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Editorial: Hepatocyte nuclear factor 4 alpha – new insights into an old receptor

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Editorial on the Research Topic

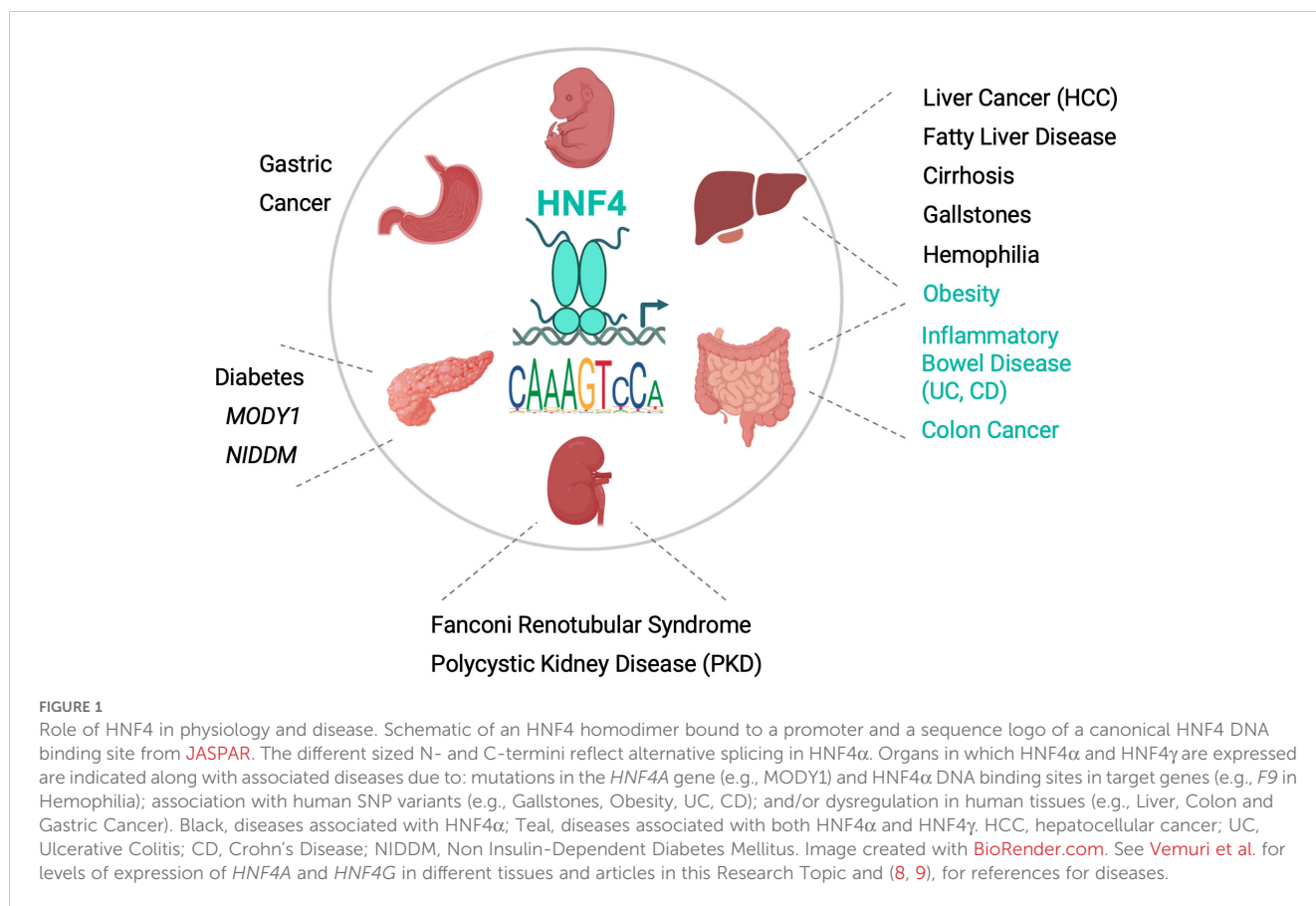
Hepatocyte nuclear factor 4 alpha – new insights into an old receptor

Hepatocyte nuclear factor 4 alpha (HNF4 α), cloned over 30 years ago based on its ability to bind a couple of DNA elements in liver-specific genes, is now considered to be the master regulator of liver-specific transcription. HNF4 α is also expressed in several other tissues, including intestines, kidney, stomach and pancreas, and is linked to several human diseases (Figure 1). As a member of the nuclear receptor (NR) superfamily of ligand-dependent transcription factors, HNF4 α has two highly conserved domains for DNA binding (DBD) and ligand binding (LBD) and binds DNA as a homodimer. This Research Topic contains four reviews and three original research articles covering some of the most important areas of research on HNF4 α and its paralog HNF4 γ .

The review by [Beinsteiner et al.](#) highlights the evolutionary origins of HNF4 α as one of two original members of the NR family which, along with RXR, have been found in the most primitive metazoans on Earth. They map several mutations in *HNF4A* found in diabetes, including Maturity Onset Diabetes of the Young 1 (MODY1), as well as numerous phosphorylation, acetylation, ubiquitination and sumoylation sites onto the 3D structure of the full length protein. In an original research article [Zhang et al.](#) identify three new mutations in *HNF4A* causing MODY1 in the Chinese population, bringing the total number of mutations mapped in the human *HNF4A* gene to well over 100, the vast majority of which are related to MODY1. The patients are heterozygous for the mutations, as are all the other MODY1 patients, demonstrating the essential nature of HNF4 α .

The review by [Rastinejad](#) summarizes the search for the endogenous HNF4 α ligand as well as the efforts to crystallize the DBD plus LBD structure of HNF4 α , the first such structure for any of the 48 human NRs. While fatty acids clearly bind HNF4 α (and HNF4 γ), their role as classical NR ligands remains ambiguous. What is clear is that the 3D structure of HNF4 α contains a ‘convergence zone’ between the DBD and LBD that allows for allosteric interactions such that signals originating from one domain can influence a distant domain.

The review by [Radi et al.](#) summarizes the long history of HNF4 α including its role in the developing embryo and adult liver. A highly conserved two-promoter structure (P1 and



P2) drives the expression of multiple transcript variants in the liver and other tissues. The authors describe an exon-swap mouse model that allows for an *in vivo* analysis of the roles of the transcripts generated from the different promoters: a useful model given that the whole body knockout is an embryonic lethal. The mechanisms underlying the switch between the two promoters, including an anti-sense transcript, a non coding RNA and DNA methylation, are discussed.

The original research article by Deans et al. uses the exon swap mice to elucidate the role of P2- versus P1-HNF4 α isoforms in the adult liver. P2-HNF4 α was originally identified in an embryonic cancer cell line but is now known to be expressed in the normal adult liver during periods of fasting, high fat diet and alcohol-associated liver disease, as well as liver cancer. The authors use multiple 'omics approaches to show not only that HNF4 α is one of the most highly expressed transcription factors in the adult liver but also that the hundreds of genes uniquely regulated by P2-HNF4 α (including several cytochrome P450 genes) are consistent with a role in metabolism. They show that the differential gene expression is likely due to interactions with co-regulators rather than alterations in DNA or chromatin binding and propose a potential role for the HNF4 α isoforms in the circadian switch between carbohydrate and lipid metabolism.

The review by Vemuri et al. focusses on the intestines which express both P1- and P2-HNF4 α as well as HNF4 γ . HNF4 α binds DNA as a homodimer and cannot heterodimerize with other NRs, with the exception of HNF4 γ . Like HNF4 α , HNF4 γ has been shown

to bind fatty acids although, as with HNF4 α , the role of ligand binding in receptor function is not clear. Both HNF4 genes play a key role in intestinal maturation, differentiation and regeneration as well as stem cell renewal (via fatty acid oxidation) and barrier function, allowing for one paralog to compensate for the loss of the other. HNF4 α intersects with the immune system in multiple ways and, along with HNF4 γ , protects against a chronic inflammatory state in the gut. Both HNF4 genes are implicated in the intestinal entry of SARS-CoV2 via regulation of the *Ace2* and *Tmprss2* genes in the intestinal epithelium. Interestingly, three distinct high fat diets have also been shown to alter the expression of these (and other) COVID-related genes as well as *Hnf4a* in the mouse intestines (1).

The original article by Kotulkar et al. explores the interaction between HNF4 α and the proto-oncogene *c-Myc* in liver regeneration after partial hepatectomy. Deletion of HNF4 α increases the expression of *c-Myc* and cyclin D1 (*Ccnd1*) while the double knockout of HNF4 α and *c-Myc* decreases hepatocyte proliferation demonstrating that HNF4 α is critical for both termination of liver regeneration and survival after partial hepatectomy. Another intriguing observation is the emergence of HNF4 α + hepatocytes in HNF4 α knockout mice, presumably from the cholangiocytes. This work highlights a role for HNF4 α in regulating cell proliferation, as well as basic metabolism.

Critical areas of future HNF4 research include the role of: i) HNF4 α in the intersection between cell metabolism and proliferation; ii) the different splice variants and the factors that

regulate splicing as well as the alternate *HNF4A* promoters; iii) post translational modifications (PMTs) in HNF4 and how they can be impacted by SNPs in the human population (2); iv) HNF4 α versus HNF4 γ in the intestines (and other tissues), including homo- versus heterodimers and their interaction with the microbiome (3); v) the incredible diversity of HNF4 and other NR binding motifs and how those might be impacted by SNPs (4); vi) the function of HNF4 in tissues outside of the liver and intestines and interorgan crosstalk with non expressing tissues such as adipose (5, 6); vii) ligand binding and identification of additional ligands, including potential therapeutic drugs; and viii) HNF4 in xenobiotic and drug metabolism (7). Finally, given the ancient origins of HNF4, it will be important to continue exploring new ways in which this ‘old’ receptor acts in all animal organisms.

Author contributions

FS: Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Conceptualization. UA: Writing – review & editing, Funding acquisition, Conceptualization. PD: Writing – review & editing, Visualization.

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