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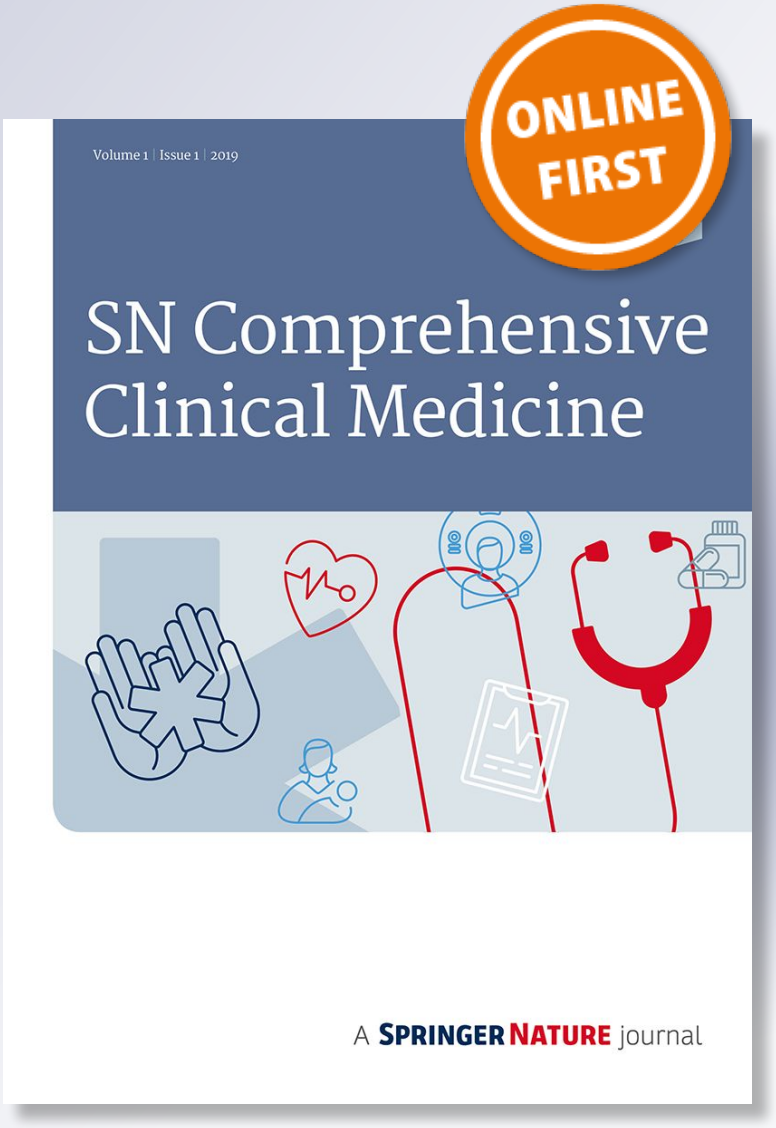

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MEDICINE

Oxytocin Receptor Genetic Alterations in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is among the leading causes of cancer-related deaths with a very poor prognosis. Consequently, there is an urgent need for better understanding the molecular mechanisms, novel prognostic biomarkers, and more effective treatment options. There is an emerging link between oxytocin (OXT), the oxytocin receptor (OXTR), and cancer. However, the role of OXT or the OXTR in HCC remains unknown. The research question of this study was as follows: are there genetic alterations in the oxytocin (OXT) and oxytocin receptor (OXTR) genes in hepatocellular carcinoma (HCC) patients and do these alterations impact overall survival and disease-free survival? In this retrospective study, we reviewed 360 individual HCC patient data from The Cancer Genome Atlas (TCGA) using cBioPortal accessed in April 2018. The data in The Cancer Genome Atlas are from various institutions in the USA. We found that 3% (11 of 360) of cases showed genetic alterations in the OXTR gene. The median months survival was lower for HCC cases with genetic alterations in the OXTR gene as compared to cases without genetic alteration in this gene (33.0 versus 60.84, respectively. Additionally, the median months disease-free survival was lower in cases with genetic alterations in the OXTR gene as compared to cases without alterations (8.64 versus 21.55, respectively). OXTR is a promising prognostic biomarker for HCC, and OXTR antagonists could have a future role as therapeutic agents for a subset of HCC patients. Further study of the detailed molecular mechanisms of OXT and OXTR in HCC is warranted.

Keywords Oxytocin receptor · Hepatocellular carcinoma · Genetic alteration · Oxytocin

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related deaths worldwide [1]. It is also the most common primary malignancy of the liver. HCC is often detected at advanced stages and most patients will therefore need systemic therapy, such as sorafenib. However, sorafenib therapy only minimally enhances patient survival. Due to the poor prognosis for HCC patients, the detailed molecular mechanisms of the disease need to be better understood to aid discovery of prognostic biomarkers and more effective therapeutic strategies.

Oxytocin is a nine-amino acid peptide hormone, synthesized mainly in the hypothalamus and secreted into the blood stream as an inactive precursor protein from the OXT gene and is activated upon binding to its G protein-coupled receptor, the oxytocin receptor (OXTR) [2]. OXT is traditionally mostly known for playing roles in the female reproductive system during pregnancy and lactation. However, newer studies have shown it to play roles in the male reproductive system as well. Even further, it has been shown to play important roles in stress, trust, anxiety, social interaction and bonding, and parental care [3, 4], and consequently on the neuropsychiatric disorders linked to these social behaviors. More recently, emerging evidence has linked OXT and OXTR to roles in various cancers [4]. Recent findings have shown that OXT promotes cell proliferation in breast, prostate, osteosarcoma, and lung cancers [5, 6]. To promote cell proliferation, OXT binds to its receptor which results in MAPK cascade activation, leading to transient ERK1/2 phosphorylation and cell proliferation [2]. While it is known that OXTR is expressed

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in liver tissues where it likely plays roles in regulating glycogen levels [7], a role for OXT and OXTR in HCC have not been reported to date.

Genetic alterations in several genes encoding proteins have been implicated in HCC pathogenesis. These include P53, P16, P73, APC, PTEN, IGF-2, BRCA2, SMAD2, SOCS, beta-catenin, retinoblastoma proteins, c-myc, and cyclin D1 proteins [8, 9]. Additionally, several signaling pathways are known to be involved in HCC development including MAPK pathway activation via the Ras protein leading to ERK1/2 activation and ultimately proliferation [8]. To our knowledge, no previous studies have tried to explore the correlation of OXT or OXTR genetic alterations and clinical features in HCC. This study aimed to assess the genetic alterations of OXT or OXTR and its correlation with overall survival and disease-free progression in HCC using data from The Cancer Genome Atlas (TCGA).

Methods

In this study, the cBioPortal for Cancer Genomics online analysis tool was used to analyze the genetic alterations (mutations, copy-number alterations, mRNA expression, protein expression in the OXT and OXTR genes in the cancer study "Liver Hepatocellular Carcinoma) using data from TCGA. The genes "OXT" and "OXTR" were entered into the input box. The data type priority "Mutation," "CNA (DNA copy-number alterations)," "mRNA expression," and "Protein expression" were selected. Clinical information of each patient with OXTR genetic alterations was also retrieved and presented in Table 1.

For survival analysis, Kaplan-Meier plots with a log rank test were performed to compare the overall survival and the disease-free survival of HCC with at least one alteration or without alteration in query gene(s). Samples with overexpression were identified by a threshold of $Z > 2$ (mean expression over 2 SDs) (Fig. 1). The a level was set at 0.05.

Results

It was found that 1.7% (6 out of 360) and 3.0% (11 out of 360) of the sequenced tissues from the HCC cases have genetic alterations in the OXT and OXTR genes, respectively. The OXT genetic alterations were amplification (1 case) and mRNA upregulation (5 cases) and the OXTR genetic alterations were either missense mutation (1 case), amplification (2 cases), or mRNA upregulation (9 cases). The median months survival was 33.02 for HCC cases with genetic alterations in the OXTR gene and 60.84 for cases without such alterations. Overall survival data was not available for the OXT gene. The median months disease-free was 8.64 for cases with alterations and 21.55 for cases without alterations in the OXTR gene as shown in Fig. 2. Table 1 shows the clinical features of each patient with either OXT or OXTR genetic alterations.

Discussion

To our knowledge, this is the first study to explore OXTR genetic alterations in HCC. Our analyses revealed that patients with genetic alterations in the OXTR gene have significantly poorer survival outcomes.

Table 1 Clinical characteristics of TCGA patients with OXTR genetic alterations in HCC

Patient no.	Genetic alteration	Gender	Race	Ethnicity	HCC risk factor	Disease-free status	Disease-free (months)	Diagnosis age (years)	Disease stage
1	OXTR	F	White	Not Hispanic	None	Recurred/processed	11.17	72	NA
2	OXTR	F	Asian	Not Hispanic	NA	NA	NA	61	Stage IIIC
3	OXTR	F	White	Not Hispanic	None	Recurred/processed	8.64	71	Stage IIIC
4	OXTR	F	White	Not Hispanic	Hepatitis C	Recurred/processed	14.85	45	Stage IIIA
5	OXTR	M	Asian	Not Hispanic	Alcohol consumption	Recurred/processed	8.57	61	Stage IIIA
6	OXTR	F	White	Not Hispanic	None	Recurred/processed	5.22	76	Stage II
7	OXTR	F	White	Not Hispanic	Alcohol consumption	Recurred/processed	35.84	61	Stage I
8	OXTR	F	Asian	Not Hispanic	None	NA	NA	51	Stage IIIA
9	OXTR	M	Black	Not Hispanic	Hepatitis B	Recurred/progressed	2.89	48	Stage II
10	OXTR	F	Asian	Not Hispanic	None	Disease-free	13.4	60	Stage III
11	OXTR	F	White	Not Hispanic	None	NA	NA	81	Stage I

F, female; *M*, male; *NA*, not applicable (data unavailable); *TCGA*, The Cancer Genome Atlas

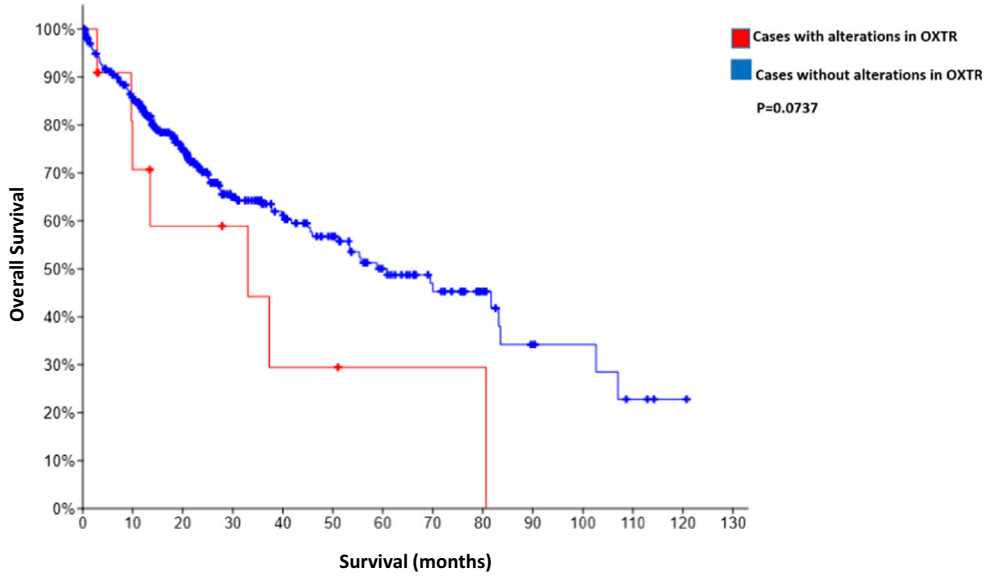

Fig. 1 Overall survival Kaplan-Meier estimate in hepatocellular carcinoma. The median months survival was 33.02 for cases with alterations (mutations, copy-number alterations, mRNA expression, protein expression and 60.84 for cases without alterations in the OXTR gene

Amico and colleagues had shown the presence of OXT in human pancreatic extracts which suggested the possibility of local synthesis of oxytocin especially since OXT is known to be an endocrine mediator of insulin and glucagon release [10]. There is also the possibility of OXT from the pancreas having a local effect on the liver, due to the proximity of these two organs. Importantly, OXT is a systemic hormone that could expectedly have widespread effects on all body organs, including the liver.

Unpublished data from our laboratory indicates that OXTR mRNA and protein overexpression is associated with human pancreatic cancer cell resistance to the chemotherapeutic agent gemcitabine. Thus, OXTR may play a role in pancreatic cancer chemoresistance. Given that HCC patients with OXTR genetic alterations have poorer survival outcomes than those without OXTR genetic alterations, it is possible that OXTR plays a role in HCC chemoresistance as well. Consequently, it would be important to conduct future studies to evaluate OXTR genetic alterations in a large cohort of HCC patients with varying responsiveness to sorafenib.

HCC cases with genetic alterations in the OXTR gene showed significantly lower median months survival as well as progression-free survival as compared to cases without OXTR gene alterations. These findings indicate the need for future experiments to elucidate the detailed molecular mechanisms of OXT and OXTR signaling in HCC. Notably, HCC cases with alterations in OXT had progression-free median months survival of 55.06 versus 20.99 for HCC cases without

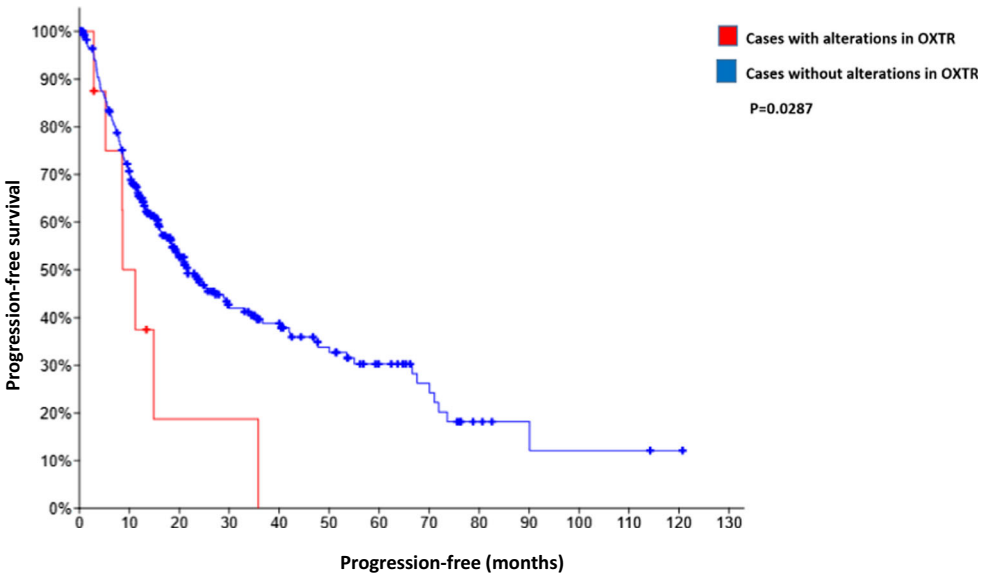

Fig. 2 Progression-free Kaplan-Meier estimate in hepatocellular carcinoma. The median months disease-free was 8.64 for cases with alterations (mutations, copy-number alterations, mRNA expression, protein expression and 21.55 for cases without alterations in the OXTR gene

OXT gene alterations. However, it is important to note that only 6 out of 360 (1.7%) HCC patients in this entire cohort had OXT gene alterations. Future studies are needed to further determine the clinical implications of this finding. The current data, nevertheless, suggests that OXT likely plays a different role from OXTR in HCC. It is critical that future studies clarify what these disparate roles and their underlying molecular mechanisms are.

Conclusions

Clearly, OXTR is a promising prognostic biomarker in HCC, and it is possible that OXTR antagonists could serve as therapeutic agents and be beneficial to a subset of HCC patients. Further investigation of the detailed molecular mechanisms of OXT and OXTR in HCC is warranted.

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Compliance with Ethical Standards

Conflict of Interest Olorunseun O. Ogunwobi is a Co-Founder of NucleoBio, Inc., a City University of New York start-up biotechnology company. There are no other conflicts of interest relevant to this article.

Ethical Approval The analysis was performed using publicly available de-identified data from The Cancer Genome Atlas. Ethical approval was unnecessary for this analysis.

Informed Consent There was no interaction with human subjects or identifiable human subject information. Hence, informed consent was unnecessary for this analysis.

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