATXN7L3 in suppression of HCC might come as a surprise to some. ATXN7L3 is a subunit of the Spt-Ada-Gcn5-Acetyltransferase (SAGA) chromatin modifying complex [6]. Together with SAGA subunit ENY2, ATXN7L3 functions to activate the SAGA deubiquitinase USP22 [7]. Overexpression of USP22 is associated with increased tumor growth, metastasis, and risk of death from cancer [8]. Recently, ATXN7L3, ENY2, and USP22 were found to be capable of leaving SAGA to meet substrates at a distance [9]. While away from SAGA, ENY2 and

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ATXN7L3 can swap USP22 for either of deubiquitinases USP27x or USP51 [10]. The reason for this elaborate swapping mechanism and the signals that regulate swapping are not clear.

The findings of Sun et al. suddenly shed light on a possible explanation for ATXN7L3's participation in both cancer-promoting and cancer-preventing pathways. It is possible that interaction with ERα and deubiquitinase swapping work together to facilitate novel interactions that work to activate tumor-suppressing pathways instead of cancer promoting pathways. In the future, it will be exciting to pursue the mechanisms that allow ERα to switch ATXN7L3 from tumor promotor to tumor suppressor. Uncovering these may help to switch HCC and other cancers off with a flip of a signal.

Declaration of Cmpeting Interest

The authors do not have conflict of interest.`

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