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Review

Emerging actions of the nuclear receptor LRH-1 in the gut ☆

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ABSTRACT

Liver receptor homolog-1 (NR5A2) is a nuclear receptor originally identified in the liver and mostly known for its regulatory role in cholesterol and bile acid homeostasis. More recently, liver receptor homolog-1 has emerged as a key regulator of intestinal function, coordinating unanticipated actions, such as cell renewal and local immune function with important implications to common intestinal diseases, including colorectal cancer and inflammatory bowel disease. Unlike most of the other nuclear receptors, liver receptor homolog-1 acts as a constitutively active transcription factor to drive the transcription of its target genes. Liver receptor homolog-1 activity however is to a major extent regulated by different corepressors and posttranslational modifications, which may account for its tissue-specific functions. This review will provide an update on the molecular aspects of liver receptor homolog-1 action and focus on some emerging aspects of its function in normal and diseased gut. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

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1. Introduction

Nuclear receptors represent one of the largest families of transcription factors in mammals [1,2]. They control the expression of genes implicated in reproduction, development and homeostasis. The activity of most nuclear receptors is regulated by a diverse set of lipid-soluble molecules, including steroid hormones, nutrients, metabolites and endo/xenobiotics. The binding of these ligands to nuclear receptors induces a conformational change leading to the dissociation of corepressors and the recruitment of coactivators that ultimately will result in the activation of downstream target genes [3,4]. Nuclear receptors and their coregulators hence sense variations in the intracellular concentration of hormones or metabolites and subsequently elicit an adaptive response by modulating the expression of downstream target genes [5]. Although ligand-dependent activity is a hallmark of the nuclear receptor family, some members do not have an established physiological ligand or display constitutive activity. These receptors are termed orphan nuclear receptors.

LRH-1 and its mammalian paralog, steroidogenic factor 1 (SF-1), belong to the NR5A subgroup of nuclear receptors. Both nuclear receptors bind as monomers to extended half sites in the promoter region of their target genes and exhibit constitutive activity [6,7]. Crystallographic studies with recombinant mouse LRH-1 revealed that the constitutive activity of LRH-1 can be ascribed to the remarkable stable conformation of certain regions in the ligand binding pocket that is associated with coactivator recruitment [8]. Even though several phospholipids have been found to bind LRH-1 *in vitro*, it is not yet established whether they also act as physiological ligands. In contrast, several corepressors are able to efficiently repress the activity of LRH-1 by interacting with the ligand binding domain of LRH-1, and several covalent modifications, including phosphorylation and sumoylation, are known to modulate LRH-1 activity [9–17].

Since the initial discovery of LRH-1 in 1993 [18], major progress has been made with regard to the understanding of its biological function. Like many nuclear receptors, LRH-1 exerts pleiotropic functions. LRH-1 is important in several aspects of life, ranging from the control of the earliest events in development to cell specification during differentiation as well as of many other metabolic, immunoregulatory and proliferative functions. In contrast to the well established involvement of LRH-1 in reverse cholesterol transport and bile acid metabolism in the liver [11,19–29], more recent studies have identified LRH-1 as a key player in the control of stem cell pluripotency [30–32] and intestinal cell renewal [33]. This review will focus on some new studies implicating LRH-1 as an essential transcriptional modulator in gut function and in a number of gut-associated common diseases, such as colorectal cancer (CRC) and inflammatory bowel disease (IBD).

2. The gut in health and disease

The gut is a highly organized structure that fulfills many vital functions in our body. Together with the skin, it represents one of the largest surfaces of the human body. The epithelium of the gut plays an essential role in nutrient, salt and water absorption, and together with the hepatocytes of the liver, it participates in the detoxification and

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disposal of toxic substances. Besides these metabolic functions, the intestinal epithelium also establishes a selective barrier and provides a first line of defense against invading pathogens [34]. Interestingly, the gut houses a large variety of commensal microorganisms, the gut microbiota, which are intimately involved in several aspects of its physiological functions [35]. This cohabitation, however, occurs without eliciting the typical inflammatory responses observed after infection, indicating that the intestinal tract has acquired complex recognition systems that distinguish the beneficial bacterial and luminal antigens from the pathogenic ones. This immunotolerance is severely compromised in patients with inflammatory bowel disease (IBD), a chronic intestinal disorder that is characterized by inappropriate inflammatory responses to intestinal microbes [36]. In both Crohn's disease and ulcerative colitis, the two major forms of IBD, a disturbance in the balance between immune tolerance and defensive inflammatory response constitutes the basis of the exacerbated inflammation.

The mucosal layer is organized as a single layer of columnar epithelial cells that is composed of several specialized cell types [37]. While the enterocytes are basically involved in the digestive and absorptive functions of the gut, the goblet and Paneth cells provide defenses against bacterial invasion through the production and secretion of mucous, antimicrobial peptides and immunoregulatory factors. Finally, the enteroendocrine cells provide a means of communication with the body, by secreting peptide hormones that influence diverse physiological processes.

As the intestinal epithelial cells are continuously exposed to a harsh luminal environment, inflammation and tissue injury may jeopardize cell integrity and normal intestinal function, often observed in IBD patients. The epithelium, however, has an astonishing capacity for self-renewal, and total renewal occurs every 4–5 days. Intestinal self-renewal is driven by pluripotent stem cells that reside in the proliferative crypt compartment, together with its uncommitted progenitors [37,38]. After a limited number of divisions, the progenitor cells differentiate into each of the specialized intestinal cell types and migrate further up the crest of the villi, with the exception of the Paneth cells that stably reside at the bottom of the crypts. Once epithelial cells reach the top of the villi, they undergo apoptosis. The final status of the intestinal tract is hence the result of a dynamic and tightly controlled process that involves the maintenance of a delicate balance between proliferation, differentiation, migration and cell death.

The canonical Wnt pathway is the primary signaling pathway that stimulates proliferation and that coordinates the transition between proliferation and differentiation of epithelial cells along the crypt/villus axis. It consists of several components, with the β-catenin/TCF4 transcriptional complex being the main player that drives Wnt target gene expression [39,40]. Similar to the proliferation gradient observed in the crypts, the Wnt pathway is most active at the bottom and gradually loses its activity when the cells move up to the villi, indicating that an active pathway is essential for the maintenance of uncommitted progenitor cells in the crypt compartment. This was further confirmed by the analysis of several loss- or gain-of-function mouse models of single genes encoding various components of the Wnt pathway and which exhibited impaired or exaggerated proliferation, respectively [41–46].

Activating mutations in the Wnt pathway have been associated with colorectal cancer (CRC), one of the most common cancers worldwide [47]. Usually these mutations either inactivate the tumor suppressor APC or activate the proto-oncogene β-catenin [48–51]. In both cases, they result in the nuclear accumulation of β-catenin and the transcriptional activation of its target genes. Mutations in the Wnt pathway are proposed to initiate the formation of benign adenomas, the initial event in the adenoma–carcinoma sequence [50,52]. These tumors can go unnoticed for several years. Only when additional mutations arise, colorectal tumors become malignant.

Both genetic and environmental factors trigger the development of CRC. Chronic inflammation is an established environmental risk factor. IBD patients are highly susceptible to develop colitis-associated cancer (CAC), linked to the chronic damage of the colon and rectum [53]. Both sporadic CRC and CAC tumors are to a major extent infiltrated with various types of immune cells. In contrast to the largely protumorigenic role of the immune cells in CAC tumors, the immune infiltrates in sporadic as well as heritable CRC tumors may also contribute to immunosurveillance, leading to the elimination of transformed cells [54]. The mechanisms by which immune cells impact on cancer initiation and progression may hence differ between CAC and CRC.

3. Gut function and nuclear receptors

System-wide analysis of 39 mouse tissues indicated that a subset of nuclear receptors is abundantly expressed in different areas of the gastrointestinal tract [55]. Many of these nuclear receptors have been earlier linked to regulatory functions in metabolic and/or immune homeostasis of the gut. Some of these receptors are established targets for the treatment of IBD, like the glucocorticoid receptor (GR) or peroxisome proliferator-activated receptor γ (PPARγ) because of the known therapeutic use in IBD of both corticosteroids and 5-aminosalicylic acid (5-ASA), established activators of GR and PPARγ, respectively [56–59].

More recently, nuclear receptors have been mapped with regard to the crypt–villus axis in the distal ileum and proximal colon of both normal and $APC^{Min/+}$ mice [60]. $APC^{Min/+}$ mice spontaneously develop intestinal adenomas as a result of a point mutation in the APC gene [61]. Interestingly, the nuclear receptor localization signature established in this study allowed the authors not only to predict the function of each receptor in the proliferation/differentiation program but also to provide an alternative approach to screen for nuclear receptors as potential targets to inhibit tumor development and growth [60]. This work adds further value to earlier studies describing functional interactions between single nuclear receptors and the Wnt signaling pathway [62] and may be used as a basis to identify additional roles for the nuclear receptor family in cell cycle regulation, cancer and gut physiology in general. Based on these studies, it is clear that nuclear receptors are well positioned to control the normal and pathological functions of the gut. This review focuses on one nuclear receptor, i.e. the liver receptor homolog-1 (LRH-1), and its emerging role in gut development, physiology and pathophysiology and highlights LRH-1 as an important transcriptional mediator at the crossroads of developmental, metabolic and inflammatory pathways.

4. Molecular and physiological actions of LRH-1

Liver receptor homolog-1 (LRH-1, NR5A2), also known as pancreas hormone receptor (PHR-1), fetoprotein transcription factor (FTF), human B1-binding factor (hB1F) or CYP7A1 promoter binding factor (CPF), belongs to the NR5A subfamily of nuclear receptors, which also comprises the Drosophila fushi tarazu-factor 1 (Ftz-F1) and the mammalian steroidogenic factor 1 (SF-1). All members of this subfamily bind as monomers to extended nuclear receptor hexomeric binding sites in the regulatory regions of their target genes. Specific recognition of the 3 base pairs-long extension is ensured by the conserved Ftz-F1 box, a stretch of about 26 amino acid residues, located C-terminal from the DNA-binding domain [63]. For a long time, members of the NR5A nuclear receptor subfamily have been considered as receptors with constitutive transcriptional activity. Some of these receptors, however, have been found to bind various phospholipids, including phosphatidyl inositols (PI: $PI(3,5)P_2$ and $PI(3,4,5)P_3$) [64–69], suggesting that these compounds could act as natural ligands (Fig. 1). More recently, the SF-1 and LRH-1 ortholog in

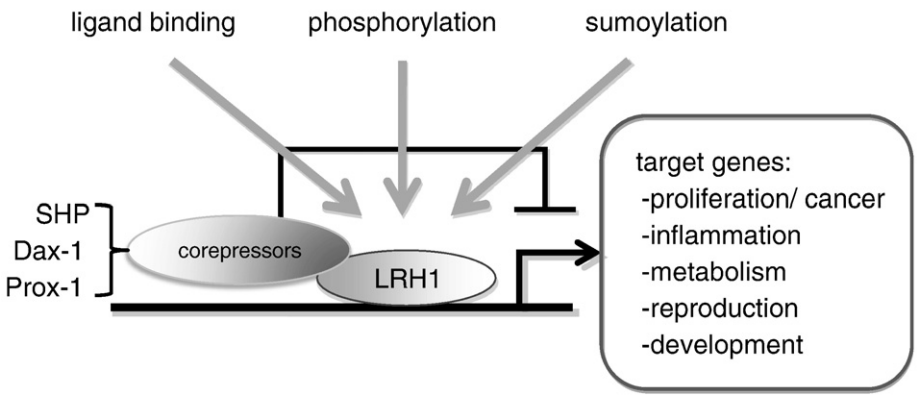

Fig. 1. Regulation of LRH-1. LRH-1 activity can be regulated by several mechanisms, which involve transcriptional coregulators, posttranslational modifications (mainly phosphorylation and sumoylation) and potentially phospholipid ligand binding (human LRH-1), although the latter mechanism is still not yet fully understood. Among the coregulators, the corepressors SHP, DAX-1 and PROX-1 are particularly relevant to modulate the constitutive activity of LRH-1.

Caenorhabditis elegans, NHR-25, was found to accommodate PI lipids containing long-chain fatty acids [70]. The enhanced intestinal fat uptake and storage observed in long-chain acyl-CoA synthase (ACS-3) mutant worms required NHR-25, and it was proposed that absence of these long-chain fatty acid-containing PI lipids could account for this effect, suggesting a functional link of PI and NHR-25 in *C. elegans*. It will be of interest to determine the physiological relevance of these molecules in mammalian systems.

Like most nuclear receptors, LRH-1 activity can also be modulated by posttranslational events. Phosphorylation by ERK of residues Ser-238 and Ser-243 of human LRH-1 enhances its activation [13]. In the same study, p38MAPK was also suggested to activate LRH-1, although to a lesser extent than ERK. Human LRH-1 is also phosphorylated by PKA at Ser-469 [9]. Interestingly, PKA-mediated phosphorylation induces LRH-1-dependent steroidogenesis in breast cell lines [9], whereas it represses LRH-1-dependent glucocorticoid production in an intestinal cell line [71], suggesting that the effect of PKA on LRH-1 activity is cell type-dependent. LRH-1 can also be sumoylated resulting in its translocation to promyelocytic leukemia (PML) bodies in the nucleus and its subsequent inactivation [10,72,73] (Fig. 1).

The high-affinity interaction of LRH-1 with the atypical nuclear receptor short heterodimer partner (SHP) has been well-defined [11,25,74,75]. Studies to demonstrate the physiological relevance of the repressor function of SHP on LRH-1 activity were initially performed in the context of the well established feedback inhibition of bile acids on its own production. When bile acids levels build up in the liver, SHP transcription is induced as a result of the activation of farnesoid X receptor (FXR), the nuclear bile acid receptor. It was demonstrated that an increase in SHP subsequently attenuates the transcriptional activity of LRH-1, leading to the repression of LRH-1 targets, including the rate-limiting enzyme of the bile acid biosynthesis pathway, cholesterol 7α-hydroxylase (CYP7A1) [11,25] and the enzyme catalyzing the production of cholic acid, cholesterol 12α-hydroxylase (CYP8B1) [20,76]. Analysis of liver-specific LRH-1 deficient mice, however, revealed that this molecular paradigm of feedback repression may not be as straightforward as initially thought. Studies from our laboratory showed that LRH-1 in mouse hepatocytes is not important for basal Cyp7a1 expression but in contrast essential for the expression of Cyp8b1 and consequently for bile acid composition [27]. Others have confirmed these findings and have shown that in addition LRH-1 is not essential for the FXR-mediated feedback regulation of bile acid synthesis [24]. An important question for the future will be to determine whether the lack of difference in feedback regulation is the result of compensatory mechanisms or whether LRH-1 is indeed dispensable in this transcriptional network.

LRH-1 also binds several other proteins that modulate its transcriptional activity. Proteins such as multiprotein bridging factor-1 (MBF1) [77]; steroid receptor coactivators (SRC)1, 2 and 3 [78] and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [79–81] bind and activate LRH-1-mediated transcription. The corepressors dosage-sensitive sex-reversal–adrenal hypoplasia congenita critical region on the X chromosome, gene 1 (Dax1) [67], prospero-related homeobox 1 (Prox-1) [14,16,82] and PIASy [12] also bind LRH-1 and inactivate it (Fig. 1).

Besides an important role in development (discussed in the section below), LRH-1 has emerged as a pleiotropic homeostatic transcriptional regulator controlling aspects of metabolism, immune function, cell proliferation and reproduction. The role of LRH-1 has been best studied in the liver. Early studies focusing on target gene identification have positioned LRH-1 as a critical regulator of reverse cholesterol transport, a process by which cholesterol is transported from peripheral tissues by high density lipoproteins (HDL) to the liver [21,22,26,29]. In addition, LRH-1 was also established as a crucial regulator of bile acid homeostasis [11,19,20,23–25,27,28]. In the gut, LRH-1 is most highly expressed in the proliferative cells residing in the base of the crypts, and its expression is progressively lost as cells differentiate and migrate towards the villi [33] (Fig. 3). This pattern of expression mimics that of β-catenin [40], which is bound and activated by LRH-1 [33]. Finally, the receptor is also expressed in adipocyte precursors [83] and in steroidogenic tissues, including the adrenal and the reproductive organs [84–86]. In the ovary, LRH-1 is strongly enriched in the granulosa cells, where it regulates multiple mechanisms essential for the maturation of ovarian follicles and for ovulation, including the appropriate control of the hormonal balance [87–89]. The importance of this discovery was underscored by the observation that mice with a targeted mutation of the lrh-1 gene in the granulosa compartment are infertile as a result of impaired ovulation [88].

5. Developmental functions of LRH-1

LRH-1 is present from the early phases of embryo development. In fact, it is highly expressed in embryonic stem cells (ES) [30,90], in all cells in the morula stage (E2.5) and in the inner cell mass and trophectoderm in the blastocyst stage (E3.5). At E5.5 (egg cylinder), its expression becomes restricted to the visceral endoderm, while ectodermal cells become negative for LRH-1. During gastrulation (E6.5–E7.5), LRH-1 is still present in the endoderm and in the primitive mesoderm. During mid-gestation (E8–E15), the receptor is abundant in tissues derived from endoderm, such as liver, pancreas and intestine, and in bone, testis and several brain regions [91,92]. Given its early developmental expression, it is not surprising that

LRH-1 deficiency is lethal already at day ~E6.5 [30,91]. In adult mice, LRH-1 is robustly expressed in the liver, exocrine pancreas, ovary and intestinal tract [18,55,90,92–94].

Several lines of evidence support a master role for LRH-1 in the initial biological processes that govern stem cell pluripotency and early development [30–32,95]. The first target of LRH-1 identified in this process was Oct4, a crucial pluripotency factor in embryonic stem cells (ESC) [30]. Expressed in the pregastrulation embryo, primordial germ cells and oocytes, Oct4 deficiency leads to embryonic lethality at the blastocyst stage and to severe dysregulation of the differentiation process *in vitro* [96]. Several nuclear receptors bind to the Oct4 promoter and induce its expression at different stages of development [97]. LRH-1 appears to be crucial for its expression as Oct4 expression is lost at the epiblast stage in the absence of LRH-1 [30]. In line with this study, others also identified LRH-1, together with Oct4, Sox2 and ERRβ, as critical components of a transcription factor regulatory network that maintains stem cell pluripotency [30,95]. Interestingly, LRH-1 can also substitute for Oct4 during the reprogramming of induced pluripotent stem cells (iPS) from mouse embryonic fibroblasts (MEFs), further stressing its vital role in the regulation of Oct4 and the establishment of pluripotency [31]. A recent report suggests, however, that Oct4 is not the only factor influenced by LRH-1 to maintain pluripotency in ESC [98]. Consistent with this observation, it was recently shown that LRH-1 also controls Nanog, another essential gene for embryo development [32]. The canonical Wnt signaling triggers this LRH-1-mediated Oct4 and Nanog induction during early embryo development and identifies LRH-1 as a novel target of β-catenin and Tcf3 [32]. Accordingly, β-catenin deficiency also leads to embryonic lethality at early embryonic stages (E6) [32]. DAX-1 is also abundantly expressed in ESCs and has been identified as an interacting partner of Nanog [95,99,100]. In view of the modulating role of DAX-1 on LRH-1 activity, it is tempting to speculate a possible functional interaction between both nuclear receptors in ESCs, although this possibility still requires further investigation.

Later during development, LRH-1 is involved in the embryonic expression of a set of proteins essential for proper liver development. In fact, LRH-1 controls the early expression of α-fetoprotein (AFP). AFP is a marker of visceral endoderm and liver differentiation and is expressed in endodermal cells that are freshly committed to the liver lineage and its expression becomes extinct in the perinatal period [90]. In addition, LRH-1 binds to the promoters and directs the transcription of the hepatic nuclear factors HNF-1α, HNF-3β and HNF-4α, which orchestrate embryonic liver development [92,101].

In combination these studies indicate that LRH-1 behaves as a master regulator of a plethora of pathways during embryonic development, ranging from the stem cell stage to the later phases of development.

6. Role of LRH-1 in intestinal renewal and cancer

Renewal of the intestinal mucosa is triggered by stem cells localized in the lower compartment of the crypts [37,38]. The dividing cells become progenitor cells and the coordinated expression of specific cell fate transcription factors, such as Notch/RBP-J/Hes, Math1, Gfi1, Mtgr1, Klf4 and others [37], will determine whether the progenitor cells will differentiate into enterocytes, goblet cells or enteroendocrine cells, which all gradually move towards the villi.

Consistent with its expression in intestinal crypts, we showed that LRH-1 coordinates intestinal cell renewal [33] (Fig. 2). Expression of LRH-1 by retroviral transduction was first shown to promote cell proliferation by enhancing cyclin-mediated G_1/S transition of the cell cycle. Two independent and complementary mechanisms account for the effect of LRH-1 on cell cycle regulation. Consistent with its role as a transcription factor, the first mechanism involves the direct binding of LRH-1 and subsequent activation of the cyclin E1 promoter, a process stimulated by β-catenin, which binds LRH-1. The second mechanism differs from the classic view by which LRH-1 controls target gene expression and consists in the induction of cyclin D1 and c-Myc transcription by β-catenin/Tcf4, a process in which LRH-1 acts as a cofactor (Fig. 2). In the same study, LRH-1 also stimulates the renewal of intestinal crypt cells in vivo, an effect that was attenuated in LRH-$1^{+/-}$ mice. Altogether, these findings not only point to a role for LRH-1 in cell cycle control, but they also extend the role of LRH-1 from a simple DNA-binding transcription factor to a coactivator via its interaction with β-catenin. In a more recent study, the role of LRH-1 with regard to cell cycle control was analyzed [24]. Mice deficient for LRH-1 in the intestinal epithelium showed reduced cyclin E1 and c-Myc mRNA levels but did not reveal any difference in the BrdU proliferation index nor in cyclin D1 gene expression. The authors concluded that this may reflect the additional requirement of other cell types in the intestine to coordinate the proliferative response of LRH-1.

Consistent with its role in intestinal cell renewal, LRH-1 also modulates intestinal tumor formation in different cancer mouse models [102]. LRH-1-haploinsufficiency significantly inhibits intestinal tumorigenesis both in the azoxymethane-induced intestinal tumor model and in $APC^{min/+}$ mice [102]. Since β-catenin plays a major role in the $APC^{min/+}$ model, these results further underscore the previously described β-catenin/LRH-1 relationship in intestinal cells and its relevance in tumorigenesis.

One of the questions that remain to be answered is the modulation of intestinal LRH-1 activity by its corepressors. Compared to the liver and with the exception of the duodenum, only minute levels of SHP are detected in the intestinal tract. This raises the question whether LRH-1 acts alone or whether alternative corepressors, such as PROX-1 or DAX-1, replace SHP to fine-tune LRH-1 activity in the intestine. Further investigation will have to address the (patho)physiological relevance of these potential interactions in vivo.

Apart from intestinal tumors, LRH-1 has also been associated to several other types of cancer. LRH-1 acts as protumorigenic factor by enhancing estradiol synthesis in preadipocytes, thus driving breast cancer growth [103]. The LRH-1 gene locus has also been found to be genetically associated with the development of exocrine pancreatic cancer [104], although no functional study has yet been performed addressing the potential role of LRH-1 in the development of this type of cancer. LRH-1, along with SF-1, was also induced in endometrial tumor cell lines where both NR5A family members enhance the expression of the steroidogenic genes, steroidogenic acute regulatory protein (star), 3b-hydroxysteroid dehydrogenase (3β-hsd) and CYP19A1, leading to an increase in estradiol production, which is considered one of the causes of endometrium tumors [105]. In the liver, LRH-1 regulates the established tumor marker AFP, whose expression is reinduced not only in hepatic but also in gastric cancers [106,107]. In addition, LRH-1 induces the expression of the hepatitis B virus [93], a leading cause of chronic hepatitis, often linked to the development of hepatocellular carcinoma.

7. LRH-1 and inflammation: implications for inflammatory bowel disease

Nuclear receptors in general, and LRH-1 in particular, have been repeatedly associated with different inflammatory pathways [71,108–111]. LRH-1 has been linked with two facets of the inflammatory response. The first one involves the control of the hepatic acute phase response (APR), defined as the host reaction in response to trauma, infection, tissue damage or acute inflammation [112]. Part of this response consists in the synthesis by hepatocytes of a set of proteins, called acute phase response proteins (APP). LRH-1 negatively regulates the expression of APPs [111,113], and this mechanism is controlled by sumoylation of LRH-1 [114].

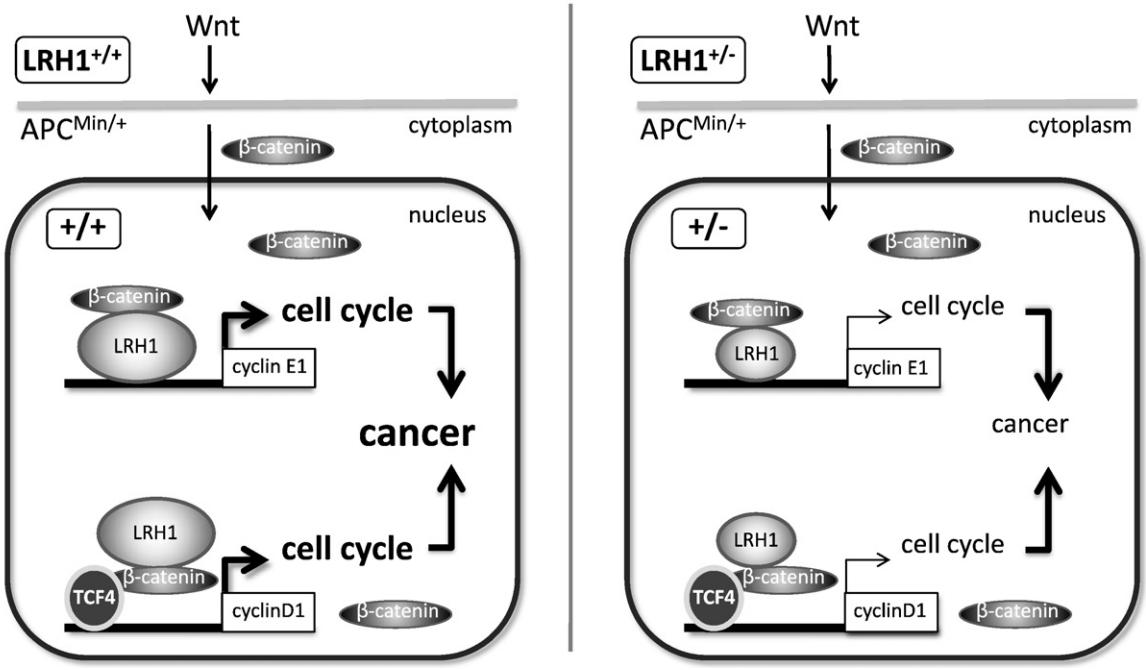

Fig. 2. LRH-1 drives cell cycle progression and tumorigenesis by synergizing with the β-catenin signaling pathway, acting directly as a transcription factor (cyclin E1) and as a cofactor for Tcf-β-catenin (cyclin D1) in the gut. LRH-1 binds and activates the promoter of cyclin E1. β-catenin acts as a cofactor via interaction with LRH-1 to enhance LRH-1-driven transcription of cyclin E1. In a similar fashion, but without direct binding to DNA, LRH-1 enhances β-catenin/Tcf4-driven transcription of another cell cycle promoter gene, cyclin D1. Through these two mechanisms, LRH-1 pushes the cell cycle and favors tumor formation in different colorectal cancer models, the $APC^{Min/+}$ (as depicted) and a chemically induced model (AOM/DSS).

The second pathway by which LRH-1 limits inflammation involves the regulation of extra-adrenal glucocorticoid production in gut. Initially, glucocorticoids production were thought to be synthesized only in the adrenal glands and to perform its functions systemically, transported by the circulatory system. Only recently, this dogma has been revisited when several unexpected organs, including the gut, were found to synthesize and secrete glucocorticoids in a paracrine fashion to regulate local immune cell homeostasis [115]. The existence of extra-adrenal glucocorticoid production in the intestine was initially established after injecting mice an anti-CD3 antibody, which triggers T cell activation. This strong immune challenge rapidly induced a counterregulatory immune response in the intestinal epithelial cells consisting in a strong induction of the steroidogenic cholesterol side-chain cleavage enzyme P450scc (CYP11A1), which converts cholesterol to pregnenolone, and 11β-hydroxylase (CYP11B1), which catalyzes the conversion of deoxycorticosterone into corticosterone (Fig. 3). Most interesting with respect to this immune response was the observation that the induction of CYP11A1 and CYP11B1 was only limited to the basal compartment of the intestinal mucosa [116], suggesting that the induction requires crypt-enriched factors. In line with this hypothesis, LRH-1, which is predominantly expressed in the proliferating cells of the crypt compartment, was shown to be essential for the local production of corticosterone via its regulation of the steroidogenic enzymes CYP11A1 and CYP11B1 [71] (Fig. 3).

Corticosterone, which is the major glucocorticoid synthesized in mice, acts as a potent inhibitor of inflammation through interference with proinflammatory pathways activated by NF-kB and AP1 and through activation of anti-inflammatory pathways. In view of these well established actions, our laboratory has investigated the potential relationship between LRH-1, intestinal corticosterone production and susceptibility to dextran sodium sulfate (DSS) and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. Interestingly, the study showed that both LRH-1 haploinsufficiency and somatic deficiency of LRH-1 in the intestinal epithelium rendered mice more susceptible to experimentally induced colitis [108]. In addition, the exacerbated inflammation was associated with decreased local intestinal glucocorticoid production. Most importantly, analysis on IBD patients revealed a significant decrease in expression of LRH-1 and of its transcriptional targets CYP11A1 and CYP11B1 in the affected tissues, compared with healthy intestine [108], hence extending the role of LRH-1 in experimental IBD mouse models to the human pathology. Apart from their immunoregulatory action on local immune cells, glucocorticoids may also induce intestinal tight junction proteins and improve epithelial barrier function [117]. In addition, other functions of LRH-1, such as its role in cell cycle progression, may contribute to the protective phenotype on inflammation and associated epithelial damage when LRH-1 levels are normal. In fact, it is plausible that after hapten-induced mucosal inflammation, the cell cycle regulatory function of LRH-1 comes into play to promote mucosal renewal and regeneration. Another indication that cell cycle and glucocorticoids are closely linked via LRH-1 stems from the finding that pharmacological inhibition of the cell cycle also strongly attenuates LRH-1 activity and corticosterone synthesis in crypt cell-like epithelial cells [118]. This effect likely explains why proliferating crypt cells progressively lose CYP11A1 and CYP11B1 expression upon differentiation.

8. Discussion

The nuclear receptor LRH-1 constitutes a clear example of a protein whose list of functions has gradually grown with time, to include at present the control of a surprisingly wide set of developmental and homeostatic pathways. This wide regulatory role is further underscored by the recent addition of the control of inflammation and cell proliferation as novel functions for this nuclear receptor. LRH-1 controls these pathways in part through its regulatory impact on steroidogenesis and via its cross talk with the β-catenin signaling pathway.

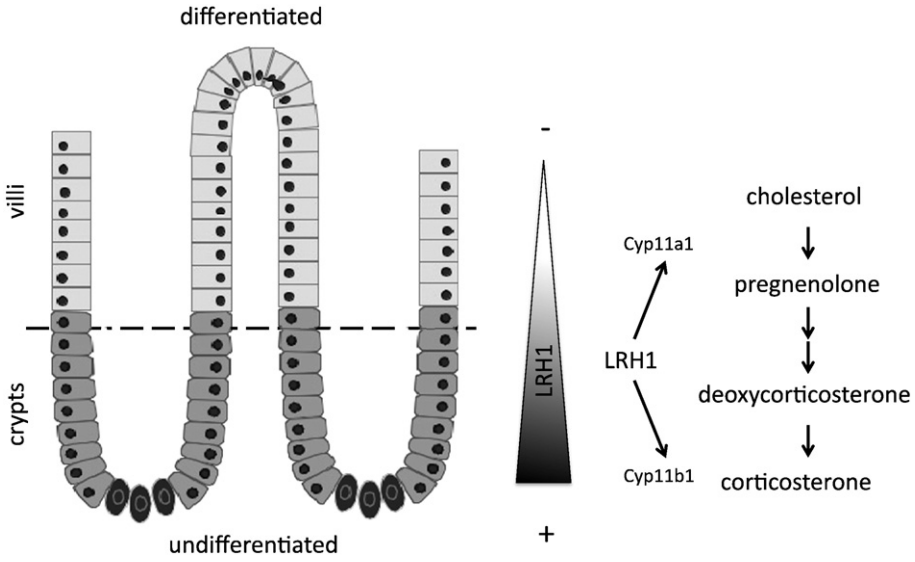

Fig. 3. LRH-1 is highly expressed in the lower undifferentiated crypt compartment and directs anti-inflammatory corticosterone production in the intestinal crypts. The figure depicts the intestinal epithelium, with the most undifferentiated cells—stem cells and progenitors—residing at the bottom of the crypts and the more differentiated enterocytes moving towards the tip of the villi, where they finally undergo apoptosis and shedding. LRH-1 is enriched at the base of the crypts coinciding with markers of undifferentiated cells. LRH-1 levels drop as enterocytes undergo differentiation. Where it is expressed, LRH-1 regulates the synthesis of corticosterone, a potent anti-inflammatory glucocorticoid, by enhancing the expression of the cytochrome p450 enzymes CYP11A1 and CYP11B1. Thus, LRH-1 plays a major role in the control of differentiation and inflammation, both of them crucial processes in the development of IBD.

Since inflammation and proliferation are two mechanisms highly relevant in the gut, it is not surprising that LRH-1 has emerged as a crucial factor impacting on the development of inflammatory and proliferative pathologies in this tissue. On the one hand, LRH-1 controls corticosterone-mediated regulation of the gut inflammatory response. In line with this finding, LRH-1 ablation in the mouse intestinal epithelium enhances inflammation, and IBD patients coherently express lower levels of LRH-1 in the intestine [108]. Also, LRH-1 promotes proliferation of intestinal cells through its ability to bind and enhance β-catenin-mediated transcription of pro-proliferative genes such as cyclin E1, cyclin D1 and c-MYC. As a consequence, intestines with only one functional allele for LRH-1 develop fewer tumors in different models of colorectal cancer [33].

The fact that LRH-1 reduces gut inflammation through corticosterone production and, at the same time, enhances proliferation and cancer may seem somehow contradictory since inflammation is generally thought to favor tumor development [119]. Further investigation is therefore required to elucidate this intriguing cross talk between cell proliferation and anti-inflammatory responses that is orchestrated by LRH-1. In particular, one should elucidate whether pro-proliferative and anti-inflammatory actions are temporally and spatially separated. For instance, tumor initiation could be driven by the cell-autonomous effects of LRH-1 on cell proliferation, whereas anti-inflammatory activities, that require cell-cell interactions, could be more relevant during the later stages of tumorigenesis. Along the same line, corticosterone production is confined to the intestinal crypt and it is currently unknown whether the steroidogenic enzymes are expressed or alternatively can be reinduced in adenomas. If not, their absence in adenomas would explain why the anti-inflammatory properties of LRH-1 are not prevailing during tumorigenesis.

Taken together, LRH-1 has evolved to become a relevant player in gut homeostasis over the last years. Modulating its activity through the use of agonists [120] could therefore constitute an interesting treatment option for pathologies in the gut and other tissues where LRH-1 acts. In this regard, it is important to note that, whereas mouse LRH-1 is constitutively active, synthetic agonists for LRH-1 have been identified and shown to activate human LRH-1 [64,120]. In IBD patients, with decreased expression of LRH-1, modulation of LRH-1 activity by synthetic agonists could prove to be a useful strategy to limit chronic inflammation in the gut. As the anti-inflammatory effect of LRH-1 is not dependent on glucocorticoid production in the adrenal but on local synthesis in the intestinal crypts, synthetic agonists for LRH-1 could provide a therapeutic strategy that avoids the negative side effects of systemic glucocorticoids, often observed in patients with IBD. The identification and further development of small molecules interfering with the interaction of the β-catenin/LRH-1 complex may constitute an even more challenging approach to combat certain forms of colorectal cancer. Further studies will be required to screen for these molecules and to examine the potential impact on the progression of these different pathologies in different models of IBD and colorectal cancer.

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