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Hepatocyte nuclear factor (HNF)-1β and its physiological importance in endometriosis (Review)

JURIA AKASAKA, CHIAKI UEKURI, HIROSHI SHIGETOMI, MATSUKI KOIKE and HIROSHI KOBAYASHI

Department of Obstetrics and Gynecology, Nara Medical University, Nara 634-8522, Japan

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Abstract. Endometriosis is associated with pelvic pain and female infertility. Endometriosis induces inflammation and is vulnerable to oxidative stress damage. To update and summarize the literature concerning the mechanisms that serve to protect genomic DNA from the oxidative damage, the present study reviews the English-language literature for biochemical studies on the transcription factor hepatocyte nuclear factor (HNF)-1β target genes. Findings demonstrated that retrograde flow of the menstrual blood might give rise to endometriosis. Iron may have a significant impact on endometriosis gene expression. HNF-1β regulates tissue-specific gene expression in endometriosis, as well as the expression of several genes, including CD44v9, which binds several molecules, including hyaluronan, epidermal growth factor receptor (EGFR), leukemia-associated Rho-guanine nucleotide exchange factor (LARG), IQ motif containing GTPase activating protein 1 (IQGAP1), macrophage migration inhibitory factor (MIF), major histocompatibility complex, class II invariant chain (CD74), cystine transporter subunit (xCT), Fas and extracellular matrix (ECM) proteins. The 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 upregulating antioxidant protein expression. This review expands current knowledge on the molecular mechanisms underlying the oxidative stress protection provided by HNF-1β and provides evidence that elevated HNF-1β activity might be associated with the CD44v9-dependent signaling cascades.

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Correspondence to: Dr Hiroshi Kobayashi, Department of Obstetrics and Gynecology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
E-mail: hirokoba@naramed-u.ac.jp

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1. Introduction

Endometriosis is an estrogen-dependent condition associated with chronic pelvic pain and infertility and increases susceptibility to the development of ovarian cancer. Accumulating evidence indicates that selective genetic alterations play a role in the pathogenesis of endometriosis. Upregulation of transcription factor hepatocyte nuclear factor (HNF)-1β expression occurs in endometriosis (1-4). However, to what extent HNF-1β overexpression is involved in its pathogenesis remains to be determined. This review summarizes recent advances in HNF-1β-mediated signaling, its target genes and binding molecules and provides the potential challenges to attempts to identify the molecular basis of this gene.

2. Review of the literature

A comprehensive review of the literature was conducted to investigate the molecular basis of HNF-1β. A Medline search of the literature was performed using the key words endometriosis, cancer, target, binding, iron, oxidative stress, cystine transporter subunit (xCT), osteopontin (OPN), epidermal growth factor receptor (EGFR), CD44v9 and hyaluronic acid (HA). English-language publications in PubMed and references from relevant articles published between 1997 and 2012 were analyzed. References in the studies identified were also searched and certain unpublished data were obtained.

3. HNF-1β, an endometriosis-specific transcription factor

Several studies demonstrated overexpression of the HNF-1β gene and protein in endometriosis. HNF-1β is a Pit-1 (POU class 1 homeobox 1)/Oct-1 (solute carrier family 22)/Unc-86 (POU)/homeodomain-containing transcription factor that regulates tissue-specific gene expression in the kidney, liver, pancreas and other epithelial organs. Mutations in this gene produce diabetes syndrome [maturity-onset diabetes of the young type 5 (MODY5)], as well as being associated with

congenital renal cysts. Expression of this gene was altered in certain types of cancer. HNF-1β overexpression increased genomic instability (5). Aberrant expression of HNF-1β in endometriosis led to the production of detoxification proteins against persistent inflammation and oxidative stress. This review enhances our ability to understand the suggested function of this gene.

4. The profiles of HNF-1β target genes

Possible genes included in the profiles of HNF-1β target genes in ovarian cancer are dipeptidyl-peptidase 4 (DPP4, also known as CD26), osteopontin, angiotensin I converting enzyme 2 (ACE2), FXYD domain containing ion transport regulator 2 (FXYD2), tissue factor pathway inhibitor 2 (TFPI2), nicotinamide N-methyltransferase (NNMT), lipopolysaccharide-induced TNF factor (LITAF/PIG7), RNA binding protein with multiple splicing (RBPMS), annexin A4 (ANXA4) and UDP glucuronosyltransferase 1 family and polypeptide A1 (UGT1A1) (2). These genes have been hypothesized as key drivers of the phenotypic characteristics. Recent reviews have demonstrated the function of this molecule in the endometriosis and ovarian cancer (2-4).

In addition, HNF-1β regulates the expression of several genes in the kidney, including encoding polycystic kidney and hepatic disease-1 (Pkhd1); encoding polycystic kidney disease-2 (Pkd2) and encoding uromodulin (Umod); kinesin family member 12 (Kif12); encoding crumbs homolog-3 (Crb3); transcription factor AP-2β (Tcfap2β); encoding transmembrane protein-27 (Tmem27); encoding bicaudal C homolog 1 (Bicc1); suppressor of cytokine signaling 3 (SOCS-3); ATPase, Na^+/K^+ transporting, α 1 polypeptide (ATP1A1); intraflagellar transport 88 homolog (IFT88) and CD44v9 (6, unpublished data). Chromatin immunoprecipitation experiments confirmed that HNF1β binds to a number of these genes. Potential target genes are involved in cell polarity, cystogenesis or both.

The Umod gene acts as an inhibitor of calcium crystallization and defense against urinary tract infections. Mutations in this gene induce the autosomal dominant renal disorders medullary cystic kidney disease-2 (MCKD2) and familial juvenile hyperuricemic nephropathy (FJHN). These diseases are characterized by juvenile onset of hyperuricemia, gout and chronic renal failure.

HNF-1β directly regulates the Pkhd1 promoter. Mutations in this gene are associated with autosomal recessive polycystic kidney disease (ARPKD). Thus, the mechanism of cyst formation in MODY5 patients might involve the downregulation of Pkhd1 gene transcription.

SOCS-3 encodes a member of the STAT (Signal transducer and activator of transcription)-induced STAT inhibitor (SSI) family. SSI family members are cytokine-inducible negative regulators of cytokine signaling. SOCS-3, induced by various cytokines including IL-6, IL-10 and interferon (IFN)-γ, has been proven to inhibit JAK-STAT signal transduction for gp130 cytokines [leukemia inhibitory factor (IL-6, IL-11, LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotropin-1 (CT-1), cardiotropin-like cytokine (CLC)], as well as insulin, IGF-1, leptin, prolactin and growth hormone (GH). Overexpression of HNF-1β results in decreased SOCS-3 expression (7).

5. CD44v9 as a potential target gene for HNF-1β

Furthermore, findings of a recent genome-wide expression analysis have showed specific expression of CD44v9, cyclin D2, spleen tyrosine kinase (Syk), prolactin, v-myb myeloblastosis viral oncogene homolog (MyB), heparin-binding EGF-like growth factor (HB-EGF), Eph-receptor B6 and p16 [also known as cyclin-dependent kinase inhibitor 2A (CDKN2A)] in the HNF-1β-transfected cancer cells. CD44 participates in a wide variety of cell functions, including lymphocyte activation, recirculation and homing, hematopoiesis, cell-cell interactions, cell adhesion, proliferation, growth, survival, motility, migration, angiogenesis, differentiation and tumor metastasis. This glycoprotein is a receptor for hyaluronic acid (HA) and interacts with other ligands, such as osteopontin, collagens and matrix metalloproteinases (MMPs). It is one of the reactive oxygen species (ROS)-sensitive genes and is upregulated upon tissue injury. HA is able to serve as a novel therapeutic intervention for organ injury via the CD44 molecules. CD44 is also one of the cell surface markers associated with cancer stem cells in several types of tumor (8). The cell markers CD44, CD133 and aldehyde dehydrogenase (ALDH) are used to identify cancer stem cells. Although CD44 standard isoform (CD44s) is expressed in almost all the normal cells (hematopoietic cells and normal epithelial cell subsets) and cancer cells, variant (CD44v) isoforms are abundant in epithelial-type carcinomas and the cells that most often undergo malignant transformation. CD44v9 is the most likely candidate stem cell marker (9). The upregulation of CD44v9 may correlate with the malignant potential of patients with endocervical adenocarcinoma, gastric, esophageal, colon, prostate and ovarian cancers, multiple myeloma and hematologic malignancies (10-18). CD44v9 expression was positively correlated with proliferative activity, glycogen synthase kinase-3β (GSK-3β) activity, epithelial mesenchymal transition (EMT) changes and inhibition of Fas-mediated apoptosis (9,19). CD44 downregulated E-cadherin expression, upregulated MT1-MMP, which resulted in cell invasion and migration, suggesting that the cells with CD44v9 overexpression underwent the EMT process. Increased expression of CD44v9 is likely to correlate with carcinogenesis, hematogenous and lymph node metastasis and is predictive of the adverse prognosis for various carcinomas. However, numerous groups have conducted investigations evaluating the role of CD44v9 with conflicting data and conclusions. The downregulation of CD44v9 may correlate with the poor prognosis of patients with squamous cell carcinoma of the tongue and uterine cervix, as well as soft tissue sarcomas (20-24). These data allow us to hypothesize that assembly of the CD44v9 molecule comprising various subsets of binding proteins has yielded conflicting findings.

CD44 binds and interacts with several proteins in regulating signal transduction. These molecules include hyaluronan, EGFR, leukemia-associated Rho-guanine nucleotide exchange factor (LARG), also known as Rho guanine nucleotide exchange factor (GEF) 12 (ARHGEF12), IQ motif containing GTPase activating protein 1 (IQGAP1), macrophage migration inhibitory factor (MIF), major histocompatibility complex, class II invariant chain (CD74), xCT, Fas and extracellular

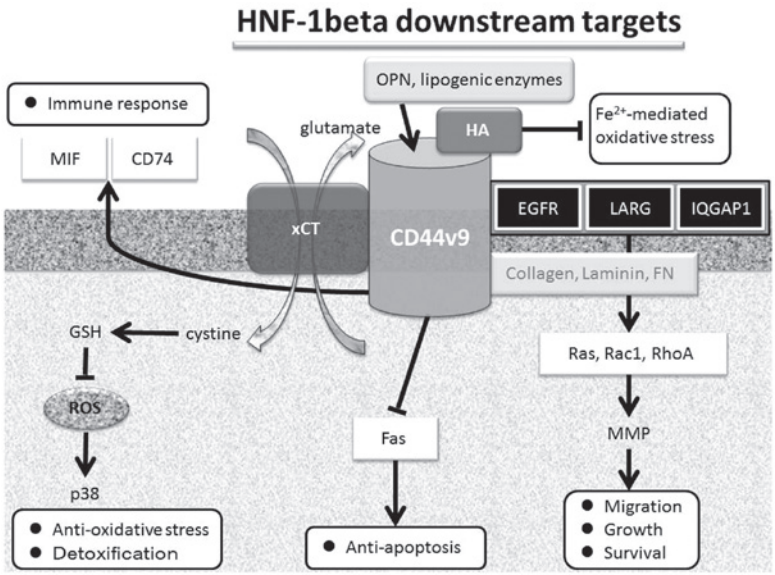

Figure 1. Proposed function of HNF-1β downstream targets. HNF-1β regulates the expression of several genes, including CD44v9, which binds several molecules, including hyaluronan, EGFR, LARG, IQGAP1, MIF, CD74, xCT, Fas and ECM proteins. Aberrant expression of HNF-1β is able to promote survival and also attenuate cell and DNA damage, probably through its anti-oxidative action and its detoxification process as well as the potential to minimize the deleterious effects of free iron on endometriotic tissue. EGRF, epidermal growth factor receptor; LARG, leukemia-associated Rho-guanine nucleotide exchange factor; IOGAP1, IQ motif containing GTPase activating protein 1; MIF, macrophage migration inhibitory factor; CD74, major histocompatibility complex, class II invariant chain; xCT, cystine transporter subunit; ECM, extracellular matrix proteins.

matrix (ECM) proteins (collagen, laminin and fibronectin) (25-27).

HA mediates the assembly of complex structures including CD44 and EGFR and induces activation of Rac1 and RhoA signaling cascades. LARG associates with CD44 and EGFR to promote several Ras and RhoA pathway effectors and MMP expression, leading to cell migration, growth, invasion and tumor survival (25). IQGAP1, an essential scaffolding protein, forms a complex with CD44 and stimulates HA-induced cell migration and growth (26). MIF binds to a CD44-CD74 complex and is involved in the regulation of macrophage function in host defense and the production of a variety of host immune modulators (27). CD74 is a chaperone that regulates antigen presentation and T-cell activation for immune response and associates with class I/II major histocompatibility complex.

Furthermore, the expression of CD44 variant forms is regulated by several molecules including OPN and lipogenic enzymes. OPN, a glycosylated, secreted multifunctional phosphoprotein, is involved in cell attachment, chemotaxis, immune cell activation, ECM remodeling, wound healing, inflammation, as well as tumor progression. OPN increases the cell surface expression of CD44 variant forms. A high OPN expression level is associated with poor prognosis and metastasis in several cancer patients.

In addition, a recent study established the association between expression of key enzymes of *de novo* lipogenesis and CD44 (28). Lipogenic enzymes, fatty acid synthase (FASN) and ATP-citrate lyase, stimulate the expression of CD44 and subsequently enhances the activation of PI3K/Akt, met proto-oncogene (hepatocyte growth factor receptor) (MET) and focal adhesion kinase; also known as protein tyrosine kinase 2 (FAK) (28).

6. Proposed function of CD44v9

Endometriotic cells may use inflammatory mechanisms to promote their growth. The proinflammatory cytokine, tumor necrosis factor (TNF)-α, is crucial to the endometriosis progression. TNF-α is highly expressed in the endometriosis microenvironment. Serum TNF-α levels were higher in patients with endometriosis compared to controls. The TNF-α receptor signals through the key regulatory transcription factor nuclear factor (NF)-κB. TNF-α upregulates the expression of CD44s and CD44 variant forms via apoptosis-related c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) pathways (29). Iron overload and oxidative stress also activate NF-κB. Excessive ROS and oxidative stress are involved in a stress-related cell cycle regulator and stimulate its downstream targets, JNK and p38 MAPK (8). ROS abundance in the inflamed tissue further amplifies several inflammatory reactions.

Endometriosis may induce mechanisms for the protection against ROS-mediated damage. The mechanisms that operate to protect genomic DNA from the oxidative damage need to be identified. HA, a major component of ECM, attenuates DNA damage by neutralizing the Fe^{2+}-mediated oxidative stress (30) (Fig. 1). HA has physiological functions, such as lubrication, water homeostasis and macromolecular filtering, as well as being a well-documented regulator of cell behaviors. Of note, high molecular weight forms of HA have anti-inflammatory properties. It has been established that HA has a protective effect on cellular genome by neutralizing oxidants (31). One mechanism involves the ability of HA to chelate or entrap Fe^{2+}, rendering Fe^{2+} unavailable for Fenton's reaction which produces oxidative species. Thus, HA attenuates the accumulation of the by-products of oxidative species and the damage

that involves the formation of DNA double-strand breaks. HA also prevents the activation of ataxia telangiectasia-mutated (ATM) protein kinase through the phosphorylation on Ser-1981 (ATM-S1981P) and of the variants of histone H2A, histone H2AX on Ser-139 that reflect DNA damage (32).

HA binds to its cell receptor CD44. HA-CD44 binding is important for the initial attachment of endometriotic cells expressing CD44 molecules to mesothelial-associated HA (33). This interaction is one of the mechanisms involved in the pathogenesis of endometriosis. Expression of CD44v9 was detected in the normal endometrial glandular cell membrane (34). CD44v9 expression was increased after cell damage (35). Although CD44v9 was not observed in normal ovarian tissues, ovarian endometriosis shares alterations of CD44 isoforms, which show the adhesive and aggressive potentials of endometriotic cells (34,36).

Upregulation of CD44 expression enhances reduced glutathione (GSH) synthesis (8). A CD44 variant, CD44v9, specifically regulates redox status (9). CD44v9 interacts with xCT, a glutamate-cystine transporter (also known as SLC7A11; solute carrier family 7) and mediates cystine-glutamate exchange (8). xCT controls the intracellular level of GSH and is thereby an important determinant of intracellular redox balance. GSH is one of the first lines of defense against ROS damage. GSH suppresses ROS-mediated p38 MAPK activation, indicating that xCT is crucially involved in the prevention of such stress signaling (Fig. 1). Ablation of CD44 induces loss of xCT and suppresses tumor growth and metastasis. Such metastasis is dependent on the activity of xCT. The xCT system is also involved in cisplatin resistance in ovarian cancer cells through maintaining higher levels of GSH. These findings establish a function for CD44v in the regulation of ROS defense and tumor progression (8).

Recent biochemical and immunohistochemical studies have noted a specific expression of HNF-1β in CCC and genetic alteration may be involved in oxidative stress (2-4). The majority of the CCC-specific genes were associated with the redox-related genes (2). Several important CCC-related genes overlap with those known to be regulated by HNF-1β. UGT1A1 and ANXA4, the HNF-β downstream targets, are also critical enzymes responsible for detoxification in CCC (2). The HNF-1β-dependent pathway might be associated with detoxification pathways, possibly through the upregulation of UGT1A1 and ANXA4 expression as well as CD44v9-xCT-dependent GSH cascade. GSH is a major cellular metabolite that protects against oxidative stress and chemical injury. HNF-1β may attenuate DNA damage and promote cell survival by upregulating the antioxidant protein expression.

7. Conclusions

The pathogenesis of endometriosis is closely associated with iron overload originating from the retrograde flow of the menstrual blood. This review provides more information regarding the molecular mechanisms underlying the protection of oxidative stress afforded by transcription factor HNF-1β. HNF-1β regulates endometriosis-specific gene expression. Fig. 1 outlines the potential challenges to understand the suggested function of HNF-1β downstream targets. HNF-1β regulates the expression of several genes, including CD44v9, which binds several target molecules. CD44v9 specifically regulates cell functions, including migration, growth, survival, anti-apoptosis, immune response and redox status. HA directly reverses the oxidative stress created by redox-active iron. CD44v9 interacts with xCT, which is responsible for exchanging intracellular glutamate for extracellular cysteine, and is able to suppress the ROS-mediated oxidative stress. The HNF-1β-dependent pathway might be associated with detoxification systems, such as the CD44v9-xCT-dependent GSH pathway. In conclusion, endometriosis may induce mechanisms for protecting against the susceptibility to oxidative stress-induced cell and DNA damage.

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