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Role of LncRNA H19 in the Regulation of IGF-1R Expression: A Possible Association between Type 2 Diabetes and Hepatocellular Carcinoma: A Review Article

NOURA SHEHABELDIN, M.Sc.; NORA M. HUSSEIN, M.D.; HEBA K. MOHAMED, M.D. and MOHAMMED A.A. ZAHRAN, M.D.

The Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University

Abstract

Background: Hepatocellular carcinoma (HCC) is a common cancer that poses a heavy economic burden on the healthcare system. In Egypt, it is the most common cause of mortality and morbidity-related cancer. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. Cancer and type II diabetes (T2DM), the world's two most prevalent diseases, share many overlapping risk factors and predisposing pathological conditions. The exact mechanisms linking those two diseases are yet to be fully understood. One postulated linking pathogenetic pathway is the Insulin-Like Growth Factor1 Receptor (IGF-1R) axis, which is regulated by several non-coding RNAs, among which is the long Non-Coding RNA (lncRNA) H19.

Aim of Study: In this review, we aim to explore the relationship between H19 and IGF-1R in the literature and how their gene expression levels are modulated in the context of HCC and DM to investigate the probability of H19/IGF-1R being a pathophysiological link between HCC and DM that may become a therapeutic target for both diseases.

Materal and Methods: An organized search of the literature was conducted with focus on electronic databases including Pub Med/Medline, SCOPUS, and Google Scholar.

Results: No studies to date have investigated the relationship between H19 and IGF-1R in the context of HCC or diabetes. In other conditions however, the relationship between H19 and IGF-1R is a source of debate in the literature. Moreover, the expression level of H19 in HCC and in diabetes, as well as its role as a potential tumor suppressor versus an oncogene remain to be controversial.

Conclusion: The relationship between H19 and IGF-1R and the exact molecular mechanisms of their interactions in HCC and T2DM need further research to be elucidated.

Key Words: *HCC – DM – T2DM – IGF-1 R – Non-coding RNA – H19 – Gene expression.*

Correspondence to: Dr. Noura Shehabeldin,
E-Mail: noura_shehabeldeen@mans.edu.eg
noura_shehab_eldeen@yahoo.com

Introduction

LIVER cancer represents a global health challenge that has a growing incidence worldwide. It is the sixth most prevalent cancer worldwide, and the fourth leading cause of cancer-related death globally **[1,2]**. Liver cancer is a highly deadly tumor, with most cases detected at late stages and an incidence-to-mortality ratio approaching **[3]**. HCC is the most common form of liver cancer and accounts for about 90% of cases **[4]**. Egypt has the second highest rate of liver cancer incidence and mortality worldwide after Mongolia **[5]**. The strongest risk factor for HCC is cirrhosis from any etiology **[6,7]**. The major risk factors for HCC comprise viral infection by hepatitis B (HBV) or C (HCV), diabetes or obesity-related non-alcoholic steatohepatitis (NASH), and chronic alcohol consumption. These major risk factors appear to be shifting, with the prevalence of HBV and HCV declining and excess body weight and diabetes increasing in many regions **[8]**.

Ras/Raf/mitogen-activated protein kinase (MAPK) pathway is the pivotal signal transduction pathway involved in HCC development. This pathway is normally responsible for cell proliferation, cell growth, differentiation, and survival. The upstream molecules of this pathway are different receptor tyrosine kinases (RTKs), including Insulin-like growth factor1 receptor (IGF-1R) **[9]**. Notably, HCC tissue consistently showed an increased IGF1-R expression level in animal models **[10]**. Other notable pathways that are increasingly activated in HCC are the phosphatidyl inositol triphosphate kinase (PI3K)/alpha serine/threonine kinase (AKT)/ mammalian target of rapamycin (mTOR), Janus kinase (JAK)/Signal transducer and activator of

transcription (STAT) and Wnt/β-catenin pathways **[11,12]**.

Diabetes mellitus (DM) is a condition of chronic hyperglycemia that causes the failure of different organs **[13]**. The International Diabetes Federation (IDF) estimates that close to one in ten adults have DM, half of whom are unaware of their condition and are undiagnosed. DM is among the top 10 causes of death in adults. Egypt was ranked the 9th in the world in terms of number of people with diabetes (8.9 million) in 2019 **[14]**. The predominant form of DM is type II diabetes (T2DM), which accounts for 90% of patients with DM **[15]**. T2DM is characterized by progressive loss of β-cell insulin secretion subsequently occurring with a background of insulin resistance (IR) **[16]**.

The most commonly proposed model for the development of T2DM suggests that IR is the initiating event in T2DM which leads to hyperinsulinemia and finally defective β-cell insulin secretion **[17]**. In IR, excess visceral adipose tissue leads to IR in the skeletal muscles and liver, through metabolic crosstalk between adipocytes and the other organs **[18-20]**. Normally, insulin exerts its action through acting on RTKs such as the insulin receptor (INSR) and IGF-1R, which activate multiple signalling pathways within cells, including both the PI3K/AKT and MAPK signalling pathways. The result of activating the MAPK pathway is a variety of cellular responses, including regulation of hypoxia inducible factor, cyclin D1 and Myc (proteins that inhibit cell death and activate cellular survival and proliferation), while the PI3K pathway is involved in the regulation of metabolic pathways including glucose uptake through glucose transporter 4 (GLUT4) translocation, glycogenesis, lipid metabolism and protein synthesis **[21,22]**. In IR, however, there is defective AKT activation, which impairs GLUT4 translocation to the plasma membrane leading to impaired glucose uptake, impaired suppression of lipolysis and enhanced free fatty acids (FFAs) release into plasma from the adipose tissue which accumulate in other tissues such as muscle or liver even more worsening IR **[23]**.

Obesity and diabetes combined are estimated to have contributed to 4.5% of all cancer cases in 2012, using a conservative model. However, the contribution was much higher in certain types of cancer. In liver cancer, for example, 23.3% of cancers in men and 27.3% of cancers in women were attributed to obesity and diabetes **[24,25]**. Interestingly, studies showed that high insulin level alone can increase the risk and mortality of certain cancers regardless of body weight **[26-28]**.

Many systemic factors that are dysregulated in obesity and T2DM have been proposed as contributing to cancer risk and progression **[29]**. For instance, the insulin-like growth factor 1 (IGF-I), a potent mitogen, demonstrates higher levels in type II diabetic subjects and may contribute to cancer progression **[30]**. Similarly, supraphysiological concentrations of insulin and glycemia to which body tissues are exposed represent a potent growth factor and energy source, respectively. They are essential for neoplastic transformation and cancer progression **[31]**. Hyperglycemia is also responsible for induction of oxidative stress and DNA damage, which may trigger the first phases of tumorigenesis 32. Moreover, Insulin resistance in type II diabetics is critically-linked with an excess accumulation of diacylglycerol in cells that leads to activation of protein-kinase C, a well-known influencer in cancer cells **[33,34]**. While the exact molecular mechanisms linking cancer and diabetes are currently not clear, one notable link between diabetes and cancer is INSR and the IGF-1R family of receptors **[35]**.

Insulin-like growth factor 1 receptor (IGF-1R) is a member of the insulin and insulin-like growth factor (IGF) family which includes ligands, receptors, and proteins that modulate ligand bioavailability, also known as IGF-binding-proteins (IGFBPs). Currently, there are three recognized ligands (insulin, IGF-I, and IGF-II), along with three cell surface receptors, including the insulin receptor (INSR), IGF-1R, and IGF-II receptor (IGF-2R), and seven IGFBPs **[36-38]**.

The INSR and IGF-1R are closely related tyrosine kinase transmembrane receptors, consisting of two extracellular α-subunits (for ligand binding) and two transmembrane β-subunits, which contain the tyrosine kinase domain. They are found as preformed homodimers or heterodimers in the absence of ligand binding. Homodimers and heterodimers of the INSR and IGF-1R have different tissue expression, ligand binding and signalling profiles. Their ligands (insulin, proinsulin, IGF-I and IGF-II) bind with differing affinities to the INSR isoforms, to IGF-1R and to hybrid receptors **[24,39-43]**. IGF-1R possesses a high affinity for IGF-I and IGF-II, but it can also bind to insulin with 50- to 100-fold lower affinity **[44]**. Similar to the INSR, binding of IGF to the IGF-1R leads to activation of two main signaling cascades: The insulin receptor substrate (IRS)-initiated PI3K/AKT/mTOR pathway, which predominantly leads to metabolic outcomes, and the SHC-initiated Ras-MAPK pathway, which controls mitogenic outcomes, such as cell growth and differentiation. These two pathways are among the most common

dysregulated signaling pathways in cancer and DM **[37,45].**

The prevalently dysregulated signaling pathways of INSR and IGF-1R in cancer and DM have been reported to be regulated at different levels by non-coding (nc) RNAs **[37,46-48].** Although around 76% of the genome is transcribed into RNA, only 2% is translated into proteins, the remaining transcripts being either short or long nc RNAs **[49].** While ncRNAs do not exhibit protein encoding ability, they have a wide variety of biological functions performed through the regulation of protein expression and functions **[48].** Among the different species of ncRNAs, the two most investigated classes are microRNAs (miRNAs) and the long non-coding RNAs (lncRNAs).

MiRNAs are RNAs about 21-25 nucleotides long that regulate gene expression post–transcriptionally by inhibiting protein translation or inducing mRNA degradation, thereby suppressing target protein production. lncRNAs, however, are a group of ncRNAs consisting of more than 200 bases. They control gene expression, protein stabilization, and enzyme activity, and consequently influence biological processes via the following mechanisms: (1) Serving as scaffolds to modulate the interaction between large molecules such as DNA, RNA, and proteins; (2) Acting as decoys for RNA-binding proteins and small RNAs, diminishing their relative abundance; (3) Acting as competitive endogenous RNA by capturing miRNAs to inhibit miRNAs function; (4) Guiding nucleic acid-binding proteins to the targeted effector molecule's site. These mechanisms are implemented in integration with each other **[37].** LncRNAs may modulate gene expression not only post-transcriptionally, but also on the transcriptional, and epigenetic levels 50,51. lncRNAs are implicated in numerous different human diseases including cancer, cardiovascular, and neurodegenerative diseases, as reviewed extensively in recent years **[52-56].**

LncRNA H19 (H19) is one of the first discovered lncRNAs. It is 2.3 kilobase in length and encoded by the H19 gene **[57].** The H19 gene contains five exons and four introns and is located on the short arm (p) of chromosome 11 at position 15.5 (11p15.5). It is transcribed by RNA polymerase II, capped, spliced, and polyadenylated, then, lncRNA H19 is exported from the nucleus to the cytoplasm **[58].** It is adjacent to the protein-coding gene insulin-like growth factor 2 (IGF-II), an important fetal growth factor. They both share regulatory sequences that control their expression, including two enhancers located 3' downstream of H19. H19 is an example of genomic imprinting as it is expressed from the maternal allele whereas IGF-II is from the paternal allele **[59,60].** Both genes are controlled by a differentially methylated region (DMR), which is located in an intergenic region of IGF-II. The H19 locus encodes several transcripts in addition to the main transcript lncRNA H19, such as the encoded miR-675 and the two antisense transcripts 91H and H19 opposite tumor suppressor (HOTS) **[60,61].**

Material and Methods

An organized literature search was conducted querying electronic databases including PubMed/ Medline, SCOPUS, and Google Scholar.

The search process included the following keywords: Hepatocellular carcinoma, diabetes mellites. Types 2 Diabetes mellites, IGF-1R, non-coding RNA, H19. gene expression. PubMed function “related articles” was employed for further search. The article in English-language were only reviewed. All types of studies were included except case reports and editorials.

Results

There is a consensus that IGF-1R is upregulated in HCC and in DM in the studied articles. However, H19's level and role, particularly in HCC are still not established. The studies investigating the relationship between IGF-1R and H19, though never before studied in HCC or DM, are also inconclusive. In the following discussion, we discuss in detail our findings and the possible reasons behind them.

Discussion

In cancer, INSR and IGF-1R expression and their signalling pathways are often dysregulated compared with normal tissues. Increased transcription of the genes encoding INSR and IGF-1R in cancer may occur owing to mutations in tumor suppressor genes, such as TP53 (where wild-type p53 suppresses both INSR and IGF1R gene transcription) and the genes encoding BRCA1, Von Hippel Lindau (VHL) and Wilms tumor protein (WT1) (the wild-type protein products of which inhibit IGF-1R transcription in breast and kidney cancer cells). Another mechanism of increased transcription of INSR and IGF-1R is through transcription factor Sp1 and high- mobility group AT-hook 1 (HMGA1) which bind to the gene promoter regions. Both INSR and IGF-1R are expressed at high levels in a number of cancers, including breast, colon and pancreatic cancer **[62-65].** Overexpression

of IGF-1R is frequently observed in HCC and is a marker for poor prognosis **[66,67]**. IGF/IGF-1R signaling mediates cell proliferation, cell survival, migration, and protein synthesis and can block apoptosis by expressing Myc and AKT1 in the liver, thereby causing invasion and metastasis of tumor cells **[68,69]**. IGF-1R is also well known as a nuclear translocation protein. IGF-1R directly binds to DNA or binds to other transcription factors to induce gene transcription. For example, IGF-1R can cause the activation of the Wnt/β-catenin signaling pathway which is associated with enhanced self-renewal in liver cancer stem cells **[68,70-72]**.

Insulin-like growth factor 1 receptor IGF-1R has a complex role in DM pathogenesis according to the stage of DM. In the pre-diabetes stage, the interruption of IGF-1R signaling in the muscles and fat tissue, the primary tissues involved in the glucose metabolism will lead to insulin resistance and progression to DM **[73,74]**. However, studies showed that during the development of T2DM, IGF-1R is activated or over expressed in other tissues and organs in reaction to hyperglycemia and hyperinsulinemia, thus causing DM deterioration. For instance, overexpression of IGF-1R was found in the brain and vascular smooth muscle cells of a murine DM model, causing diabetic encephalopathy and atherosclerosis, two frequent DM complications 75,76. From this data it can be inferred that hyperinsulinemia activates IGF-1R and downstream target effectors in DM **[37]**. Additionally, IGF-1R signaling has interactions with molecules implicated in inflammation, which is incriminated in the pathogenesis of cancer and DM. For example, the overproduction of inflammatory cytokines, in particular TNF-α and IL-6, has been found to be associated with insulin resistance and the initiation and development of DM and cancer **[77]**.

LncRNA H19 is highly expressed in fetal life especially during the development of the fetal liver **[78,79]**. After birth, however, H19 expression is strongly downregulated in all tissues, except for the skeletal muscles and heart **[80]**. H19 can be reactivated in different tumors, including HCC **[81-83]**. However, in HCC, the expression of lnc RNA H19 and its role in hepatocarcinogenesis remain controversial **[58,61]**. H19 was previously reported to be down regulated in human HCC tissues in comparison with adjacent healthy ones. Schultheiss et al. (2017) reported that H19 is also down regulated in HCC in vitro and in vivo **[84]**. Interestingly, Lv et al. (2014) investigated the effect of lnc RNA H19 and its processed miRNA, miR-675, on migration and invasion of HCC cells, finding that suppression of lncRNA H19 and miR-675 promoted migration and invasion of HCC cells through the AKT/GSK-3β/Cell division cycle 25 A (Cdc25A) signaling pathway **[85]**. Additionally, Zhang et al. [86] indicated that the expression of H19 in primary tumors from 33 HCC patients was significantly lower than in their adjacent non-tumor tissues, although H19 was dramatically up regulated in tumor tissue in some cases. The researchers also found that H19 expression was significantly lower in the invasive HCC samples than in the non-invasive HCC tumors. Moreover, Yoshimizu et al. [87] reported that H19 acts as a tumor suppressor in a murine model of HCC. H19 has been known to inhibit hepatocyte proliferation and the Wnt/β-catenin pathway in fetal life **[79]**. Yang et al. **[88]** also noted that up regulation of H19 inhibited the transforming growth factor β 1 (TGF-β1)-induced proliferation of hepatic stellate cells88. The a for ementioned data support the opinion that H19 is a tumor suppressor gene.

Contrastingly, several in vivo and in vitro studies have reported that H19 is an oncogene in HCC. Rojas et al. **[89]** noted the up regulation of H19 in HCC human samples and in vivo mice tumor tissues. They also remarked that lncRNA H19 may be essential for the self-renewal of HCC stem cells. Zhou et al. **[90]** found that H19 was significantly increased in HCC human tissue and cell lines, and that H19 knockdown markedly suppressed tumor cell proliferation through upregulating miR-15b-5p which suppresses the tumorigenic axis: Cell division cycle protein 42 (CDC42)/P21 activated kinase 1 (PAK1). Khan et al. **[91]** also reported that suppression of H19 expression leads to inhibition of the Wnt/β-catenin pathway, one of the known pathways in the pathogenesis of HCC **[12]**. Other mechanisms by which H19 is theorized to cause carcinogenesis are reviewed by Yang et al. **[51]**. The imprinting of H19 can be lost in HCC, negating its downregulation in adult livers **[60]**. This is called loss of imprinting (LOI) and it is correlated with hypomethylation occurring in response to the exposure to environmental risk factors of HCC **[92]**. One possible explanation for this controverse regarding H19 expression in HCC is that HCC is a wildly heterogenous tumor with various molecular subtypes **[93,94]**.

In diabetes, altered expression of H19 contributes to the development of IR by affecting metabolic pathways such as hepatic gluconeogenesis and lipogenesis. However, studies are contradictory as to whether H19 is over- or under-expressed in hyperglycemia. Gao et al. **[95]** reported that H19

was significantly decreased in the muscles of human subjects with type-2 diabetes and in rodents with IR. Inhibition of H19 was found by Goyal et al. **[96]** to cause hyperglycemia and increased gluconeogenesis in mice. In contrast, Fawzy et al. **[97]** discovered that relative H19 plasma expression levels were significantly increased in T2DM patients compared to controls. Hepatic over–expression of H19 was shown to promote hyperglycemia in mice, as well **[98]**.

H19's effect on IGF-1R has never been studied in the setting of HCC and/or diabetes. Nonetheless, depletion of H19 was found to increase the bioavailability of let-7, a family of miRNAs which decrease insulin sensitivity through targeting multiple key factors such as IGF-1R, INSR, and IRS-2. Since let-7a typically causes downregulation of IGF-1R, H19 downregulation will ideally lead to inhibition of IGF-1R expression99. In prostate cancer cells, Wang et al. **[100]** observed that H19 upregulation significantly elevated the expression of IGF-1R **[101]**. Lowered H19 expression led to higher activity of let-7, which targets and inhibits IGF-1R expression in normal endometrial tissues in a study by Ghazal et al. **[102]**. However, it was found that depletion of lncRNA H19 can be concomitant with IGF-1R overexpression. This is mediated by the miR-675 **[103]**. Yang et al. **[88]** also reported that H19 overexpression in hepatic stellate cells downregulated the expression of IGF-1R88. H19 was reported to downregulate IGF-1R through miR-675 in the placenta, as well **[78]**.

Conclusion:

To summarize, the relationship between H19 and IGF-1R and the exact molecular mechanisms of their interactions in HCC and T2DM need further research to be elucidated.

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دور الحمض النووى الريبوزى الطويل الغير مكود هـ ١٩ فى تنظيم التعبير الجينى لمستقبل عامل النمو الأول المشابه للإنسولين علاقة محتملة بين مرض السكر من النوع الثانى وسرطان الكبد : مقالة مرجعية

مقدمة : سرطان الخلايا الكبدية هو سرطان شائع يشكل عبئاً اقتصادياً ثقيلاً على نظام الرعاية الصحية. فى مصر، وهو السبب الأكثر شيوعاً للوفيات والاعتلال المرتبط بالسرطان. داء السكرى هو اضطراب فى الأيض يتميز بارتفاع السكر فى الدم. السرطان والسكرى من النوع الثانى، وهما أكثر الأمراض انتشاراً فى العالم، يشتركان فى العديد من عوامل الخطر المتداخلة والحالات المرضية. الآليات الدقيقة التى تربط هذين المرضين لم يتم فهمها بالكامل بعد. أحد المسارات الممرضة المفترضة هو محور مستقبل عامل النمو الأول المشابه للإنسولين (IGF-1R)، والذى ينظمه العديد من الأحماض النووية البريبوزية الغير مكودة، من بينها الحمض النووى الريبوزى الطويل هـ (lncRNA H19).

الهدف من الدراسة : فى هذه المقالة المرجعية، نهدف إلى استكشاف العلاقة بين H19 و IGF-1R فى الأدب العلمى وكيف يتم تعديل مستويات التعبير الجينى فى سياق سرطان الكبد و مرض السكرى للتحقيق فى احتمال أن يكون IGF-1R/H19 رابطاً فيسيولوجياً مرضياً بين سرطان الكبد. ومريض السكر مما قد يجعله هدفاً علاجياً لكلا المرضين.

الخطة البحثية : تم إجراء بحث منظم فى الأدب العلمى مع التركيز على قواعد البيانات الإلكترونية بما فى ذلك Medline PubMed وSCOPUS وGoogle Scholar.

النتائج : لم تبحث أى دراسات حتى الآن فى العلا قة بين H19 و IGF-1R فى سياق سرطان الكبد أو مرض السكرى. ومع ذلك، فى أمراض أخرى، نجد أن العلاقة بين H19 و IGF-1R مصدراً للجدال فى الدراسات. علاوة على ذلك، لا يزال مستوى التعبير عن H19 فى سرطان الكبد ومرض السكرى، بالإضافة إلى دورة كمثبط محتمل للورم مقابل كونهجين محفز للأورام موضع جدل.

الاستنتاج : العلاقة بين H19 و IGF-1R والآليات الجزيئية الدقيقة لتفاعلاتهما فى سرطان الكبد ومرض السكر من النوع الثانى يحتاجان إلى مزيد من البحث لتوضيحهما.