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Review

Hepatocyte nuclear factor-1ß(HNF-1ß) in human urogenital organs: Its expression and role in embryogenesis and tumorigenesis

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Summary. Molecules responsible for embryogenesis are often involved in tumorigenesis. Recent exhaustive cDNA microarray analyses in human neoplasms expanded knowledge of such molecules. Hepatocyte nuclear factor-1ß (HNF-1ß) is a homeobox transcription factor that functions as a homodimer or heterodimer with HNF-1α. In contrast to HNF-1α, HNF-1ß is very weakly expressed in the liver and is commonly expressed in the kidneys. During human embryonic stage, HNF-1ß plays an important role in organogenesis, especially of the urogenital system. In the human fetus, HNF-1ß expression is common in mesonephric duct derivatives and metanephros (permanent kidneys). *HNF-1ß* germline mutations cause malformations of these structures. Recent microarray analyses have disclosed that *HNF-1ß* is aberrantly up-regulated in clear cell carcinoma of the ovary, which is a carcinoma of müllerian nature, but which was initially misnamed "mesonephroma". HNF-1ß is also expressed in ovarian endometriosis, which is a probable origin of clear cell carcinoma. On the other hand, *HNF-1ß* is down-regulated in renal neoplasms, such as chromophobe cell carcinoma. In this review, we first summarize HNF-1ß expression in the developing urogenital system of the human embryo. Then, we describe the *HNF-1ß* status in human urogenital neoplasms and discuss its role in tumorigenesis.

Key words: Hepatocyte nuclear factor-1ß, Urogenital organs, Human, Embryogenesis, Clear cell carcinoma of ovary

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Introduction

Hepatocyte nuclear factor-1ß (HNF-1ß), also called variant HNF or LFB3, is a homeobox transcription factor that shares a high degree of homology with hepatocyte nuclear factor-1α (HNF-1α) in regions important for DNA binding (De Simone et al., 1991; Rey-Campos et al., 1991). HNF-1ß functions as a homodimer or heterodimer with HNF-1α. The expression of HNF-1ß overlaps with that of HNF-1α in many organs, but the ratio of expression differs in each organ (Blumenfeld et al., 1991; Ott et al., 1991). Although HNF-1ß, as well as HNF-1α, is capable of transactivating the promoters of liver-specific genes such as *albumin* (Rey-Campos et al., 1991), HNF-1ß is very weakly expressed in the liver, where HNF-1α constitutes >95% of the total HNF-1-like protein (Blumenfeld et al., 1991). In the mouse kidney, HNF-1α expression is confined to the proximal tubules, whereas HNF-1ß is also expressed in the distal tubules and collecting ducts (Ott et al., 1991; Pontoglio et al., 1996; Coffinier et al., 1999a,b).

HNF-1ß plays an essential role in the organogenesis of mammalian embryos. HNF-1ß is expressed from the first stage of organogenesis, whereas HNF-1α is expressed later, when differentiation is more advanced (Cereghini et al., 1992; Barbacci et al., 1999; Coffinier et al., 1999). Gene knockout mice revealed that *HNF-1ß -/-* mouse embryos die around the 1st week after conception because of a defect in visceral endoderm differentiation (Barbacci et al., 1999; Coffinier et al., 1999), whereas *HNF-1α-/-* mice do not die, but exhibit postnatal dysfunctions of the liver, pancreas and kidneys (Pontoglio et al., 1996). In humans, heterozygous germline mutations in *HNF-1ß* cause maturity-onset diabetes of the young, subtype 5 (MODY5), which is associated with congenital abnormalities, including

polycystic kidneys, an abnormal genital tract and severe pancreatic hypoplasia (Horikawa et al., 1997). In contrast, patients with heterozygous germline mutations in *HNF-1α* (MODY3) do not show abnormal organogenesis, but show functional disturbance of the liver, pancreas and kidneys (Yamagata et al., 1996). Thus, the expression pattern, timing and role are different between HNF-1α and HNF-1ß. HNF-1ß plays an important role in organogenesis, especially of the urogenital system.

Recently, it has been revealed that HNF-1ß is aberrantly expressed in some human neoplasms. cDNA microarray analyses revealed that *HNF-1ß* is significantly up-regulated in clear cell carcinoma of the ovary (Schwartz et al., 2002; Tsuchiya et al., 2003; Lu et al., 2004). In the kidneys, the occurrence of chromophobe cell carcinoma has been reported in patients with *HNF-1ß* germline mutations, and the sporadic form of chromophobe cell carcinoma is also associated with a decrease in HNF-1ß expression (Rebouissou et al., 2005). It is likely that HNF-1ß is responsible not only for organogenesis, but also for tumorigenesis, in humans.

In this article, we review the expression and role of HNF-1ß in human urogenital organs during both the embryonic stage and neoplastic process.

HNF-1beta expression in human urogenital organs

Embryonic stage

During the embryonic stage, 3 different kidney systems, including pronephros, mesonephros and metanephros, develop one after another (Sadler, 1990). Among them, pronephros and mesonephros are rudimentary or temporary organs. The permanent kidney is formed by metanephros and a ureteric bud: the metanephros differentiates into the Bowman's capsule and renal tubule, whereas the ureteric bud differentiates into the collecting duct and pelvis. HNF-1ß is highly expressed in the developing permanent kidney system of humans (Figs. 1, 2). *In situ* hybridization revealed the most prominent expression in the collecting ducts, a lower level of expression in the renal tubules, but no significant expression in the glomeruli or pelvis (Kolatsi-Joannou et al., 2001; Haumaitre et al., 2006). Immunohistochemistry for HNF-1ß also confirmed these findings (Kato and Motoyama, 2009). Such an expression pattern explains the association of germline *HNF-1ß* mutations with renal malformations, such as dysplastic or cystic kidney and single kidney (Bingham et al., 2001, 2002; Bellanne-Chantelot et al., 2004; Edghill et al., 2006).

The ureteric bud originally derives from the mesonephric duct (Wolffian duct) around the 5th gestational week (Sadler, 1990) (Fig. 1). After that the fate of the mesonephric duct is different between male and female fetuses. In the male fetus, the mesonephric duct differentiates into the efferent duct, epididymis, vas deferens or seminal vesicle under the effect of androgen. Both *in situ* hybridization and immunohistochemistry demonstrated HNF-1ß expression in these mesonephric duct derivatives (Haumaitre et al., 2006; Kato and Motoyama, 2009) (Fig. 2). Clinically, *HNF-1ß* mutant males not only show malformations of the kidneys, but also malformations of the mesonephric duct derivatives, including epididymal cysts, epididymal hypoplasia or atresia of the vas deferens (Bellanne-Chantelot et al., 2004). It is most likely that HNF-1ß is responsible for the development of mesonephric duct derivatives in male fetuses. In the female fetus, the mesonephric duct regresses, except for some remnants. HNF-1ß expression, however, is still conserved in these remnants adjacent to the fallopian tube (Kato and Motoyama, 2009).

As for *HNF-1ß* status in the müllerian duct (paramesonephric duct), *HNF-1ß* mRNA was detected in the müllerian duct of a human fetus at the 8th gestational week (Haumaitre et al., 2006). Immunohistochemistry, however, failed to detect HNF-1ß expression in the fallopian tubes or uteri of female fetuses after the 18th gestational week (Kato and Motoyama, 2009). Clinically, *HNF-1ß* mutant females often show genital tract malformations, including uterus didelphys, uterus bicornis or double vagina (Lindner et al., 1999; Bingham et al., 2002; Bellanne-Chantelot et al., 2004; Edghill et al., 2006), all of which are abnormalities of müllerian duct fusion (Robboy et al., 1994). Müllerian duct fusion is usually completed by the 10th gestational week (Sadler, 1990). These facts imply that HNF-1ß is responsible for müllerian duct fusion, and its expression in the developing müllerian duct is limited to the earlier embryonic period when müllerian duct fusion occurs.

In human gonads during the embryonic stage, no

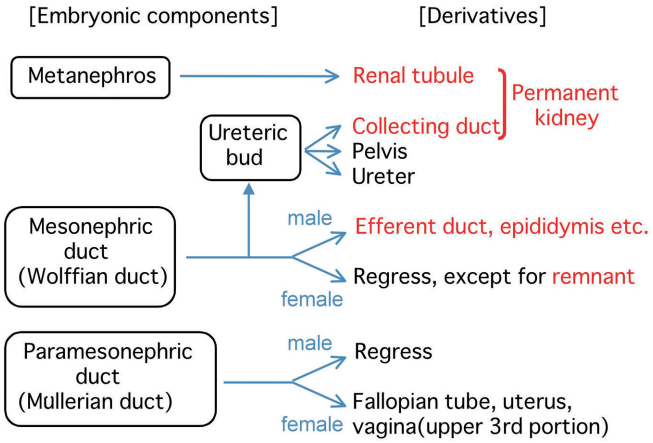

Fig. 1. Expression of hepatocyte nuclear factor-1ß(HNF-1ß) in the developing urogenital system of the human fetus. HNF-1ß expression is common in the tissue/organ indicated in red. In the developing paramesonephric duct (müllerian duct), HNF-1ß expression is most likely to be limited to the early embryonic stage.

significant *HNF-1ß* expression has been detected at either the mRNA or protein levels.

Adult stage

In the kidneys, renal tubules and collecting ducts express HNF-1ß. Immunohistochemically, both the intensity and frequency of HNF-1ß expression are more accentuated in the collecting duct, distal tubule and Henle's loop than in the proximal tubule. Such an expression pattern is possibly related to the ratio of HNF-1α and HNF-1ß expression. In the mouse kidney, both HNF-1α and HNF-1ß, are expressed in the proximal tubules, whereas HNF-1ß is almost exclusively expressed in the distal tubules and collecting ducts (Ott et al., 1991; Pontoglio et al., 1996; Coffinier et al., 1999a,b). In mesonephric duct derivatives, such as efferent ducts or the epididymis, HNF-1ß is still expressed during infancy, but rarely expressed in the adult stage. Interestingly, HNF-1ß expression is conserved in the remnants of the mesonephric duct lying in the mesovarium or mesosalpinx of the adult female throughout life (Kato and Motoyama, 2009).

Among müllerian duct derivatives, HNF-1ß expression is almost exclusively limited to the late secretary endometrium of the menstrual cycle or hypersecretary endometrium of pregnancy (Arias-Stella change) (Yamamoto et al., 2007), both of which contain glycogen in the cytoplasm. This finding suggests that HNF-1ß expression is regulated by sex steroid hormone or chorionic gonadotropin in the endometrium.

In both the testes and ovaries, no significant expression of HNF-1ß was detected by immunohistochemistry, although low levels of *HNF-1ß* transcripts were detected by RNA analysis (Haumaitre et al., 2006).

Aberrant expression of HNF-1ß in urogenital neoplasms

Clear cell carcinoma of the ovary

Clear cell carcinoma is a type of ovarian surface epithelial-stromal cancer (Scully et al., 1998), and represents 5-6% of surface epithelial-stromal cancers in European or American populations, but more than 20% in the Japanese population. Clear cell carcinoma is characterized by the presence of clear cells (containing glycogen) or hobnail cells (with large nuclei that

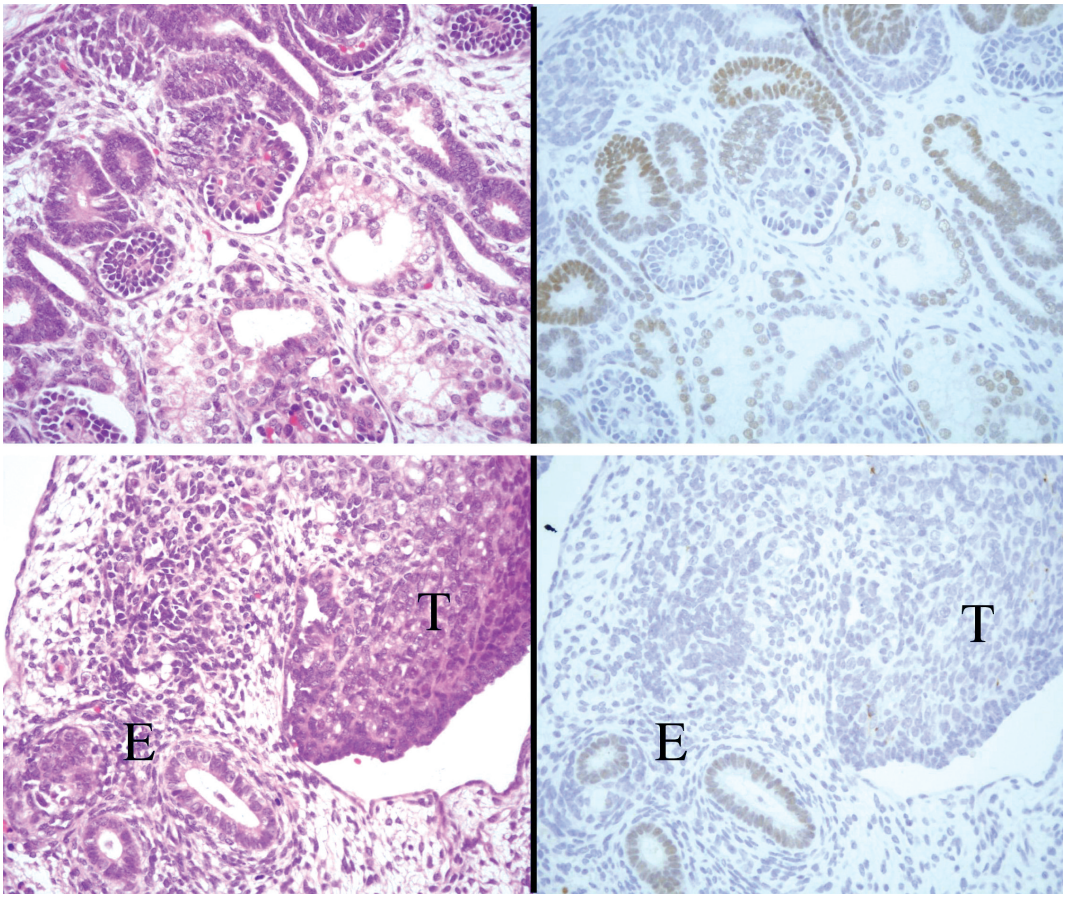

Fig. 2. Top. Immunohistochemistry for HNF-1ß in a human male fetus at 12 gestational weeks. Upper. In the metanephric kidney (metanephros), renal tubules and collecting ducts showed distinct nuclear immunoreactivity for HNF-1ß, but glomeruli were negative for HNF-1ß. **Bottom.** The efferent duct or epididymis (E) showed distinct immunoreactivity for HNF-1ß , whereas the testis (T), including surface coelomic epithelium, was negative for HNF-1ß. (Left, H.E.; right, streptavidin and biotin with hematoxylin counterstain). x 40

protrude into the lumen). The glands of clear cell carcinoma resemble the hypersecretory müllerian glands of Arias-Stella change. Recently, cDNA microarray analyses revealed that HNF-1ß is up-regulated in ovarian clear cell carcinoma (Schwartz et al., 2002; Tsuchiya et al., 2003; Lu et al., 2004). *HNF-1ß* is also overexpressed in borderline and benign clear cell tumors (Kato et al., 2006), which often coexist with clear cell carcinoma. It is suggested that HNF-1ß is involved in the differentiation into the clear cell lineage, rather than in the malignant transformation. Because HNF-1ß is very rarely expressed in other types of ovarian surface epithelial-stromal tumor, including serous, mucinous, endometrioid or Brenner tumors (Tsuchiya et al., 2003; Kato et al., 2006), it is a useful molecular marker for clear cell tumor of the ovary. This is also in the case for ascitic fluid cytology, since clear cell carcinoma cells floating in the ascites still express HNF-1ß , whereas carcinoma cells of other types or mesothelial cells do not show HNF-1ß expression (Kato et al., 2007).

HNF-1ß also sheds light on the histogenesis of clear cell carcinoma. Clear cell carcinoma was initially considered to arise from mesonephric remnants, and the designation "mesonephroma" was used. Clinico-pathological features, however, contradict the mesonephric origin of this tumor (Scully and Barlow, 1967). Ovarian clear cell carcinoma is frequently (~54%) accompanied by ovarian endometriosis (Sainz de la Cuesta et al., 1996; Fukunaga et al., 1997), and the endometriotic epithelium adjacent to clear cell carcinoma frequently shows atypical features, so-called atypical endometriosis (Fukunaga et al., 1997). These facts suggest that a significant number of clear cell carcinomas originate from endometriosis. HNF-1ß provides molecular evidence for this: HNF-1ß is also expressed in the endometriosis adjacent to clear cell carcinoma. Furthermore, approximately 40% of ovarian endometriosis cases without a neoplasm also contain HNF-1ß-positive cells and the HNF-1ß expression is almost exclusively observed in the cells showing reactive atypia (Kato et al., 2006). It is indicated that early differentiation into the clear cell lineage already begins in endometriosis with degenerative and regenarative changes, and clonal expansion of such cells is probably responsible for the occurrence of clear cell carcinoma (Fig. 3).

The mechanism of aberrant up-regulation of *HNF-1ß* in clear cell carcinoma has been studied by some groups. One of the probable mechanisms is hypomethylation of the *HNF-1ß* CpG island. The CpG islands are most often found in the promoter and first exon of genes, and genes can be transcribed from methylation-free promoters (Jones and Takai, 2001). The *HNF-1ß* CpG island was hypomethylated in ovarian clear cell carcinoma, but hypermethylated in ovarian carcinomas of the non-clear cell type or normal ovaries (Terasawa et al., 2006; Kato et al., 2008). The hypomethylation of the *HNF-1ß* CpG island correlates with HNF-1ß overexpression (Kato et al., 2008). Alternatively, another potential contributor to HNF-1ß overexpression is histone acetylation. A previous study showed that methylation was associated with histone deacetylation, and when treating cells with a histone deacetylase inhibitor combined with a methyltransferase inhibitor, *HNF-1ß* expression was synergistically induced (Terasawa et al., 2006).

Clear cell carcinoma of the uterus and vagina

Clear cell carcinoma arises not only in the ovaries, but also in the uterus and vagina, which compose a main trunk of müllerian duct derivatives. In the endometrium, clear cell carcinoma appears either in pure form or in combination with other carcinomas of the müllerian cell type. Clear cell carcinoma of the endometrium also expresses HNF-1ß, whereas other types of endometrial carcinoma do not (Yamamoto et al., 2007). Although less frequently, clear cell carcinoma arises in the uterine cervix or vagina, mostly accompanied by adenosis of the müllerian type. In the past, intrauterine exposure to diethylstilbestrol (DES) caused clear cell carcinoma of the cervix or vagina in girls and young women (Herbst et al., 1974). In our experience, clear cell carcinoma of the uterine cervix also shows distinct expression of HNF-1ß (unpublished data). All of these facts indicate that HNF-1ß is involved in differentiation into the clear cell lineage not only in ovarian tumors, but also in uterine tumors.

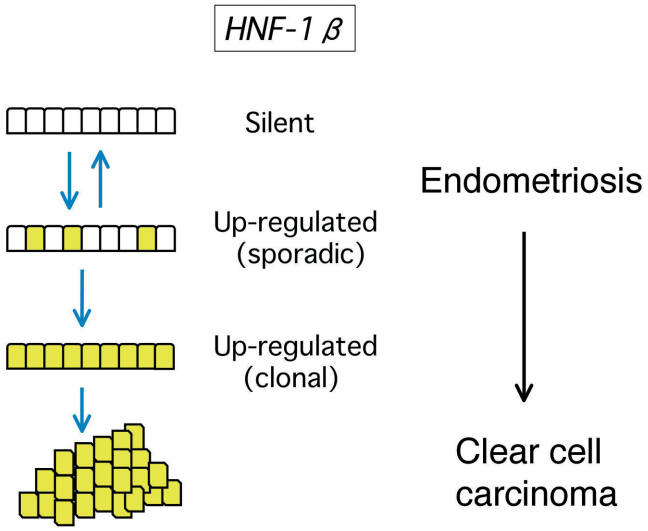

Fig. 3. Schematic representation of HNF-1ß expression and histogenesis of clear cell carcinoma. Up-regulation of HNF-1ß (yellow) sporadically occurs in the endometriotic epithelium during the regeneration and degeneration process. Although such cells have already started to differentiate into the clear cell lineage, most of them are denuded by repeated hemorrhage or inflammation. If clonal expansion of such cells takes place and they undergo malignant transformation, clear cell carcinoma develops.

Chromophobe cell carcinoma of the kidney

Chromophobe cell carcinoma constitutes approximately 5% of renal neoplasms. The tumor cells are characterized by abundant pale acidophilic cytoplasm with well-defined cell borders (Murphy et al., 2004). Ultrastructurally, it is characterized by abundant cytoplasmic microvesicles resembling those observed in normal intercalated cells of the collecting ducts. This finding implies that chromophobe cell carcinoma originates from, or differentiates into, intercalated cells of collecting duct (Storkel et al., 1989).

Rebouissou et al. described 2 patients with a germline *HNF-1ß* mutation who developed chromophobe cell carcinoma of the kidney (Rebouissou et al., 2005). Both patients also had somatic deletion of the wild-type HNF-1ß allele. The finding of a biallelic *HNF-1ß* inactivation in chromophobe renal cell carcinoma suggests that *HNF-1ß* plays a role as a tumor suppressor gene in the development of this tumor. Cytogenetically, chromophobe cell carcinoma is characterized by frequent losses of many entire chromosomes, including chromosome 17 (Bugert et al., 1997), where *HNF-1ß* resides. Although *HNF-1ß* mutations were rarely detected in sporadic chromophobe cell carcinomas (Gad et al., 2007), *HNF-1ß* mRNA was significantly reduced when compared with normal renal tissues (Rebouissou et al., 2005). Epigenetic alterations, such as promoter hypermethylation or histone deacethylation, may act as a second hit for *HNF-1ß* inactivation in the sporadic form of chromophobe renal cell carcinomas.

Potential target genes of HNF-1ß

Potential target genes of HNF-1ß have been identified by experimental reduction or induction of HNF-1ß expression (Fig. 4). In the mouse, renal-specific inactivation of *HNF-1ß* led to polycystic kidney disease, accompanied by down-regulation of several genes involved in cystogenesis, including *Pkhd1*, *Umod* and *Pkd2*, at both the mRNA and protein levels (Gresh et al., 2004). In humans, however, a direct hierarchy between *HNF-1ß* and the *PKHD1, UMOD* and *PKD2* genes has not been shown so far: in human fetal kidneys carrying *HNF-1ß* germline mutations, the renal cysts still expressed PKHD1, UMOD and PKD2. There is a possibility that HNF-1ß protein is transcribed from a wild allele at a sufficient level to sustain the expression of these genes, but the expression is below the critical level that leads to cyst formation (Haumaitre et al., 2006). *Collectrin*, a homologue of *angiotensin converting enzyme 2*, is also a potential target gene of HNF-1ß. Collectrin is localized in the vesicles near the peri-basal body region and primary cilia of collecting duct cells, and probably mediates specific vesicle transport to cilia. The kidneys of *HNF-1ß* deletion mutant mice showed a reduction of collectrin expression and cyst formation (Zhang et al., 2007).

Recently, Senkel et al. established a human embryonic kidney cell line (HEK293) conditionally expressing HNF-1ß and identified 25 potential target genes, including *dipeptidyl peptidase 4, angiotensin converting enzyme 2*, and *osteopontin* (Senkel et al., 2005). Interestingly, up to eight of the 25 genes were also up-regulated in the cell lines of ovarian clear cell carcinoma, showing HNF-1ß overexpression (Schwartz et al., 2002; Tsuchiya et al., 2003). In both HEK293 and ovarian clear cell carcinoma cell lines, one of the most markedly up-regulated genes was *osteopontin*, which is probably a direct target gene of HNF-1ß , because the *osteopontin* promoter contains functional HNF-1ß binding sites at –213 bp and –195 bp (Senkel et al., 2005). In fact, osteopontin is expressed in the developing and developed kidneys. Addition of anti-osteopontin antibodies to rat metanephric organ cultures prevented normal tubulogenesis (Rogers et al., 1997). It is suggested that osteopontin paticipates in morphogenesis and function of kidneys as a member of the HNF-1ß transcriptional network. As for ovarian clear cell carcinoma, a close association between HNF-1ß and osteopontin expression has been shown by immunohistochemistry (Kato and Motoyama, 2008). In the process of tumorigenesis, osteopontin plays several roles, including the inhibition of apoptosis (Hsieh et al., 2006). Clinically, the most important problem in ovarian clear cell carcinoma is resistance to cisplatinum-based chemotherapy (Sugiyama et al., 2000). The fundamental effect of cisplatinum is induction of apoptosis (Pommier et al., 2004). In ovarian clear cell carcinomas, overexpressed osteopontin might interfere with the ability of cisplatinum to induce apoptosis, resulting in a low response to chemotherapy. In this context, it is interesting that knockdown of *HNF-1ß* by RNA interference causes apoptosis of clear cell carcinoma cell lines (Tsuchiya et al., 2003). The reduction of HNF-1ß

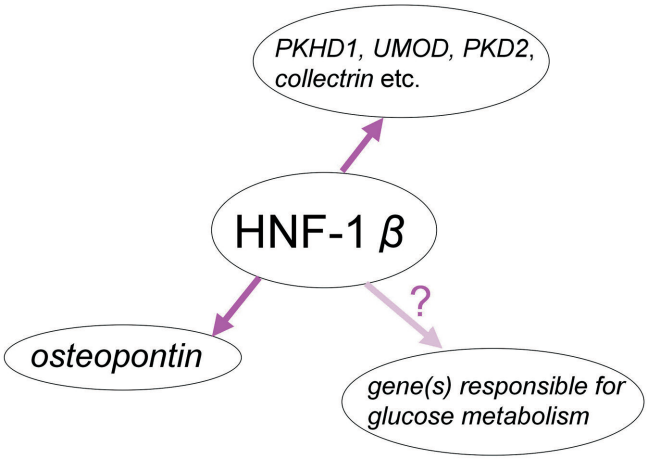

Fig. 4. Potential transcriptional targets of HNF-1ß in human urogenital organs.

might have caused a reduction of osteopontin, followed by an increase in apoptotic activity.

Finally, the fact that clear cell carcinomas of the ovary and uterus, as well as hypersecretory müllerian glands of Arias-Stella change, contain glycogen in the cytoplasm suggests that HNF-1ß affects glucose metabolism. In the mouse, both HNF-1α and HNF-1ß bind to the promoter of *aldolase B* and up-regulate expression of aldolase B, which is involved in both glycolysis and gluconeogenesis (Gregori et al., 2002). On the other hand, it has been shown that HNF-1α directly controls expression of sodium-dependent glucose transporter 2 (SGLT2), which is involved in glucose transport into the cells, in both the mouse and humans (Pontoglio et al., 2000). Although there are no data concerning HNF-1ß and SGLT2, HNF-1ß may transactivate SGLT2 via interaction with HNF-1α or other transcription factors. Further study is needed to clarify the role of HNF-1ß in glucose metabolism in humans.

Conclusions

HNF-1ß is responsible for both malformations and neoplasms in human urogenital organs. During the embryonic stage, HNF-1ß expression is common in the metanephros and mesonephric duct derivatives, but transient in the müllerian duct. In either case, there is a strong correlation between malformations of these structures and *HNF-1ß* germline mutations. Among urogenital neoplasms, clear cell carcinoma of the ovary shows aberrant up-regulation of *HNF-1ß* . HNF-1ß expression is also found in its benign and borderline counterparts, and in ovarian endometriosis, which is a probable origin of clear cell carcinoma. It is indicated that HNF-1ß is involved in the early differentiation into the clear cell lineage, rather than in the malignant transformation. In the kidney, biallelic inactivation of *HNF-1ß* is accompanied by development of chromophobe cell carcinoma, as if *HNF-1ß* acts as a tumor suppressor gene. Finally, such a divergent role of HNF-1ß in both organogenesis and tumorigenesis is most likely explained by the diversity of transcriptional networks where HNF-1ß participates.

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