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Mini Review

Expression of Hepatocyte Nuclear Factor-1β Regulates the Pathogenesis of Clear Cell Carcinoma of Ovary; A Short Review

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Abstract

Clear cell carcinoma (CCC) of the ovary has certain features that distinguishing it from other epithelial ovarian carcinomas (EOC). Its characteristic, biology and histology, frequent concurrence with endometrial lesion, low proliferative activity and high chemo-resistant nature make its prognosis extremely poor. This article reviews several data in the context of endometriosis and CCC biology. Over the past several decades, the steady increase in the incidence of clear cell carcinoma (CCC) has been observed in Japan. The incidence of CCC among EOC is 3.7% to 12.1% worldwide. Recent studies have noted specific expression of hepatocyte nuclear factor (HNF) 1β in ovarian clear-cell carcinoma. HNF-1β act as a modulator of female reproduction, playing a role in endometrial regeneration, differentiation, decidualization, glycogen synthesis, detoxification, cell cycle regulation, implantation, uterine receptivity and a successful pregnancy. HNF-1β regulates tissue-specific gene expression in endometriosis as well as the expression of several genes, including CD44v9. This CD44v9 system is involved in cell migration, growth, survival, anti-apoptosis, immune response and anti-oxidative stress through maintaining higher levels of antioxidants. HNF-1β may serve to alleviate damage and promote survival of cells experiencing stress by up-regulating antioxidant protein expression. HNF-1 beta also have a close association with Osteopontin (OPN) up-regulation in OCCC, which is expressed in a variety of normal and tumor tissues, and OPN is the most direct target gene of HNF-1 beta. From the review of our literature, we concluded that hepatocyte nuclear factor-1β has specific expression in endometriosis and CCC, suggesting that early differentiation into the clear cell lineage takes place in the endometriosis. Our review highlights the role of HNF-1β in pathogenesis of Clear cell carcinoma of ovary.

Keywords: *Ovary; Clear Cell Carcinoma; Endometriosis; Hepatocyte Nuclear Factor-1beta; Osteopontin (OPN)*

Introduction

Ovarian clear cell carcinoma is a unique histological form of ovarian cancers which accounts for 5 - 25% of all ovarian carcinomas depending on the population which has been selected previously for study purpose. This is the second most common ovarian cancer. Endometriosis considered being a key factor in occurrence of this cancer. According to a research conducted in 2011, Japanese females have the highest prevalence (15 - 25%) among all population [1].

Epithelial ovarian cancer (EOC) are a heterogeneous group with varying pathologies remains the most lethal form of gynecologic cancers worldwide and are broadly categorized into serous, mucinous, endometrioid and clear cell histotypes. Clear cell carcinoma demonstrates a distinctly different clinical behavior from other EOC. A number of studies have noted a particularly unfavorable prognosis for the CCC. Recurrences and poor response rate to platinum-based regimens may be related to the intrinsic chemo-resistance of these tumors [2,3].

Recent advances in molecular biology have improved our understanding of the gene alterations that lead to the development of endometriosis-associated EOC. It's possible that the deletion of a driver gene on the chromosomal arm may lead to development of CCC [4]. If CCC arises from endometriosis, one would expect to find genetic alterations common to both endometriosis and CCC. According to some

allele-typing studies, 30% to 50% of endometriosis lesions have somatic genetic changes in chromosomal regions supposed to contain genes involved in ovarian tumor formation. A proportion of cases of endometriosis exhibited LOH at one or more loci on chromosome arms 5q,31 6p,31 6q,32 9p,32-34 10q,32-34 11q,33-35 13q,31 17q,31,36 and 22q. There are marked similarities in the chromosomal LOH pattern among endometrial foci and adjacent CCC, providing more convincing evidence [5].

A majority of pathological functions of CCC is governed by HNF-1β-dependent and possible interacting pathways. Hepatocyte nuclear factor is a homeodomain protein that plays a key role in the liver-specific expression of many genes during differentiation and development. Hepatocyte nuclear factor-1β is normally expressed in epithelial cells of kidney, urogenital tract, liver, lung, gut, and pancreas. Its expression is actually involved in loss of mesenchymal cell phenotype and acquisition of epithelial fates. Hepatocyte nuclear factor-1β is also expressed in human endometrium and physiologically regulated during the menstrual cycle and gestational state. Hepatocyte nuclear factor -1β expression may be a common genetic lineage among the mid-to-late secretory endometrium, endometriosis, and CCC. The up-regulation of HNF-1β expression has been reported in endometriosis, including the atypical and inflammatory endometriotic lesions. The reduction of HNF-1β expression by RNA interference induced apoptotic cell death in CCC cell lines suggests that the expression of HNF-1β was tightly linked to CCC and essential for its survival [5,6].

Ovarian carcinomas are usually detected late thus have poor prognoses than any gynecological carcinoma. Late diagnosis leads to dissemination in the peritoneal cavity which is detected by cytology of ascitic fluid tap. The floating cells in ascites degenerate quickly hence making it difficult to cytologically differentiate between CCC cells and non-CCC cells. The obvious nucleoli, irregular chromatin clumping, vary in shape and size, high mitotic rate and increased nuclear/cytoplasmic ratio with the reactive mesothelial cells in ascitic fluid resembles adenocarcinoma causing an indefinite diagnosis. Hence for cytological diagnosis, an immunohistochemical marker is required. Presence of HNF-1β in ovarian CCC in both neoplastic tissues and ascitic fluid suggests that it can be applied as a CCC-specific immunocytochemical marker of ascites [7,8].

Review of Literature

The literature review was carried out to investigate the Role of Hepatocyte Nuclear Factor-1β in the Pathogenesis of Clear Cell Carcinoma of the Ovary. Medical literature search was conducted on searching engines like Pubmed, Google scholar and Cinahl. Mesh and Non-mesh terms like Ovary, clear cell carcinoma, endometriosis, hepatocyte nuclear factor-1beta, osteopontin (OPN) were used. Relevant literature published from 2000 to 2017 was thoroughly analyzed.

Epidemiological Aspect

Ovarian clear cell carcinoma is increasing in East Asia compared to Europe and USA. There has been reported an increased incidence of cancer in women with endometriosis. Endometriosis is a common gynecological disease, with an estimated prevalence of 5 - 15% in women of reproductive age [9,10]. It is a serious clinical problem caused when a tiny patch of endometrial tissue bleeds, sloughs off, becomes transplanted, grows and enlarges inside the ovaries leading to its adverse consequences which includes pain, infertility and development of ovarian cancer. Clear cell tumors of the ovary are frequently associated with ovarian endometriosis. The frequency was reported as 33% in borderline and benign clear cell tumors and as high as 54% in a large series of clear cell carcinomas. It has been proposed that clear cell tumors develop from endometriosis, an additional pathway may also involve a progression sequence from clear cell adenofibroma to carcinoma [6].

Epidemiologic studies demonstrated that endometriosis has an increased risk of developing ovarian cancer. According to a database from the Shizuoka Cancer Registry [SCR] an increase in the incidence of ovarian cancer since the late 1980s has been documented. Several retrospective studies in Japan also suggest that estrogen has a prominent role in the pathogenesis of ovarian cancer and that there may be an association between endometriosis and increased risk of ovarian cancer. To assess the long-term risk of ovarian cancer following ovarian endometrioma, the Shizuoka Cohort Study on Endometriosis and Ovarian Cancer Program conducted a cohort study of women who had clinical diagnosis of ovarian endometrioma during the period 1985-1995, with follow-up through 2002 [10].

During the 17 years follow-up, 46 incidents of ovarian cancers were identified, suggesting that patients with ovarian endometrioma are at an increased risk of developing ovarian carcinoma. The risk increased with increasing age at ovarian endometrioma diagnosis, with a SIR equal to 13.2 in women above 50 years of age [10].

CCC-Specific Genetic Signaling

There are two characteristics that define CCC cells, hormone independency and HNF-1β over-expression. Gene expression analyses have led to the identification of sets of CCC-specific genes and their targets, and highlighted a circuitry responsible for CCC development its maintenance and progression. It is known that CCC tumor cells are negative for Wilms tumor 1 (WT1), estrogen receptor (ER), progesterone receptor (PR), and p53 but positive for insulin-like growth factor binding protein-1 (IGFBP-1) and HNF-1β [11].

In cells of endometrioid origin the expression of ER and PR, is more elevated than in those of non-endometrioid origin. The endometrioid carcinoma which develops from the endometriotic epithelium due to endometrial hyperplasia with unopposed estrogen signaling, the ER and PR expression plays an important role in its progression. CCC has shown weak staining for ER and PR. The periodic loss of estrogen function may be a turning point in CCC progression and aggressiveness [11].

The majority of CCC cases showed the expression of the HNF-1β gene, as compared to non-CCC tumors. HNF-1β and its target genes show a close linkage with the CCC-specific genes and it may be the key marker in differentiating endometriosis from CCC. Genes associated with chemoresistance, detoxification and glycogen synthesis are somewhat similar to the HNF-1β related genes which plays a role in the cellular stress response in CCC through its regulation of cytoprotective genes [11].

Role of HNF-1β in CCC

Hepatocyte nuclear factor is a protein that plays a key role in the liver-specific expression of many genes. Hepatocyte nuclear factor-1β is expressed in human endometrium during mid-to-late secretory phase and gestational endometrium and physiologically regulated during the menstrual cycle and gestational state. It's up-regulation has been reported in both atypical and inflammatory endometriosis although overexpression of HNF-1β is not an oncogenic event in CCC tumorigenesis [5,12].

HNF-1β-dependent and its interacting pathways govern majority of the biological pathways of CCC. Studies suggest that interference at the RNA expression of HNF-1β induced apoptotic cell death in CCC cell lines, indicating that the expression of HNF-1β is essential for the survival and progression of CCC. Therefore, HNF-1β is considered a molecular marker for CCC as well as a molecular target for its therapy. Certain genes that play an important role in CCC are identified as the direct target of HNF-1β which includes osteopontin, dipeptidyl peptidase IV (DPPIV (CD26)), glycogen, FXYD2, TFPI2, NNMT, RBPMS ANXA4, CD44v9, UGT1A1, and angiotensin converting enzyme-II (ACE-II).The identification of genes targeted by HNF-1β is essential to our understanding of the pathophysiology of CCC [5].

The ECM protein Osteopontin (OPN) contains an integrin-binding arginine-glycine-aspartate sequence (RGD).nuclear factor-kappa B (NF-κB), is activated by the interaction between the alpha v beta 3, alpha-5 beta-1 and the RGD domain. This signal transduction results in the increased expression of a number of proteins which includes urokinase plasminogen activator (uPA) and matrix metalloproteinase (MMPs). These proteins are essential for the regulation of cell migration, ECM invasion, and metastasis in cancer cells. OPN is considered a direct target gene for HNF-1β, because its promoter region contains functional HNF1 binding sites. OPN is expressed in the decidual stromal cells and natural killer cells, cyclic endometrium, and higher expression has been detected in the later gestational phase compared with the early gestational phase. Studies demonstrated that OPN protein was detected in ovarian cancer, cervical cancer and corpus cancer. Osteopontin (OPN) expression in serous adenocarcinoma tissues and OCCC was significantly higher as compared to the other histological types [13].

Glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide have a number of important biological effects, which include release of insulin and inhibition of glucagon. Dipeptidyl peptidase IV (DPPIV [CD26]) regulates their biological activity and terminates their Hormone action. The glucose metabolism and glycogen synthesis is modified by expressions of DPPIV and incretins. During the secretory phase, HNF-1β expressed in the endometrium stimulates progesterone-induced DPPIV expression and subsequently glycogen storage, suggesting that DPPIV expression is up regulated by progesterone. At present, however, there is no data suggesting incretins are expressed by either endometrium or CCC [5].

Two other important hormones estrogen and progesterone regulates glycogen metabolism by regulation of glycogen phosphorylase and glycogen synthase in uterine endometrium. Progesterone activates glycogen synthase and inhibits glycogen synthase kinase-3β in the human endometrium during the secretory phase thus facilitating glycogen synthesis [5,9].

During the peri-implantation period one of the key metabolic changes that occur is the rise in uterine endometrial glycogen content. Thus, indicating the possibility that HNF-1β expression plays a role in glycogen synthesis during secretory phase endometrium. Overexpression of HNF-1β in the epithelium Modifies glycogen metabolism that results in cytoplasmic glycogen accumulation, which gives rise to CCC morphology [5].

CCC is known to produce excessive levels of TF thus is more likely to develop thromboembolism in the cancerous tissues. TFPI 2 regulates the production of TF and helps in protecting the tissue from hypercoagulable and prothrombotic state [5].

It is known that angiotensin II plays a role in ferritin induction and iron deposition. The presence of ACE II receptors in the endometrium provides strong evidence that it plays a role in anti-proliferative activity of CCC because one of the HNF-1 regulated gene controls the ferritin up-regulation in CCC tissues. Hence up-regulation of ACE II is responsible for the low proliferative activity of CCC [5].

HNF-1β regulates the expression of several genes, including CD44v9. CD44v9 specifically regulates cell functions, including migration, growth, survival, anti-apoptosis, immune response and redox status. CD44v9 interacts with xCT, which replaces intracellular glutamate for extracellular cysteine, and suppresses the ROS-mediated oxidative stress. The HNF-1β-dependent pathway is associated with detoxification systems, such as the CD44v9-xCT-dependent GSH pathway. Hence, endometriosis may induce mechanisms for protecting against the susceptibility to oxidative stress-induced cell and DNA damage and lead to CCC [14].

It is known that CCC is resistant to chemotherapy. The likely cause of this mechanism is drug resistance. ANXA4 and UGT 1A1 are the HNF-1β target genes and they are associated with the resistance from paclitaxel and irinotecan respectively. In addition, the previously reported CCC markers which include GLR, superoxide dismutase (SOD2) and glutathione peroxidase 3 are considered to promote the general detoxification. Thus chemotherapy resistance is a function of HNF-1β-dependent detoxification pathway [3,5].

HNF-1β is the transcription activator of NNMT which plays an important role in the drug detoxification and biotransformation. Its over-expression affects the normal metabolism of the antineoplastic drugs thus it hinders in the chemotherapy [5].

Conclusion

Hepatocyte nuclear factor-1β has been found to regulate glycogen accumulation, anti-apoptosis, and detoxification. It is also indicated that it plays an important role via regulating certain genes which play an important role in the pathophysiology of CCC which include DPPIV, osteopontin, ACE-II and others as discussed previously. From the above discussion, we hypothesize that HNF-1β may play an important role in the pathogenesis and clinical behavior of Clear Cell Carcinoma but as it holds little importance in distinguishing the clear cell carcinoma from other benign forms or the endometrial serous carcinomas, it should not be used as a reliable marker for clear cell carcinoma. Nevertheless it helps in the distinction between endometroid carcinoma and clear cell carcinoma hence can be used a diagnostic marker for these differential consideration [15].

Disclosure of Interest

I, Syeda Beenish Bareeqa as corresponding author, on the behalf of all co-authors hereby declare that there is no conflict of interest regarding the publication of our study.

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Bibliography

1. Anglesio MS., *et al*. "Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010". *Gynecologic Oncology* 121.2 (2011): 407-415.

2. Kajihara H., *et al*. "Clear cell carcinoma of the ovary: potential pathogenic mechanisms". *Oncology Reports* 23.5 (2010): 1193-1203.

3. Sugiyama T., *et al*. "Clinical characteristics of clear cell carcinoma of the ovary". *Cancer* 88.11 (2000): 2584-2589.

4. Mikami Y. "Endometriosis-related ovarian neoplasms: pathogenesis and histopathologic features". *Diagnostic Histopathology* 20.9 (2014): 357-363.

5. Kobayashi H., *et al*. "The role of hepatocyte nuclear factor-1β in the pathogenesis of clear cell carcinoma of the ovary". *International Journal of Gynecological Cancer* 19.3 (2009): 471-479.

6. Kato N., *et al*. "Expression of hepatocyte nuclear factor-1beta (HNF-1beta) in clear cell tumors and endometriosis of the ovary". *Modern Pathology* 19.1 (2006): 83-89.

7. Higashiguchi A., *et al*. "Specific expression of hepatocyte nuclear factor-1β in the ovarian clear cell adenocarcinoma and its application to cytological diagnosis". *Cancer Science* 98.3 (2007): 387-391.

8. Kato N., *et al*. "Immunocytochemistry for hepatocyte nuclear factor-1β (HNF-1β): A marker for ovarian clear cell carcinoma". *Diagnostic Cytopathology* 35.4 (2007): 193-197.

9. Ness RB. "Endometriosis and ovarian cancer: thoughts on shared pathophysiology". *American Journal of Obstetrics and Gynecology* 189.1 (2003): 280-294.

10. Kobayashi H., *et al*. "Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan". *International Journal of Gynecological Cancer* 17.1 (2007): 37-43.

11. Uekuri C., *et al*. "Toward an understanding of the pathophysiology of clear cell carcinoma of the ovary". *Oncology Letters* 6.5 (2013): 1163-1173.

12. Kao YC., *et al*. "Utility of hepatocyte nuclear factor-1β as a diagnostic marker in ovarian carcinomas with clear cells". *Histopathology* 61.5 (2012): 760-768.

13. Matsuura M., *et al*. "Osteopontin is a new target molecule for ovarian clear cell carcinoma therapy". *Cancer Science* 101.8 (2010): 1828-1833.

14. Akasaka J., *et al*. "Hepatocyte nuclear factor (HNF)-1β and its physiological importance in endometriosis". *Biomedical Reports* 1.1 (2013): 13-17.

15. Fadare O and SX Liang. "Diagnostic utility of hepatocyte nuclear factor 1-beta immunoreactivity in endometrial carcinomas: lack of specificity for endometrial clear cell carcinoma". *Applied Immunohistochemistry and Molecular Morphology* 20.6 (2012): 580-587.

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