**INTRODUCTION**

Hepatocyte nuclear factors (HNFs) exist as an assembly of transcription factors that have a vital role in the expression regulation of genes pertaining to the liver. Conversely, these transcription factors are not restricted to hepatocytes, their expression has been observed in other tissues. There are four major families of HNFs namely HNF1, HNF3, HNF4 and HNF6. The HNF1 family members; HNF1-α/A and HNF1-β/B comprise a POU-homeodomain and bind to DNA as homodimers or heterodimers. Hepatocyte nuclear factor 1 beta (HNF1 β/B) exists as a homeobox transcription factor having a vital role in the embryonic development of organs mainly liver, kidney and pancreas. Initially described as a gene causing maturity-onset diabetes of the young (MODY), HNF1β expression deregulation and single nucleotide polymorphisms in HNF1β have now been associated with several tumours including endometrial, prostate, ovarian, hepatocellular, renal and colorectal cancers. Its function has been studied either as homodimer or heterodimer with HNF1α. In this review, the role of HNF1B in different cancers will be discussed along with the role of its splice variants, and its emerging role as a potential biomarker in cancer.

**KEYWORDS**
cancer, hepatocyte nuclear factor 1beta, splice variants, transcription factor
inheritance, early onset of diabetes mellitus, commonly before 25 years of age, and pancreatic beta-cell disruption. Renal cysts were found to be the main clinical aspect with \textit{HNF1B} mutations and the linkage of renal cysts with diabetes steered to the description of renal cysts and diabetes syndrome. Supplementary phenotypes detected in patients include urogenital tract anomalies, condensed exocrine function, anomalous liver function tests, pancreatic hypoplasia, biliary disorders, hypomagnesaemia, hyperuricaemia and early-onset gout.\textsuperscript{8,9}

Ever since the advent of single nucleotide polymorphism (SNP) genotyping arrays, genome-wide association studies (GWAS) are performed to detect numerous loci associated with multiple diseases, including cancer. The vast majority of these SNPs are in intergenic or intronic regions influencing gene regulation.\textsuperscript{10-12} Fine-mapping analysis has revealed an complex genetic architecture at \textit{HNF1B} gene loci, relating to different cancer types.\textsuperscript{13} The current review summarises the emerging role of \textit{HNF1B} and its association with cancer risk in several tumours, and its importance in tumorigenesis.

2 | GENETICS AND EPIGENETICS OF \textit{HNF1B}

Genetic predisposition in human cancer has always been an intriguing area of study, wherein population-based studies have led to genetic models being implemented to explain patterns of the rate of disease occurrences in specific population.\textsuperscript{14} GWAS have identified SNPs in \textit{HNF1B} associated with endometrial cancer (EC) risk in European ancestry and identified rs4430796 SNP as an EC susceptible locus near \textit{HNF1B}\textsuperscript{15} and was replicated in multiethnic replication studies.\textsuperscript{16,17} Nevertheless, these studies emphasized the requirement of large cohorts and stringent tumour stage grouping to classify novel genetic polymorphisms linked with EC vulnerability. Setiawan et al. in a large case-control cohort study on \textit{HNF1B} variants identified rs7501939 SNP in addition to the rs4430796 SNP and confirmed their association with EC risk, demonstrating the association of this locus with both EC type I as well as II tumours.\textsuperscript{18} Fine-mapping studies and laboratory analysis of the \textit{HNF1B} locus, identified potentially causal variants that may mediate the risk of EC. The SNPs detected in this study were
also reported to be associated with HNF1B methylation.\textsuperscript{13} The minor allele of rs11263763 and rs8064454 SNPs are correlated with decreased HNF1B promotor activity suggesting the risk observed at the HNF1B locus is likely mediated due to altered HNF1B gene expression.\textsuperscript{13}

The initial report on HNF1B association with prostate cancer risk came from a GWAS in Iceland\textsuperscript{4} and was later replicated in the USA and UK populations\textsuperscript{19,20} which showed two distinct prostate cancer risk-associated loci on chromosome 17q. SNP rs4430796, in HNF1B, was strongly linked to prostate cancer risk and was one of the first loci to be identified for prostate cancer.\textsuperscript{21} Another independent SNP, rs11649743, found on chromosome 17q12 was later established to correspond with prostate cancer risk.\textsuperscript{21} Widespread fine-mapping studies have been conducted in the region 17q12 and have confirmed the previously documented signals associated with prostate cancer risk. A fine-mapping study in European ancestry indicated the role of five SNPs (rs4430796, rs4794758, rs3094509, rs7405696 and rs1016990) as the best predictors for prostate cancer risk in HNF1B gene loci.\textsuperscript{22} Another study conducted by Olama et al. identified two novel causal variants, rs11263763 and rs718961 in the HNF1B region, along with rs2229295 within 3'UTR to be another potential causal variant for further investigation.\textsuperscript{23} The novel SNPs, rs11263763 in the first intron and rs718961 in the fourth intron overlapping with several bio features were regarded as promising candidates with functional impact. Further, Zhang et al. discovered the loci linked with prostate cancer in North Chinese inhabitants pointing out that the risk allele of the rs4430796 SNP can be associated with high PSA levels.\textsuperscript{24} Another study on non-Hispanic white families by Levin et al. showed SNPs rs4430796 and rs7501939 to be potential risk alleles in primary prostate tumours.\textsuperscript{25} Machiela et al when examining common variants between type-2 diabetes (T2D) and prostate cancer found rs757210 in HNF1B to be significantly associated with prostate cancer risk. The data presented by the authors found a shared genetic association between T2D and prostate cancer risk.\textsuperscript{26} Additionally, diabetogenic variants were also shown to be associated with multiple myeloma. A study by Rios-Tamayo et al. investigated the impact of these diabetogenic variants on the overall survival of multiple myeloma patients.\textsuperscript{27} The intronic rs7501939 SNP was reported to be significantly associated with poor survival in multiple myeloma patients. The authors argued that the functional effects of this SNP could be mediated by non-insulin-dependent mechanisms contributing to tumour progression. Although there was no supporting evidence for this hypothesis, in-depth investigation is required into associating these risk variants with differential regulation of transcript variants/isoforms which may have tumour suppressor and/or oncogenic roles.

SNPs at HNF1B gene loci are also associated with biochemical failure and tumour aggressiveness. Logistic regression analysis in Korean patients (240 prostate cancer subjects and 223 controls) to evaluate the effects of 47 SNPs in HNF1B on prostate risk.\textsuperscript{28} The rs11868513 SNP was found to be more prevalent in patients with higher aggressive tumour stage compared to the low aggressive tumour stage. Strong prostate cancer risk association was observed in patients with rs4430796 and rs2074429 haplotypes with a Gleason score of $\geq 7$. Although this study was the first in associating HNF1B polymorphisms with prostate cancer risk in Korean men, the statistical significance of the SNPs was limited due to the small sample size. Additionally, the comparisons were between prostate cancer patients and non-malignant BPH patients which could have influenced the final results. Using a multilevel molecular epidemiology approach in patients with prostatectomy and biochemical failure,\textsuperscript{29} the rs4430796 SNP was found to be significantly associated with increased biochemical failure ($p = 0.02$), highlighting the biological relevance of this SNP in disease progression. All these studies highlighting the use of SNPs in identifying biochemical failure or tumour aggressiveness, seem to be limited in their approach due to their analysis in small cohorts. Validation in large cohorts may provide a strong basis for using these data in clinical applications.

HNF1B has also been found to be associated with testicular germ cell tumour. Researchers in Sweden performed a GWAS by genotyping 610,240 SNPs from patients and control samples from Norway and Sweden.\textsuperscript{30} After finding no novel associations in the discovery phase, a replication study found 15 novel regions to be associated with the disease. Genome-wide significance was obtained for the SNP at HNF1B gene loci. Although some of the known major risk loci (KITLG, SPRY4, BAK1 and DMRT1) were also implicated with this cancer risk, some of the low penetrant risk alleles such as rs7501938 SNP also need to considered for a better understanding of the genetic cause of this disease.

Despite the great knowledge of mutations in HNF1B in MODY, few studies have highlighted the role of mutations in cancer. Nemecjova et al while understanding the genetic changes of HNF1B in endometrial lesions, revealed truncated variants in ovarian clear cell carcinoma (CCC).\textsuperscript{31} The study identified 4 sequence variations and one missense mutation in ovarian CCC patients. In silico analysis suggested a nonsense mutation (p.Gln152X) to lead to premature translation termination and another missense variant in the DNA binding domain (p.Ala283Val) to have a damaging effect on the function of the protein (Refer to Table 1).

### 2.1 HNF1B and epigenetics

Genetic modifications and Epigenetic mechanisms influence carcinogenesis. Identification of mutations and its associated effect on the epigenome through next-generation sequencing
has broadened our understanding of cancer regulatory pathways affecting cellular characteristics. DNA methylation is associated with gene transcription regulation. In a study conducted to investigate the role of GATA4 and HNF1B methylation in Ovarian cancer (OC) patients, around 32.8% HNF1B methylation positive patterns were observed in OC tissue samples compared to controls. Unmethylated HNF1B regions in control samples correlated with higher survival rate in patients suffering from OC. Overall, the methylation pattern for both genes was found to be 65.6%, highlighting the potential of these genes as methylation prognostic panel markers.

The methylation profile of HNF1B was further characterised by Terasawa et al in OC cell lines and tissue samples. Epigenetic silencing of the HNF1B gene was observed in the cell lines due to methylation, decreasing the expression of HNF4α suggesting the role of hepatocyte nuclear factor network of genes in tumours. The study also reported the role of histone deacetylation organized with methylation to be involved in tumorigenesis in ovarian cancer. Additionally, this group also highlighted HNF1B methylation patterns in colorectal, gastric and pancreatic cell lines, all of which showed silencing of HNF1B gene expression due to methylation. Moreover, in breast tumours, methylation of homeobox genes including HOXB13 and HNF1B, CpG islands has been found to be significant and more pronounced compared to normal samples. Early-stage breast cancer samples exhibited 73% methylation patterns establishing the role of HNF1B methylation with epigenetic reprogramming and carcinogenesis in breast tumours, confirming the role of the epigenome in carcinogenesis. These results give an indication of the epigenetic mechanisms involved with homeobox genes including HNF1B in tumorigenesis.

Distinct DNA methylation patterns were observed for the different histological tumour subtypes, underlying divergent mechanisms involved in ovarian cancer subtypes. Unmethylated HNF1B promoter displayed expression of the protein in clear cell tumours whereas serous tumours which displayed methylation at HNF1B lacked the protein expression. The research also suggested a negative correlation between HNF1B promoter methylation and CpG island hypermethylation. After identifying causal SNPs in the HNF1B region, the SNP-HNF1B promoter DNA methylation was found to overlap with a polycomb repressive complex 2 mark in serous ovarian cancer. Molecular signatures like these (HNF1B status or CIMP) may help classify subtypes of clear cell carcinomas. A study to understand DNA methylation in colorectal cancer identified HNF1B methylation in colorectal patients. HNF1B was found to be highly methylated in addition to 4 other genes (RUNX3, PCDH10, SFRP5, IGF2), which repressed its expression indicating varying extent of methylation for HNF1B gene. In clear cell carcinoma, a pattern of hypomethylation has a positive correlation to increased expression suggesting an oncogenic role in this disease. Alternatively, the negative correlation in methylation: expression patterns indicate a tumour suppressor role of HNF1B in high grade serous ovarian cancer. Altogether, the methylation patterns in HNF1B may be used as prognostic predictors, highlighting the value of performing a pan-cancer methylation study in a large cohort of patients.

### Table 1: HNF1B variants association with different cancers

| Cancer       | GWAS SNP         | Location     | Reference |
|--------------|------------------|--------------|-----------|
| Endometrial  | rs4430796,       | Intron_variant | 13,16,18  |
|              | rs7501939,       |              |           |
|              | rs11263763,      |              |           |
|              | rs8064454,       |              |           |
| Prostate     | rs4430796,       | Intron_variant | 4,19-28   |
|              | rs11649743,      |              |           |
|              | rs4794758,       |              |           |
|              | rs3094509,       |              |           |
|              | rs7405696,       |              |           |
|              | rs1016990,       |              |           |
|              | rs11263763,      |              |           |
|              | rs2229295,       |              |           |
|              | rs718961,        |              |           |
|              | rs757210,        |              |           |
|              | rs11868513,      |              |           |
|              | rs2074429,       |              |           |
| Testicular   | rs7501938        | Intron_variant | 30        |
| germ cell    |                  |              |           |
| Ovarian CCC  | rs757210         | Intron_variant | 32        |

**TABLE 1 HNF1B variants association with different cancers**

Alternative splicing has been vastly studied in cancer, changing the landscape and functions of many oncogenes and tumour suppressor genes. It’s strenuous to interpret the role for these transcripts, since the translated alternative splice exons code for critical functional domains of the encoded protein, for instance, BCL2 family, wherein intron 2 of the Bcl2L1 gene, coding for Bcl-X protein undergoes alternative splicing, the mRNA produced could have a different function such as, the classical large protein having anti-apoptic function and the novel truncated protein lacking the BH domain has a pro-apoptic function. Several tumour suppressor genes also undergo alternative splicing, causing, complete or partial loss of function. For example, TP53, coding for p53 protein gives rise to multiple isoforms having different protein functions. Alternative splice variants of P53 can induce cell cycle arrest in G1/G2 cell cycle phase or could activate/
regulate cell cycle arrest in G2/M phases. These are few examples that highlight the scope of alternative splicing generating multiple proteins from a single gene which would result in contrasting functions impacting cell function.

Alternative mRNA splicing events are conserved amongst species. However, a substantial amount of genes identified to be alternatively spliced in human, do not form numerous transcript variants in rodents. Alternate splicing may give rise to different HNF1A, B and HNF4A genes and diverse isoforms (eight isoforms in HNF1A and four isoforms in HNF1B; 9 in HNF4A) in humans by an arrangement of differential polyadenylation sites, alternate promoter usage and alternative splicing. HNF1A, HNF1B and HNF4A transcription factors are present in a synchronized feedback circuit in majority tissues, although the specific essence of collective regulation might vary amongst tissues.

The alterations among transcript variants lead to the formation of proteins with different properties. HNF1A and B function just as dimers, so even minimal amounts of the isoforms can alter overall activity in vivo. Human HNF1B gene encodes three transcript variants (Figure 1), HNF1B (A), HNF1B (B) and HNF1B (C) (Figure 2). HNF1B (A) and HNF1B (B) variants are analogous structurally and hence could exhibit functional anomaly. It was observed that higher levels of HNF1B (C), a repressor molecule could lead to a decline in HNF1B activity in rodents. Data have suggested that HNF1A (B), HNF1A(C), HNF4A3 and HNF4A9 might have a function in human beta cells as their existence can alter MODY phenotype. A study by Harries et al indicated HNF1B (C) isoform as predominant in Benign Prostate Hyperplasia (BPH), amounting to 90% of the total gene's expression. However, in prostate cancer tissues HNF1B (B) isoform contributed to 95% of the total HNF1B expression. HNF1B (C) accounted for only 3% while HNF1B (A) proportion did not change. HNF1B (C) variant has also been detected to negatively control GSTA (Glutathione-S-transferase A) promoter. The role of HNF1B splice variants needs to be well defined in cancer and a better understanding of the mechanisms might lead to a breakthrough in therapeutic applications.

4 | HNF1B INTERACTIONS AND TARGET GENES

To understand the cellular processes, it is essential to identify the target genes affected by the transcription factor. Several studies have identified the individual target genes of HNF1B in hepatic-cell, ovarian and kidney cell lines (Figure 2). HNF1B suppression has been found to downregulate the expression of the HNF family members-including HNF1A, HNF4A, HNF6, HNF3 (HNF3α, β and γ) in mouse liver cells. Other genes like HNF1, insulin-like growth factor binding protein 1, Albumin, α-fetoprotein were downregulated in mouse hepatoma cells on suppression of HNF1B by RNAi, whereas apolipoprotein, α1-antitrypsin, alcohol dehydrogenase 2 and α-fibrinogen showed increased expression. Hu et al. reported HNF1B as a prostate cancer risk gene with its mechanism of action assessed in a wide array of prostate cancer cell lines. Twelve genes were found to be associated with...
HNF1B, six of them (BAG1, ERBB4, ESr1, HSPD1, NR4A1 and PIK3CG) mapped to KEGG pathways (Figure 2). A study understanding the regulation of the UDP glucuronosyltransferase 2B17 gene promoter found elevated expression of this gene by HNF1B in LNCaP prostate cancer cell line. Wang et al further demonstrated the enhancer of the zeste homolog 2 (EZH2) as one of the downstream targets of HNF1B along with its overexpression shown to be associated with prostate cancer malignancy. EZH2 binds to the HNF1B locus which then suppresses HNF1B expression in prostate cell lines, although when the function of HNF1B restored the expression of EZH2 is repressed with increased invasion and migration. Together these studies highlight the transcriptional role of HNF1B and its network in prostate cancer, although extensive studies on its mechanism are required to interpret its role in disease.

Overexpression of HNF1B in pancreatic B cells has been linked to apoptosis and cell cycle, underlying its importance in B cell growth, although the exact pathway is not clearly understood. It is likely that, apoptosis and differential control of cell cycle occurs with increased expression of HNF1B in pancreatic B cells, underlying its importance in B cell growth, although the exact pathway is still unclear. Protein tyrosine phosphatase-BL (PTP-BL or ptpn13), an HNF1B modulated protein in the B-cell has been identified conjointly with its function in INS-1 B cells. Welters and Morgan observed elevated PTP-BL protein levels on subsequent induction of HNF1B expression in INS-1 Flip-In T-Rex cell. Amplified HNF1B protein expression leads to compromised insulin secretion, augmented apoptosis and a decline in cell proliferation in INS-1 cells but the investigation of these responses showed their differential sensitivity to PTP-BL. The results from this study indicated that Wnt signalling pathway modulating mature B-cell growth is regulated by HNF1B (Figure 2).

Osteopontin (OPN) gene expression has been found to be elevated in ovarian CCC and its expression to be associated with HNF1B overexpression. OPN comprises of HNF1B functional binding sites in its promoter stretch, validating as a direct target gene of HNF1B. OPN plays a crucial role in tumorigenesis by inhibiting apoptosis or activating matrix-degrading proteases. Research on ovarian CCC has suggested HNF1B to be at the centre of a functional circuit, identifying susceptible targets of HNF1B. Chk1 (Checkpoint kinase 1) protein has been observed to be stimulated in the HNF-1B-overexpressing CCC cells. Chk1 has a role in the cellular existence pathways which augment DNA damage repair. The inhibition of Chk1 expression specifically chemosensitizes HNF1B-overexpressing CCC cells in vitro, underlying its importance as a novel therapeutic target in HNF1B positive cells. Senkel et al identified HNF1B regulated genes in the human embryonic kidney cell line (HEK293) and identified eight genes to be upregulated in ovarian CCC in comparison to other subtypes. Increased expression of HNF1B caused deregulation of genes including SPP1, DPP4, SAH, RBPM5, CD24, NID2, LAMB1, RHOB and SOX9 in ovarian CCC. SPP1 and Dipeptidyl Peptidase 4 (DPP4) had HNF1B binding sites in their promoter stretch, identifying them as a direct target. Additional studies in ovarian CCC revealed 22 genes as downstream targets of HNF1B. Furthermore, it has also been demonstrated that HNF1B could be associated with the genetic alterations most likely to be involved in the essential function of cell physiology of Ovarian CCC, such as oxidative stress (DPPIV, ACE2, Collectrin, TFFP2, Octamer4, PAX8), detoxification pathway, metabolism (GLUT2, ALDOB), adhesion and signal transduction (MAP3 K5/ASK1, mTOR). This genetic profile could lead to validation amongst stages of OCC in comparison to histological subtypes. It also highlights HNF1B as a unique molecular signature for pathophysiology of ovarian CCC. Additionally, Wiedmann and group characterised the interaction of DNA binding domain of HNF1B to Importin-α isoforms using pull-down assays. Also, HNF1B nuclear localisation signal (NLS) identified through biophysical techniques elucidated its role in facilitating the interactions of NLS peptide to Importin-α. This has opened new avenues for developing new therapeutics against HNF1B selectively targeting the HNF1B-Importinα interaction.

HNF1B has been observed to be directly regulating HNF4α in humans. Various pathways related to HNF1B need to be explored which could provide new insights to developing anticancer agents targeting these HNF1B regulated circuits. HNF1B induced expression of clotting factors in tumour cells, including elements involved in clotting cascade like prothrombin, fibrinogen, factor XIII, contributing to prothrombotic state in malignancy. The findings also indicated starch and sucrose metabolism genes as HNF1B targets. Xu et al identified a putative binding site in NNMT (Nicotinamide N-methyltransferase) gene promoter region, which is greatly expressed in papillary thyroid cancers including the cell lines. These findings suggest HNF1B be a transcriptional activator of NNMT gene expression in some papillary thyroid cancers.

Co-immunoprecipitation experiments by Choi et al indicated zyxin, a focal adhesion protein, as a novel interacting partner of HNF1B in renal epithelial cells. The study established the importance of an additional LIM domain of zyxin interacting with HNF1B. Additionally, it established the role of zyxin bound to CREB Binding Protein (CBP) stimulating the transcription of HNF1B. Co-localization of zyxin with HNF1B was observed in the nucleus. Increased expression of zyxin leads to the transcriptional activity of HNF1B, on the contrary siRNA (RNA mediated) silencing of zyxin impeded the HNF1B-dependent transcription. Expression of dominant-negative mutant HNF1B, silencing of zyxin, resulted in reduced EGF-induced cell migration.
These results suggest a novel route for regulating HNF1B which is vital for renal epithelial differentiation. Previous studies have reported that HNF1B is essential for renal tubulogenesis by regulating the gene expression of SOCS3. This pathway showcases another route through which HNF1B might control tubulogenesis throughout kidney development. Also, the initial decline in HNF1B expression is linked with the over-expression of one of its target genes, SOCS3, which is a requisite for renal repair. During developmental stages, HNF1B as a transcription factor has been identified to control a network of genes involved in duct morphogenesis. Inactivation of HNF1B by Cre-Sox9 recombination was found to cause chronic pancreatitis with dilution of ducts, acinar-to-ductal metaplasia and lipomatosi.

Inactivated HNF1B in mouse ductal cells was seen to decrease the expression of Proxl, Pkhdl, Spp1 and Cys1, which play an important role in maintaining tubule structure. This led to chronic pancreatitis and formation of neoplasia through KRAS activation in mature acinar cells. This study identifies HNF1B as a potential tumour suppressor gene in pancreatic cancer.

Hypoxia is regularly attributed to various tumours linked by disease progression along with treatment resistance. Hypoxia-inducible factor 1 (HIF-1) complex regulates many oxygen-responsive genes. HIF-1α overexpression, evident with accumulated immunostaining, has been described in various human cancers (including prostate cancer) during their metastases. Current evidence proposes that HIF-1 is engaged with notch-responsive promoters in hypoxic conditions to initiate transcriptional targets. Hypoxia induces initial up-regulation of HNF1B from 1 to 24 hours in vitro, independent of the HIF-1α expression. When continued, hypoxia-induced HNF1B down-regulation while normoxia led to HNF1B normalization. Early reduction in HNF1B expression has been linked with transient overexpression of its target gene Soc3, which is vital for renal repair. Additionally, in a recent study by Li et al on polycystic kidney disease (PKD), HNF1B was shown to have been regulated by p53S, a mutant version of the tumour suppressor gene amongst various human cancers signifying its role as the tumour suppressor gene. HNF1A is a main regulator for plasma protein fucosylation and plasma levels of C-reactive protein. By mutating HNF1A by small interfering RNA in hepatocellular carcinoma cells increases overexpression of numerous genes translating cell cycle and angiogenesis regulators, growth factors, receptors and components of translational machinery. HNF1B has been confirmed as a common cause of monogenic disorders such as developmental renal disease. Janky et al also reflected HNF1A/B as top enriched genes involved in the functioning of normal pancreatic tissue in comparison to regulatory network Pancreatic Ductal Adenocarcinoma (PDAC). HNF1B has shown to be implicated in balancing the beta-cell transcription factor network and is essential for glucose sensing or glycolytic signalling in the pancreatic beta cell. HNF1B was shown to be down-regulated in vitro in PDAC cells functioning via microRNA mechanism implying has-miR-24-23a. HNF1B deregulation has shown to be associated with epithelial to mesenchymal transition which might occur due to the destabilisation of the E-cadherin and B-catenin initiating altered cadherin/catenin nexus implicating the Wnt-targeted genes in PDAC. Janky et al predicted HNF1A/B to be amongst the top transcription regulators in normal pancreatic tissue.

Loss of protein expression in malignant ductal cells of the pancreas suggested tumour suppressive roles of HNF1A/B in pancreatic cancer. Moreover, it has been demonstrated that HNF1B, a paralogue of HNF1A, acts as both a cofactor of HNF1A or compensate the loss of HNF1A activity.

## 5 ROLE OF HNF1B IN CANCER

### 5.1 Tumour-suppressive function

HNF1B is of the identified gene/s as per pathway analysis of GWAS data carried out by Li et al. HNF1B being a transcription factor, monitors development and differentiation in embryonic pancreas while also maintaining pancreatic homeostasis. PDX1, NR5A2, HNF1A and HNF1B function collectively carrying out regulated feedback circuit nursing pancreatic development and differentiation. There have been reports of somatic mutations of the HNF1A gene amongst various human cancers signifying its role as the tumour suppressor gene. HNF1A is a main regulator for plasma protein fucosylation and plasma levels of C-reactive protein. By mutating HNF1A by small interfering RNA in hepatocellular carcinoma cells increases overexpression of numerous genes translating cell cycle and angiogenesis regulators, growth factors, receptors and components of translational machinery. HNF1B has been confirmed as a common cause of monogenic disorders such as developmental renal disease. Janky et al also reflected HNF1A/B as top enriched genes involved in the functioning of normal pancreatic tissue in comparison to regulatory network Pancreatic Ductal Adenocarcinoma (PDAC). HNF1B has shown to be implicated in balancing the beta-cell transcription factor network and is essential for glucose sensing or glycolytic signalling in the pancreatic beta cell. HNF1B was shown to be down-regulated in vitro in PDAC cells functioning via microRNA mechanism implying has-miR-24-23a. HNF1B deregulation has shown to be associated with epithelial to mesenchymal transition which might occur due to the destabilisation of the E-cadherin and B-catenin initiating altered cadherin/catenin nexus implicating the Wnt-targeted genes in PDAC. Janky et al predicted HNF1A/B to be amongst the top transcription regulators in normal pancreatic tissue. Loss of protein expression in malignant ductal cells of the pancreas suggested tumour suppressive roles of HNF1A/B in pancreatic cancer. Moreover, it has been demonstrated that HNF1B, a paralogue of HNF1A, acts as both a cofactor of HNF1A or compensate the loss of HNF1A activity.
HNF1B transcription factor is essential in the regulation of gene expression for organs such as pancreas, kidney, liver and gut. Renal diseases are homogenous phenotype which is usually associated with the mutation in transcription factor. Mostly these deformities have pancreatic atrophy and exocrine dysfunction. It has been observed that patients suffering from HNF1B mutations have varying renal functions from normal until dialysis-dependent/transplanted. Buchner et al highlighted the role of HNF1B in metastatic renal cell carcinoma and demonstrated levels of HNF1B mRNA expression drastically declines in metastatic tumours whereas patients with higher HNF1B mRNA levels would have a better prognosis. Another case study carried out by Grunfeld et al. suggested a germline mutation of HNF1B (46delC) was associated with cystic kidney disease and chromophobe renal cell carcinoma, whereas a somatic deletion of HNF1B was reported for renal tumour. Chromophobe renal cell carcinoma was found to be associated with patients having biallelic inactivation of hepatocyte nuclear factor 1 beta. The study further confirms the role of HNF1B expression in renal neoplasms and its potential as a diagnostic marker for Chromophobe renal cell carcinoma. Nephrologists have also identified autosomal dominant mutation of HNF1B linked with polycystic kidney disease, diabetic nephropathy and cystic kidney disease (CKD) of unknown cause. Moreover, there has been widespread screening for individuals lacking HNF1B and HNF1A. In most of the disease states, genes such as PKHD1 (polycystic kidney and hepatic disease 1) and UMOD (Uromodulin), two genes regulated by HNF1B have been found to be inactivated. Rebuissou et al suggested the role of HNF1B as tumour suppressor gene in CRCC via the regulation of PKHD1. On the other hand another study carried out by Gad et al highlighted mutations in BHD and TP53 which is responsible for sporadic CRCC and found extremely rare events related to HNF1B mutation. Latest report by Bartu et al reflected the consequences of somatic exonic mutations of HNF1B along with its role in the pathogenesis of kidney tumours emphasizing HNF1B could act as oncogene in papillary renal cell carcinoma (reduced HNF1B was exhibited along elevated tumour grade with T stage) whereas it may behave as a tumour suppressor in CCRCC and CHRCC (no mutations was observed whilst promoter methylation was present). Many studies have pointed HNF1B locus with respect to SNP associations, although expression studies have conflicting data of these risk alleles in prostate cancer. Functional studies suggested the role of HNF1B as a pro-differentiation factor that represses epithelial-mesenchymal transition (EMT) in unmethylated normal tissues. Once methylated, the activity of HNF1B as a tumour suppressor is lost in course to the development of prostate cancer. Yamamoto et al. established that HNF1B immunoreactivity contrasted significantly between CCC and other pathological features in both the ovary and the endometrium, proposing HNF1B to be an eminent marker for differentiating CCCs from additional lesions together; the ovary and the endometrium. It was revealed by Kao and colleagues that the overexpression of HNF1B is specific for ovarian CCC amongst ovarian carcinomas. Ablation of HNF1B expression in ovarian CCC cells leads to a substantial proliferation, while increased expression of HNF1B in the serous Ovarian cancer (OC) cell line decreased cell growth. Decreased expression of HNF1B could impart drug resistance in OC and that HNF1B may contribute to drug resistance through regulating four pathways comprising p53 signalling, focal adhesion and ErbB signalling in addition to apoptosis (Refer to Table 2).

### 5.2 Oncogenic roles

HNF1B deletion has been observed to cause condensation of pancreatic multipotent progenitor cells (MPCs) owing to reduced proliferation and increased apoptosis. De Vas et al detected that the Notch signalling pathway is dysregulated in Hnf1b mutant pancreas, displaying a reduction in Delta-like Canonical Notch Ligand 1 (Dll1) expression and increased expression of Hairy and Enhancer of split related basic helix-loop-helix (Hey) repressors. HNF1B was found to be upregulated in ovarian cell carcinomas and clear cell variant of ductal adenocarcinoma.

| Cancer                | Oncogene/Tumour suppressor gene     | Pathway affected                                                                                                           | Reference |
|----------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------|
| Pancreatic cancer    | Tumour suppressor gene             | Apoptosis, pancreatic development, hedgehog, Helicobacter pylori lacto/neolacto and Th1/Th2 immune response               | 85,86     |
| Renal Cell carcinoma | Tumour suppressor gene             | Invasive alteration and dedifferentiation                                                                                   | 90-95     |
| Ovarian cancer       | Tumour suppressor gene             | Epigenetic silencing                                                                                                       | 97-99     |
| Prostate cancer      | Oncogene/tumour suppressor gene    | Epigenetic silencing                                                                                                       | 32        |
| Endometrial cancer   | Oncogene                           | Reduced promotor activity                                                                                                  | 13        |
| Breast cancer        | Oncogene                           | Epithelial-mesenchymal transition (EMT)                                                                                    | 108       |
| Kidney cancer        | Oncogene                           | Late tubular separation                                                                                                    | 104       |
Trisomy and tetrasomy of chromosome 17 have been highlighted as a cause for papillary renal cell tumours (RCT). A comprehensive detailed analysis has shown HNF1B gene loci amplification in RCT; the protein being detected in papillary RCTs, mucinous tubular and spindle cell carcinomas (MTSCC) and metanephric adenomas. Differentiating tubules of the fetal kidney produced HNF1B protein, while high expression was observed in adult carcinomas of embroyonal origin. The copy number changes and increased expression of the HNF1B gene were linked with late tubular separation in precursor lesions (Refer to Table 2).

HNF1B is associated with cancer cell proliferation, tumour progression, and castration-resistant prostate cancer. Painter et al. highlighted the role of the HNF1B protective rs11263763 SNP allele in EC with reduced promoter activity, indicating HNF1B’s oncogenic role. Similarly, Larson and colleagues performed trans-EQTL studies and identified risk alleles increasing HNF1B expression, suggesting a probable oncogenic role in PCa. This study also found intronic rs3110641 SNP to be associated with changes in HNF1B isoform expression. Additional studies in breast cancer have also emphasized HNF1B overexpression in inducing EMT in epithelial NMuMG cells. A study corroborating key role of EMT in metastasis and therapeutic resistance has shed light on the prospect of developing new strategies targeting EMT signalling. However, contrasting evidence shows that inhibition of EMT does not prevent metastasis. Targeting transcription factors has always been a challenge with them being called ‘undruggable’. As previously discussed, lower levels of HNF1B in prostate cancer has now been associated with higher EZH2, promoting EMT and metastasis. A new therapeutic approach targeting this axis could help in treating tumour growth.

6 | HNF1B AS A BIOMARKER IN CANCER

HNF1B has been well characterised in liver, pancreas and kidney, while diagnosing its related disease has been challenging due to phenotypic variability. Among the first to identify the potential of HNF1B in hepatocellular carcinoma (HCC), Ninomiya et al highlighted the ratio of HNF1A/HNF1B expression in HCC tissues to be higher in well-differentiated cases compared to undifferentiated and poorly differentiated cases. Similarly, Wang et al reported the ratio of HNF1A: HNF1B expression to be related to histologically differentiated disease. The expression of HNF1B was found to be higher in differentiated HCC compared to non-cancerous tissues. These studies emphasize the potential role of HNF1B as a biomarker. Several studies have highlighted the role of HNF1 family members in regulating alpha-fetoprotein (AFP) promoter expression during hepatic development and carcinogenesis. Immunohistochemistry studies in liver transplant patients with HCC revealed that HNF1B has been associated with serum AFP level and AFP expression. Transcriptional regulation of AFP through HNF1B may function during different stages of HCC progression following recurrence. The expression of HNF1B in tumour tissue, thus, can predict relapse and mortality after transplantation. Shim et al. also monitored the relevance of HNF1B in hepatocellular carcinoma following liver transplantation which corresponded with the findings. Additionally, Yu et al. investigated the expression of HNF1B with clinicopathological features and prognosis in HCC and cholangiocarcinoma (ICC) patients. HNF1B expression was found to be positively correlated with recurrence in HCC indicating poor prognosis. However, no correlation was found with its expression in ICC and survival. Further studies need to be conducted on developing HNF1B as a prognostic marker predicting recurrence in HCC.

In the latest study by Nie et al., HNF1B expression was observed to be higher in uterine corpus endometrial carcinoma, bladder urothelial carcinoma and liver hepatocellular carcinoma and minimal expression levels in liver hepatocellular carcinoma, colon carcinoma, glioblastoma multiforme, kidney chromophobe and kidney renal clear cell carcinoma. HNF1B expression is associated along with heterogenous immune cell infiltration levels in distinct cancers. For instance, HNF1B expression is correlated with the infiltration grades of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils along with Dendritic cells in cancer. Patients were categorized into low and high HNF1B expression groups based on the CD4+ T cell, CD8+ T cell along with B-cell levels, which were further grouped based on overall survival of cancer patients into different subsets. This study emphasizes the correlation amongst HNF1B and immune cells and the need for further investigation into the HNF1B expression for patients undergoing immunotherapy. Moreover, the group also demonstrated HNF1B mRNA dysregulation in different cancers that lead to differential expression of HNF1B leading to distinct prognosis.

Pancreatic abnormalities have been tested for HNF1B mutations and its prospectus as a biomarker being widely debated in renal hyperplasia and cysts. Yang and colleagues investigated the role of HNF1B in PDAC as a diagnostic marker in a large cohort of 127 primary and 17 metastatic PDACs, 47 biliary adenocarcinoma and 231 pancreaticobiliary carcinomas. Majority of pancreatic and biliary epithelium carcinomas had an expression of HNF1B, with statistical analysis showing 84% sensitivity and 85% predictive value overall. The expression of HNF1B was associated with tumour size and grade highlighting the potential of the gene as a biomarker in PDAC. Likewise, HNF1B was shown to be part of five gene expression signature predictive of relapse in prostate cancer patients.
Kaplan-Meier analysis revealed that relapse of predictor markers are highly useful in the classification of patients into subgroups with distinct relapse-free survival after therapy. Furthermore, Harries et al reported a probable role of alternatively spliced mRNA of HNF1B and MSMB genes in the cause of prostate cancer.

Ovarian CCC has a poor prognosis of all the epithelial ovarian cancers. Immunohistochemical analysis showed HNF1B nuclear staining in clear cell carcinoma specimens but minimal nuclear staining in non-clear cell carcinoma specimens. HNF1B may be an excellent CCC-specific molecular marker. Apoptotic cell death was seen in TOV-21G and JHOC-5 ovarian CCC cell lines induced by reduction of HNF1B expression by RNA interference indicating that, HNF1B is an excellent CCC-specific molecular marker and can also be used as the molecular target therapy for Ovarian CCC. Similarly, Huang and colleagues also showed expression of HNF1B in ovarian CCC patients with a statistical specificity of 76.5% and selectivity of 85.2%. In a study investigating HNF1B expression in ovarian clear cell tumours, there was a clear distinction of the levels of the protein being present between clear cell carcinomas vs non-clear cell carcinoma, indicating its potential as a molecular marker for ovarian CCC irrespective of benign or malignant lesions. Cuff et al defined HNF1B as an extensive marker for clear cell phenotypes, endorsing a mechanistic association to glycogen aggregation and thrombosis. This outcome suggests a novel mechanism of tumour linked thrombosis centred on cancer cells directly producing clotting factors.

HNF1B and ER (oestrogen receptor) may be used as a diagnostic panel to discriminate endometrioid from clear cell carcinoma besides serous carcinoma of the endometrium. CCC of the urinary tract has been identified as a rare malignancy, which mimics the clear cell carcinoma of the female genital tract morphologically. One of the studies described HNF1B as a biomarker in distinguishing clear cell adenocarcinomas of the bladder/urethra besides other primary tumours of the urinary bladder, specifically aggressive urothelial tumour with clear cell change. Davidson et al advocated the central part of HNF1B marker in serous effusion diagnosis, with the data suggesting HNF1B to be an important biomarker which may differentiate CCC from serous ovarian carcinoma and cells of mesothelial origin.

In a nutshell, a wide array of expression changes in different cancers and its subtypes does point towards the role of this gene as a potential biomarker. However, even after identifying its involvement in development and progression to tumour relapse, the details about the regulatory pathways still are missing, further studies which highlight these missing links can help in finally helping the potential of HNF1B to become a biomarker in different cancers.

7 CONCLUSION

HNF1B was first reported as a potential candidate gene for MODY although extensive research indicated it as an important gene having a role in tumorigenesis. HNF1B profiles in different tumours throw light on different mechanisms governing HNF1B function and expression. GWAS identifying HNF1B risk loci and epigenetic alterations has unravelled the risk alleles and the role of DNA methylation and their potential as biomarkers for disease prognosis. The function of HNF1B as a potential tumour suppressor gene has highlighted its possible role as a therapeutic target followed by identifying the role of HNF1B as a unique marker for characterizing CCCs from other lesions in ovary and endometrium. Moreover, the expression of HNF1B has been associated with immune cell infiltration which in turn influences the prognosis of immune cells in some cancers highlighting HNF1B as a potential immunotherapeutic target. Likewise, evaluating the functional role of the transcript variants may be crucial for developing accurate biomarkers and effective therapeutic strategies. Regulatory pathways and mechanisms involving HNF1B still need to be elucidated and studied in depth to explore the networking of the HNF family. Understanding splice variants of HNF1B and their role will broaden the scope of pursuing new downstream targets, its associated signalling pathways and transcriptional efficacy governing different gene sets. In-depth characterization of HNF1B and its splice variants are warranted to compliment its ever-growing importance in different cancers.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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