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Review

Nuclear receptors, intestinal architecture and colon cancer: an intriguing link

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Abstract. The intestinal epithelium is structured in crypt-villus units which are responsible for its continuous renewal. These units are organized in a dynamic scenario in which proliferating progenitor cells are generated from stem cells in the crypts and migrate along the villus axis until their extrusion as differentiated cells at the surface epithelium. The mechanisms controlling cell transition involve transcription factors that switch on and off compartment-specific genes. The Wnt cascade represents the dominant force controlling cell fate in the crypt-villus axis. Mutations in this cascade result in the development of colorectal cancer. Life-style modifications and dietary regimens are epidemiologically recognized contributing factors for intestinal tumorigenesis. Nuclear receptors are a family of transcription factors functioning as sensors of dietary and endogenous molecules, thus translating nutritional and hormonal stimuli into transcriptional modifications. This review presents the role of nuclear receptors in intestinal carcinogenesis and explores their influence in maintenance of intestinal epithelium architecture.

Keywords. Crypts, gene expression, intestine, nuclear receptors, stem cells, villus.

Intestinal architecture and mucosa self-renewal

The intestinal tract consists of the small intestine (duodenum, jejunum and ileum) and the large intestine or colon. The absorptive epithelium of the small intestine contains large numbers of invaginations termed the crypts of Lieberkühn. Differentiated cells (enterocytes, enteroendocrine cells and goblet cells) occupy the villi, while another type of differentiated cells, the Paneth cells, reside at the bottom of the crypts and secrete antimicrobial agents. The remaining part of the crypts constitutes the stem cells and proliferating progenitor compartment [1]. Stem cells reside near the bottom of the crypt and give rise to progenitor cells that are capable of differentiating toward all epithelial lineages. Stem cells self-renew to regenerate the epithelium after injury, while progenitor cells arrest their cell cycle and differentiate when they reach the crypt-villus junction [2]. The presence of these cells renders the intestinal epithelium the most rapidly self-renewing tissue in adult mammals. Epithelial renewal occurs in the crypts through a coordinated series of events such as proliferation, differentiation and migration toward the intestinal lumen [3]. In this way, the large number of cells produced by the crypt compartment is compensated by apoptosis at the tip of the villus in a process that requires about 3 – 5 days [4]. Proliferating crypt precursors and differentiated villus cells form a

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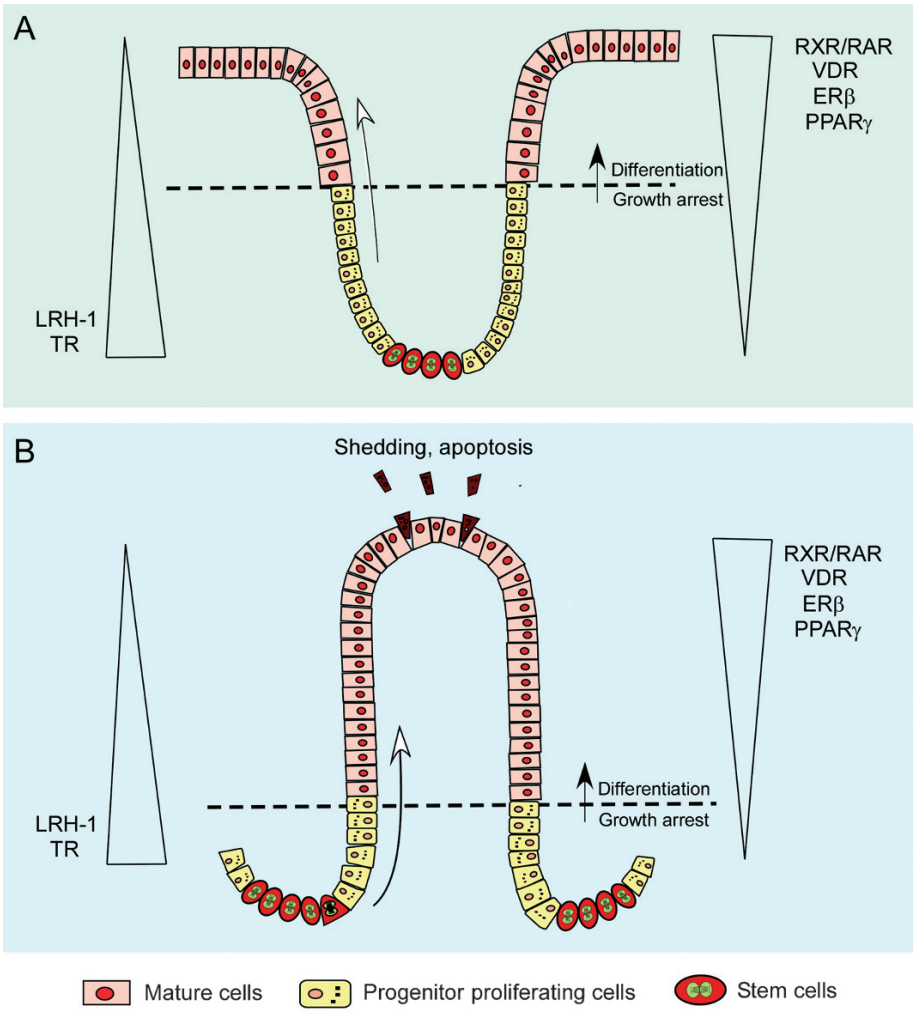

Figure 1. Intestinal epithelium self-renewal and nuclear receptors. (*A*) Colonic epithelium tissue anatomy. At the bottom of the crypt, progenitor proliferating cells and stem cells. On the top of the villus, mature cells. (*B*) Small intestine tissue anatomy. At the bottom, progenitor proliferating cells and stem cells; at the top, mature and shedding cells. In the intestinal epithelium, the proliferating crypt precursors and differentiated villus cells form a contiguous sheet of cells that is in perpetual upward motion. Stem cells reside near the bottom of the crypt and give rise to progenitor cells that are capable of differentiating toward all epithelial lineages. Proliferative progenitor cells arrest their cell cycle and differentiate when they reach the crypt-villus junction (interrupted line). In this way, the large number of cell produced by the crypt compartment is compensated by apoptosis at the tip of the villus in a process that requires about 3–5 days. Adapted from Reya and Clevers [1,2]. Vertical arrows indicate expression levels of some nuclear receptors in the different compartments of the two anatomical regions. LRH-I, liver receptor homology 1; TR, thyroid hormone receptor; RXR/RAR, retinoid x receptor/retinoid acid receptor; VDR, vitamin D receptor; ERβ, estrogen receptor β; PPARγ, peroxisome proliferator-activated receptor γ.

continuous sheet of cells in perpetual upward motion (Fig. 1). Stem cells and Paneth cells at the crypt bottom escape this flow [5]. Clearly, modulation of this continuous scenario is of great pathophysiological and functional relevance for intestinal cancer development.

Intestinal tumorigenesis and colon cancer

Current evidence indicates that the Wnt cascade is the dominant force in controlling cell fate along the crypt-villus axis. Wnt activates the canonical Wnt/β-catenin pathway, which is involved in adult tissue self-renewal. The signaling initiates when Wnt ligands engage their cognate receptor complex, consisting of a seven-pass transmembrane receptor, Frizzeld (Fz), and a member of the LDL receptor family, Lrp5/6. The central player of this mechanism is a cytoplasmic protein, β-catenin, the stability of which is regulated by the 'destruction complex'. When Wnt receptors are not engaged, two scaffolding proteins in the 'destruction complex', the tumor suppressor adenomatous polyposis coli (APC) and axin, bind newly synthesized β-catenin [1]. Two kinases residing in the destruction complex, CKI and GSK3β, phosphorylate a set of serine and threonine

residues in the amino terminus of β-catenin, which is than recognized by the F box/WD repeat protein β-TrCP, a component of a E3 ubiquitin ligase complex. As a consequence, β-catenin is ubiquitinated and targeted for rapid destruction by the proteasome [6]. Upon receptor activation by Wnt ligands, the intrinsic kinase activity of the APC complex for β-catenin is inhibited and stable, nonphosphorylated β-catenin accumulates and translocates into the nucleus where it binds to the N-terminus of LEF/TCF (lymphoid enhancer factor/T cell factor) transcription factors. In absence of Wnt signals, TCF acts as a transcriptional repressor, but the interaction with β-catenin transiently converts it into an activator [7–9]. Thus Wnt signals promote the transcription of TCF target genes. Is it commonly reported that Wnt signaling is associated with maintenance and activation of stem cells, and several studies have identified TCF target genes involved in cancer development, such as c-Myc [10] and cyclin D1 [11]. Loss of components of the Wnt pathway results in a dramatic phenotype that affects a wide variety of organs and tissues. The transition of an intestinal epithelial cell into a transformed, metastatic cancer cell requires mutations in multiple proto-oncogenes and tumor suppressor genes [12]. The APC gene has been cloned from the genetic disorder familial adenomatous polyposis (FAP) [13]. Early in life FAP patients inheriting one defective APC allele develop large numbers of colon polyps, or adenomas. These adenomas often lead to the appearance of adenocarcinomas due to clonal evolution, which responds to an accumulation of mutations in additional oncogenes and tumor suppressor genes, such as K-Ras [14, 15], p53 [16–19] and Smad4 [20]. Remarkably, loss of APC also occurs in most sporadic colorectal cancers. Mutational inactivation of APC, in fact, leads to inappropriate stabilization of β-catenin [21], conferring a stem cell phenotype to epithelial cells through steady activation of the Wnt cascade.

While the mechanisms controlling cell transition from the crypt to the villus are complex and still incompletely understood, it is becoming more and more obvious that they involve specific transcription factors, conferring compartment-specific gene expression along the crypt-villus axis [22]. Indeed, during crypt-villus migration and differentiation, transcriptional activation of specific gene programs helps the cells to acquire their final function. A good example is villin, which is a major structural complex of the cytoskeleton of villi. The microvilli constitute a specialized domain at the apical surface of intestinal epithelial differentiated cells, named brush border [23]. Another example of specific gene activation is the caudal-related homeobox transcription factor (CDX2), which stands as one of the major regulatory factors controlling intestinal cell differentiation [24]. CDX2 upregulates the expression of genes involved in cell-cell or cell-substratum interaction such as LI-cadherin [25], E-cadherin [26] and claudin-2 [27] in various human colonic adenocarcinoma models. CDX2 also activates the expression of intestine-specific genes such as MUC2 [28], sucrase-isomaltase (SI) [29], KLF4 [30] and p21 [31].

Colon cancer affects both males and females, causing a high rate of deaths. This tumor, whose progression is associated with different genetic and epigenetic alterations (Fig. 2), is significantly influenced by dietary factors. Epidemiological studies have indicated that a diet enriched in fat can augment the risk of colon cancer [32, 33]. In recent years several laboratories have tried to shed light on the possible mechanisms whereby dietary lipids influence the progression of colon cancer. Nuclear receptors (NRs) constitute a family of transcription factors that function as sensors for dietary and endogenous molecules, thus translating nutritional and hormonal stimuli into transcriptional modifications of gene expression. This review aims to examine the role of nuclear receptors possibly involved in colon cancer initiation and progression. Activation or inhibition of some NRs in the crypt/villus axis generates an intriguing, sometimes contradictory scenario, underling the complexity of this particular scientific field.

NR superfamily

NRs are transcription factors regulated by small lipophilic ligands, including hormones, metabolites such as steroids, retinoids (vitamin A metabolites), vitamin D, fatty acids, oxysterols, bile acids and numerous dietary derived lipids [34–36]. Additional members of this family are called orphan nuclear receptors, since endogenous ligands are yet unknown [36, 37], and true orphans, which regulate transcription independently of ligand binding [34, 38]. Ligand binding to NRs triggers changes in the conformational and dynamic behavior of the receptors and regulates the recruitment of coregulators and chromatin-modifying machineries [39]. NRs represent the largest family of transcription factors found in metazoans [39]. They share a conserved modular structure that includes the ligand-independent activation function domain (AF-1), which is a region of the receptor involved in protein-protein interaction and transcriptional activation of target-gene expression; the highly conserved DNA-binding domain (DBD), composed of two zinc fingers, which plays an important role in receptor dimerization and its binding to specific DNA sequences [40]; the ligand-binding domain (LBD),

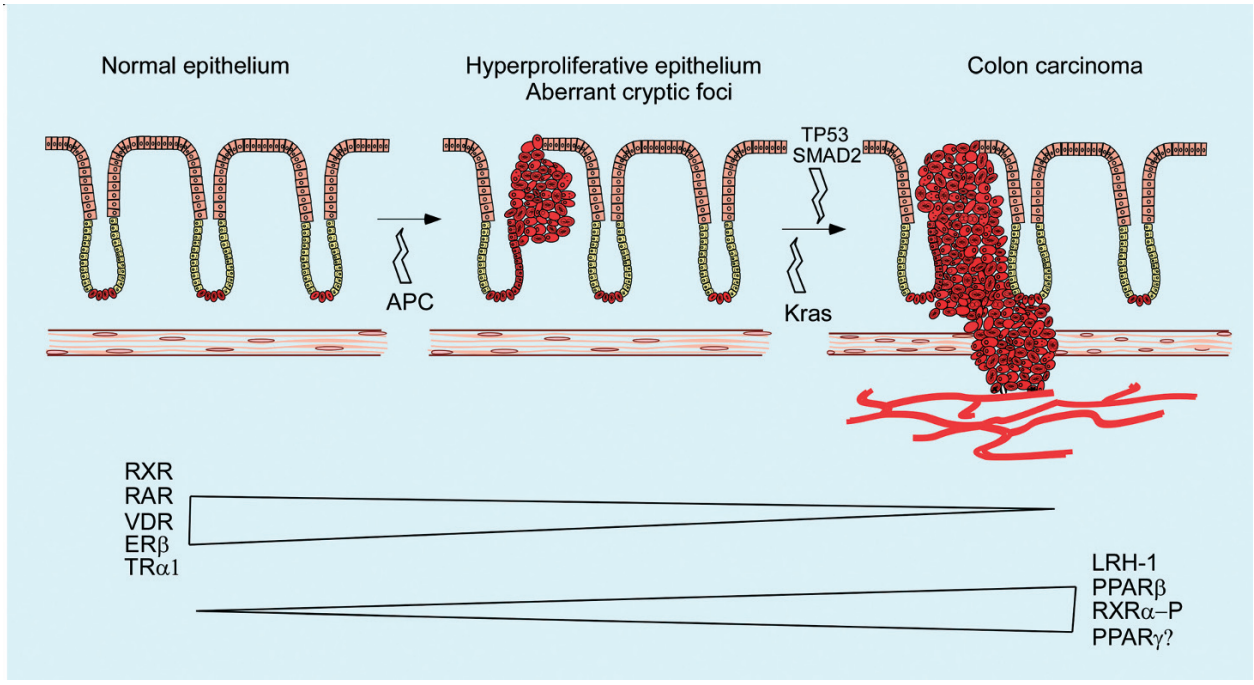

Figure 2. Schematic representation of colon cancer development and nuclear receptors. Specific genetic events, shown by vertical arrows, accompany the multi-step process that leads to colon carcinoma from normal epithelium to aberrant cryptic foci and cancer invasion. Adapted from Fearon and Vogelstein [261]. Horizontal arrows indicate nuclear receptor expression during colon cancer growth. APC, adenomatous polyposis coli; TP53, tumor protein 53; SMAD2, Small mothers against decapentaplegic homolog 2.

which contains a conserved ligand-dependent activation function-2 (AF-2) motif that mediates coactivator recruitment; and a hinge domain between DBD and LBD. Forty-eight NRs have been identified in the human genome and are divided into several groups [39]. NRs can form monomers, as in the case of steroidogenic factor-1 (SF-1), homodimers as for the androgen receptors (AR), estrogen receptors (ERs), mineralcorticoid receptor, and progesterone receptor (PR), and heterodimers with retinoid X receptor (RXR), as happens for the thyroid receptor (TR), vitamin D receptor (VDR), retinoic acid (RA) receptor (RAR), RXR, peroxisome proliferator-activated receptors (PPARs) and several orphan nuclear receptors [39]. Monomers, homodimers and heterodimers bind their response elements within the regulatory region of target genes. The response elements are derivatives of the canonical sequence RGGTCA (where R indicates a purine), known as hormone response element (HRE). There are HREs selective for a given receptor or for class of receptors which are generated by modifications of the canonical sequence. Thus HREs can differ one from the other due to their extension, or can be organized in duplications with alternate relative orientations of the repeats (direct, inverted and everted) [39, 41].

In the absence of ligand, the LBD of many NRs is bound to transcriptional co-repressor complexes containing nuclear receptor corepressor (N-CoR) or silencing mediator of retinoid and thyroid receptors (SMRT), which recruit transcriptional complexes that contain specific histone deacetylases (HDACs). HDACs cause chromatin condensation and thus gene silencing. Activation of NRs following ligand binding induces a conformational change that results in the dissociation of the corepressor complex and recruitment of coactivator complexes [34, 38, 42]. The NR field now covers a multiplicity of areas from structural and functional analysis of the molecular mechanisms that govern gene transcription to drug design and preclinical studies addressing metabolic diseases and cancer [43, 44]. Despite their structural conservation, NRs show considerable specificity in their activation and tissue-specific expression [45], and are considered promising drug targets. Actually, an enormous pharmacopoeia has been developed to contrast disorders generated by aberrant nuclear receptors signaling [36]. Thus a prerequisite for a normal physiological state is a network in which correctly controlled tissue-specific expression of NRs and ligand availability coexist [36]. Questions remain about NRs and provide cues for novel research areas. One example is NRs working as xenobiotic sensors which respond to drugs, environmental contaminants and toxic molecules, as in the case of the steroid xenobiotic receptor SXR [46] and of the constitutive

androstane receptor CAR (reviewed in [47]). Studying the interaction of these NRs with other NR agonists or antagoniss could reveal the metabolic fate of these compounds *in vivo* [36]. Another intriguing aspect is the quest for ligand identification for several orphan NRs. Indeed, it is not clear whether the transitory binding of an endogenous ligand regulates their transcriptional activities. Another hypothesis is that these nuclear receptors constitutively bind to an abundant cellular lipid, which becomes part of the ligand binding domain, stabilizing the interaction with other proteins [48].

In this review particular attention is paid to colorectal cancer, which is associated with different genetic and epigenetic alterations. Novel intriguing observations are discussed regarding the role of some NRs such as liver receptor homolog 1 (LRH-1), ERβ, PPARγ, PPARβ/δ, VDR, TR, RXR and RAR and AR in the regulation of cell growth and differentiation in the intestine with respect to colon cancer.

NRs and intestinal pathophysiology

LRH-1

LRH1 is an orphan nuclear receptor predominantly expressed in the enterohepatic axis and ovary [49]. It belongs to the NR5A of the Ftz-F1 subfamily of NRs, and it binds the sequence YCAAGGYCR (Y = pyrimidine, R = purine) as monomer via the C-terminus of its DBD [49]. For long time LRH1 was considered an orphan NR, but recently phosphatidyl inositols have been proposed as ligands for the human form [50–52].

LRH-1 plays a critical role in early development and differentiation, as demonstrated by the embryonic lethality of LRH-1 null mice [53, 54]. Also, LRH-1 has different expression levels during development, and it is highly expressed in mouse pluripotent embryonic stem cells [55]. During the early stage of development it is detectable in the yolk sac endoderm, branchial arch and neural crest [56]; later, in a second phase of organogenesis, it is confined to the development of intestine, liver and pancreas. During this stage, LRH-1 controls and is controlled by various developmental transcription factors which determine the enterohepatic phenotype [56–58]. In the adult stage, LRH-1 is predominantly expressed in enterohepatic tissues such as the liver [55], exocrine pancreas [59] and intestinal crypts [54], where it participates in the control of the complex regulatory pathways that govern cholesterol and bile acid homeostasis [49], and in the ovary [60], where its main function involves the regulation of cholesterol delivery and steroid production [61–63].

The promoters of human [64] and mouse [57] LRH-1 genes contain several regulatory sequences that control their expression. Three binding sites for GATA transcription factors and one motif that recognizes Nkx homeodomain proteins are shared by the two promoters [57, 64]. However, there is species specificity for other promoter sequences. This is the case for LRH-1 and hepatocyte nuclear factor (HNF4α) response elements that have been identified in the mouse [57] but not in the human [64] LRH-1 promoter. The opposite happens for HNF-1 and HNF-3β, which activate the human [64] but not the mouse [57] LRH-1 promoter.

Although it is well known that LRH-1 plays a key role in the regulation of genes involved in removing sterols and bile acids from liver and intestine [65, 66], an unexpected role was also found in the intestine regarding the control of cell renewal [54]. It has been reported that LRH-1 promotes cell cycle progression by two distinct mechanisms. First, LRH-1 acts as coactivator of β-catenin/Tcf4, inducing cyclin D1 and c-Myc expression in a DNA binding-independent manner. Second, LRH-1 binds a conserved LRH-1 response element on the promoter of cyclin E1 and SHP. Combination of both DNA-dependent and –independent transcriptional events contributes to induce G1 cyclins and leads to accelerated cell cycle progression [54]. Recent data show that LRH-1 exerts a protective role against intestinal epithelium inflammation and confirm its involvement in epithelium regeneration [67]. In fact, LRH-$1^{+/-}$ mice show a higher degree of colon inflammation with a significant increase in the colon weight/length ratio compared to $LRH^{+/+}$ mice [67]. These features indicate an increased proneness to inflammation and a decreased ability of the epithelium to regenerate [67]. Moreover, in the intestine LRH-1 regulates response after immunological stress, triggering the enterocyte-dependent production of glucocorticoids [67]. Indeed, in the colonic epithelium of LRH-1-deficient mice, local glucocorticoid production is considerably reduced [67]. These observations establish a role for LRH-1 not only in cell proliferation and renewal but also in the control of intestinal inflammation, underlining the potential danger of uncontrolled proliferation associated with aberrant LRH-1 expression and/or activity. Overexpression of cyclin D1, cyclin E1 and c-Myc, downstream targets of the LRH-1 and β-catenin signaling pathways, is frequently associated with human tumors, including those in the gastrointestinal tract [68–70]. In line with these findings, LRH-1 haploinsufficiency blunts intestinal tumorigenesis in $Apc^{Min/+}$ mice and decreases susceptibility to colon cancer formation elicited by the carcinogen azoxymethane [71].

ERβ

In 1986 the first estrogen receptor (ERα) was cloned [72, 73] and was considered the only receptor existing until a second form (ERβ) was cloned from a rat prostate cDNA library [74]. ERα and ERβ belong to the steroid/thyroid hormone superfamily of NRs and share a common structural architecture, represented by an NH_2-terminal domain, a DBD and an LBD. Dissimilarity in the NH_2-terminal regions of ERα and ERβ may be the reason for the difference between the two receptors in their response to various ligands. The DBD which plays an important role in receptor dimerization and sequence-specific binding to DNA, is highly conserved in the two receptors. Thus they can interact with various estrogen-response elements (EREs) with similar specificity and affinity [75]. The essential EREs consist of the consensus sequence GGTCAnnnTGACC [76, 77]. The symmetry of the sequence facilitates the binding of ER as a homodimer [78, 79]. However, only a few highly estrogen-responsive genes have perfect consensus sequences, the majority of genes contain EREs that vary from the consensus by one or more nucleotides resulting in lower ER-ERE affinity [80–82]. When bound to their EREs as homodimers or heterodimers, ERα and ERβ activate or repress target gene expression [75]. However, non-genomic regulatory pathways should be also taken into account when observing an effect of ERs and their ligands. Studies focusing on ERβ ligand specificity [83–85] and tissue distribution [86–89] showed that 17β-estradiol (E2) is the most potent endogenous ligand for ERβ (although it binds equally well to ERα) [90] and that tissues simultaneously expressing ERα and ERβ exhibit cell-type-specific patterns of expression [91]. For example, while ERα is able to enhance cell proliferation through the transactivation of other transcription factors, such as activator protein-1 and Sp1 [92], ERβ negatively regulates the E2-dependent activities of ERα that stimulate cell growth [93, 94]. ERβ plays a role in many tissues and organs, such as the ovary, uterus, mammary gland, ventral prostate, salivary gland, immune system, central nervous system and colon epithelium [74, 75, 95–99]. In some tissues both NRs are expressed; in others, such as the mature ventral prostate epithelium, only ERβ is expressed [98]. In colon epithelium, ERβ is the predominant ER, and its expression decreases along with the loss of enterocyte differentiation in colon cancer [100, 101]. ERβ expression is selectively lost in human malignant colon tissues [99], and its gene is methylated in 90% of colon cancers [102]. In this tissue ERα and ERβ expression differs by location within the colonic crypt unit in particular, ERβ is prominently expressed in the villi of colon surface epithelium, while ERα is mostly expressed at the base of the crypt [103]. ERβ loss in $Er\beta^{-/-}$ mice is correlated with loss of differentiation. Indeed, the colonic epithelium of Erβ-null mice presents hyperproliferation, loss of differentiation and decreased apoptosis [104]. Another intriguing aspect is the observation of a causal association between the loss of E2 (the most potent endogenous ligand for ERβ) in women after menopause and colorectal cancer (CRC) [105]. Hormone replacement therapy (HRT) confers protection against the incidence and size of adenomas, which are colorectal cancer precursor lesions [106]. Phytoestrogens, such as the soy isoflavone genistein and the coumestan coumestrol, are used as alternative to HRT. Epidemiological studies have shown that the soy-rich diet in Asian countries determines a reduction in CRC incidence among women [107–109]. Isoflavones and coumestans bind ER and induce ER-responsive gene transcription, suggesting that estrogens and their plant-derived homologs can participate in CRC prevention [83, 108, 110, 111]. This hypothesis is supported by the observation that $Apc^{Min/+}$ adenomas are hormonally responsive [112]. In fact, ovariectomy of $Apc^{Min/+}$ female mice leads to a strong increase in intestinal tumor number, which results to be reduced after treatment with E2 [112]. This effect has been explained as an increased expression of ERβ and a decrease in ERα levels in enterocytes, which means that the protective effect of E2 is mediated by ERβ [112]. It was later demonstrated that coumestrol but not genistein prevents Apc-associated tumorigenesis in intestinal epithelium of $Apc^{Min/+}$ mice [113]. It has also been reported that another diet derivate molecule, resveratrol, can modulate ER action. Resveratrol is a phytoestrogen with anticancer and cardioprotective properties naturally found in grapes [114–116] which has the ability to bind and activate ERs [117]. In particular, it has been proposed that resveratrol binds ERα and ERβ with comparable affinity even if much lower than E2 [118]. Recently, novel transgenic mouse models have been generated to study the effect of genetic loss of ER on colon cancer formation and progression in $Apc^{Min/+}$ mice. Indeed, it is now clear that ERα and especially ERβ are inhibitory modifiers of Apc-dependent tumorigenesis in the intestine [103]. Taken together these data indicate that modulation of ER-mediated signaling could play an effective role in CRC prevention.

PPARγ

PPARγ belongs to the PPAR subfamily, together with PPARα and PPARβ (also called PPARδ). PPARs heterodimerize with RXR and regulate transcription of target genes that directly bind specific DNA sequences. These response elements (PPREs) consist

of a direct repeat of the NR hexameric DNA core recognition motif AGGTCA spaced by one nucleotide (DR-1) [119]. PPARγ has been shown to occupy the 5′ half-site of the DR1 element, with RXR occupying the 3′ half-site [120, 121].

A wide range of substances have been identified as natural ligands for PPARγ, including fatty acids and arachidonic acid metabolites [122], eicosanoids [123], components of oxidized low-density lipoproteins [124] and oxidized alkyl phospholipids, including lysophosphatidic acid [125] and nitrolinoleic acid [126]. Thiazolidinediones (TZDs) [127, 128], 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-J_2) [128, 129], L-tyrosine-based compounds [130] and FMOC-L-leucine [131] are the main synthetic PPARγ ligands. PPARγ plays a pivotal role in adipocyte differentiation and metabolism. Interestingly, high levels of PPARγ have been also found in the colon. Stomach, small intestine, liver and pancreas also express lower but significant levels of this NR [122]. Due to its expression and involvement in cell proliferation, PPARγ has become a point of interest in colon cancer studies. PPARγ seems to control cell cycle destiny not only through the expression of genes involved in differentiation but also by negatively regulating cell cycle. It has been demonstrated that overexpression of PPARγ in fibroblasts [132] and muscle cells [133] induces their differentiation into adipocytes. The differentiation process occurs only after a prior and permanent exit from the cell cycle [134]. PPARγ activation reduces S-phase entry in different ways, inhibiting E2F/DP DNA binding [135] and phosphorylation of the retinoblastoma protein [134], inducing the cyclin-dependent kinase inhibitors p18 and p21, and decreasing cyclin D1 expression [136]. Different studies have shown that PPARγ activation inhibits the proliferation of malignant cells deriving from liposarcoma, breast adenocarcinoma, prostate carcinoma, colorectal carcinoma, nonsmall cell lung carcinoma, pancreatic carcinoma, bladder cancer and gastric carcinoma (reviewed in [119]). Obviously, this growth inhibition is not only due to PPARγ activation but is also the consequence of changes in expression of genes linked to growth regulation and cell maturation. Several studies have focused on the putative association or linkage between the various polymorphisms and mutations in the PPARγ gene and the occurrence of cancer. In a first study, in 55 sporadic colon cancers, 4 somatic PPARγ gene mutations, which reduce its function, are described [137]. In another study, 5 of 8 follicular thyroid carcinomas present mutation, which consist of a fusion of the DNA binding domains of the thyroid transcription factor PAX8 to PPARγ, the resulting fusion protein inhibited PPARγ in a dominant-negative manner [138]. However, another larger study in which the analysis of 397 clinical cancer specimens of different origin (including colon, prostate, breast, lung and leukemia) showed the absence of PPARγ gene mutations [139]. Also, the *in vivo* evidence to support an antitumorigenic role of PPARγ seems to be conflicting. Two different studies demonstrated that ligand activation of PPARγ promotes the development of colon tumors in $Apc^{Min/+}$ mice [140, 141]. A similar increase in the frequency of colon tumors was also found in mice on a high-fat diet [142], rising the idea that PPARγ could mediate the effects of high-fat diet on colon cancer. In agreement with this hypothesis, it has been observed that more than 85% of human colon tumors and premalignant adenomas overexpress cyclooxigenase 2 (COX2) [143, 144], which converts arachidonic acid into its downstream metabolites. COX2 levels are induced by high-fat diets rich in ω-6 polyunsaturated fatty acids [145]. Since PPARs can alter gene expression in response to fatty acids, eicosanoids and prostaglandins, these NRs are considered to be associated with neoplastic reaction to high-fat diet [141]. In contrast to these observations which describe PPARγ as a tumor inducer or enhancer, other studies showed that PPARγ acts as a tumor suppressor. Indeed, ligand activation of PPARγ inhibited tumor growth in a xenograft model [146] and reduced the formation of aberrant crypt foci after chemical induction by azoxymethane treatment [147]. However, the antitumoral effects of the PPAR ligand troglitazone might also depend on its intrinsic anti-oxidant properties [122]. Apparently, PPARγ is able to modulate both proliferation and apoptosis in the intestine. These divergent effects might be related to the different models and/or ligand concentration and bioavailability. Not enough evidence is available to establish whether PPARγ has pro- or anti-tumorigenic activities, and the question is still open. Recently, a retrospective analysis on around 90000 individuals showed a mild trend toward risk reduction of colorectal cancer among diabetic patients treated with TDZ. Although this difference did not reach statistical significance, it provides the impetus to address this important issue in population-based prospectic controlled studies [148].

PPAR β/δ

Like PPARγ, PPARβ/δ is expressed in the colon and can be activated by fatty acids. Recently, it was shown that PPARβ/δ is particularly expressed at the bottom of the crypt of the small intestine, where it plays a central role in the differentiation of Paneth cells and innate immunity [149]. It has also been shown that PPARβ/δ is involved in the development of colorectal cancer [150]. Conflicting data published so far suggest that PPARβ/δ could either promote or attenuate

colon cancer progression and development. It has been reported that PPARβ/δ levels increase in colorectal tumor in response to inactivation of the APC gene, or after treatment with the potent carcinogen azoxymethane [150, 151]. PPARβ/δ expression levels in colorectal tumors are higher then in normal mucosa, in agreement with the hypothesis that APC suppresses activity of β-catenin/Tcf-4 transcription of target genes, including PPARβ/δ, c-myc and cyclin D1 [150, 151]. Xenograft models in nude mice using PPARβ/δ-null HCT116 cells show a decrease in tumor formation [152]. Moreover, treating $Apc^{Min/+}$ mice with a specific PPARβ/δ ligand (GW501516) leads to an increase in the number and size of small intestinal adenomas, even if their absolute number in colon does not change [153]. All these studies suggest that when the expression of APC is lost, there is an increase in the expression of PPARβ/δ through the β-catenin/Tcf-4 transcriptional pathway, causing an increase in tumorigenesis. On the other hand, several other studies have shown different results. The comparison between normal colonic epithelium and adenomas from $Apc^{Min/+}$ mice, as well as between normal and cancer human tissues, shows that the expression of PPARβ/δ in tumors is reduced [154]. These observations are in agreement with what observed in the mouse intestine, where APC alleles are mutated through targeted deletions. In these samples, PPARβ/δ mRNA and protein levels are decreased and, as expected, c-Myc levels increased along with accumulation of β-catenin [155].

To clarify whether PPARβ/δ attenuates or potentiates intestinal tumorigenesis, two kind of intercrossed mice have been produced, $Apc^{Min/+}$ PPARβ/$\delta^{-/-}$ [155] and $Mlh1^{-/-}$ PPARβ/$\delta^{-/-}$ [156]. Mlh-null mice represent a mouse model of neoplasia, consisting of null mutation in the mismatch repair (MMR) gene Mlh1 [156]. These mice are prone to develop different types of neoplasias, including lymphomas and intestinal tumors [157]. Also in humans germline mutations of MLH1 gene are involved in hereditary non-polyposis CRC [158]. These two mouse models yielded different results. While $Apc^{Min/+}$ PPARβ/$\delta^{-/-}$ have increased numbers of colon tumors, indicating that PPARβ/δ deficiency promotes intestinal neoplasia [155, 159, 160], no significant differences are evident in the number and size of intestinal adenomas between $Mlh1^{-/-}$ PPARβ/$\delta^{-/-}$ and $Mlh1^{-/-}$ PPARβ/$\delta^{+/+}$ [156]. It has been recently reported that PPARβ/δ participates in the signaling transduction of retinoic acid (RA), leading to cell survival, proliferation and tumor growth [161]. It is well known that RA displays anticarcinogenic, pro-apoptotic activity through RAR. There is a tight link between RAR and PPAR isotypes in their response to RAs. Ligands that activate RAR and PPAR isotypes also bind intracellular lipid binding proteins (iLBPs) with distinct selectivity. Members of this iLBP family are the cellular RA binding proteins (CRABPI and II) specifically associated with RA and the fatty acid-binding proteins (FABPs), which bind a variety of fatty acid derivatives. Once in the intracellular milieu, RA can follow two opposite destinies; it can bind the CRABP-II or the FABP5, depending on the ratio between the two proteins, leading the cells in two opposite directions. If RA binds FABP5, cell survival and proliferation are favored with a consequent increase of tumor growth; if RA binds CRABP-II, cells go toward apoptosis and growth arrest with resulting anticancer activity [161]. In both situations RXR is indispensable as a dimerization partner of the NRs involved in the signaling pathway. In analogy to FABP5, another FABP, the adipocyte FABP4, enhances the activity of PPARγ. The three iLBPs mentioned share the intriguing feature that on association with ligands they translocate from the cytosol to the nucleus. Once they reach the nucleus, iLBPs recruit their cognate receptors trough protein-protein interaction, thus forming a molecular complex that delivers the ligand to the NR. In this way, these proteins control the transcriptional activities of their cognate PPARs in the nucleus [162]. Obviously, RA is not the only PPARβ/δ physiological ligand, and since this nuclear receptor is near ubiquitously expressed [163], other molecules are involved in its activation in tissues that do not display RA signaling. PPARβ/δ presents a much larger ligand binding pocket than other NRs [164], and it could accommodate multiple ligands, such as various long-chain fatty acids and eicosanoids, as activators [165]. The literature is full of controversy about the safety of PPARβ/δ ligands, in particular of those used in cancer model studies. With respect to colon cancer, it has been reported that the potent PPARβ/δ ligand GW501516 inhibits serum withdrawal-induced apoptosis and increases phosphorylation of protein kinase B (PKB/Akt) in human colon cancer cell lines [153, 166], where it also causes an increase of vascular endothelial growth factor (VEGF) expression [167]. It has also been shown that cyclooxygenase-derived prostaglandin E2 (PGE2), which is the predominant prostanoid found in most CRC and is known to promote colon carcinoma growth and invasion, indirectly transactivates PPARβ/δ through PKB/Akt signaling, thus promoting cell survival and intestinal adenoma formation [166]. Other studies reveal that colon cancer cell lines are nonresponsive to PPARβ/δ-stimulated cell growth in the presence or absence of serum [168, 169]. This evidence does not agree with other reports, which show that two PPARβ/δ ligands, GW0742 and GW501516, increase neither cell growth

nor phosphorylation of Akt and do not increase the expression of VEGF or COX2 in any colon cancer cell line, in the presence or absence of serum [169]. Moreover it has been shown that PPARβ/δ increases with sodium butyrate induced differentiation of HT29 [170]. The reason for the discrepancies present in the literature should be searched among the differences between *in vivo* and cancer cell line models and the wide variety of PPARβ/δ ligand structures.

VDR

VDR is a ligand-regulated transcription factor that mediates the biological effects of the physiologically most active form of vitamin D, 1α,25-dihydroxyvitamin D_3 [171]. For long time VDR was considered to be located exclusively in the nucleus. Now it has been established that it continuously shuttles between the nucleus and cytoplasm. Ligand binding and heterodimerization of VDR with RXRs increase its accumulation inside the nucleus [172], and its DNA binding and transcriptional activity [41]. VDR binds to vitamin D-responsive elements (VDREs), which consist of the direct repeat sequence AGGTCA spaced by three nucleotides (DR3) [173]. Hormone binding causes a conformational change in VDR that leads to VDR-RXR heterodimerization and DNA binding and finally results in the release of corepressors. Minimal VDR expression has been observed in normal colonic epithelial cells, where it is predominantly localized in the nucleus [174]. The intriguing aspect of this finding is that when a malignant transformation occurs, VDR expression increases markedly during early stage of colon cancer. But it is downregulated during late colon cancer progression [174–176], causing failure of therapy with vitamin D analogs. Vitamin D has a well-known role in mineral and skeletal homeostasis, but it is also widely accepted and demonstrated that it induces differentiation and apoptosis in various normal and tumor cells, including large intestine cells [177–179]. Vitamin D intake and sunlight exposure play a protective role against colorectal carcinogenesis [180]. It has been reported that a Western-style diet with decreased levels of calcium and vitamin D increases the incidence of pre-neoplasic intestinal lesions in mouse models of intestinal tumorigenesis [181]. Addition of dietary calcium and vitamin D significantly suppresses Western-diet induced changes, both in normal and Apc mutant mice [181]. VDR mediates repression or activation of specific proto-oncogenes or tumor-suppressor genes, including Waf1, Kip1, c-Myc, laminin, tenascin, fibronectin, cyclin C, c-Fos, c-Jun, Plcγ and members of the transforming growth factor-β (TGF- β) family involved in cell proliferation and differentiation [182]. The predominant effect of 1α,25-dihydroxyvitamin D_3 depends on cell type and specificity of target gene expression. For example, it has been reported that 1α,25-dihydroxyvitamin D_3 promotes the differentiation and inhibits the proliferation of human colon cancer cells (SW480-ADH) expressing high levels of VDR [183]. These effects are mediated by the induction of E-cadherin and of other adhesion proteins and by the inhibition of the transcriptional activity of β-catenin on its target genes, such as c-myc, TCF1 and CD44 [183]. Thus, 1α,25-dihydroxyvitamin D_3 regulates genes both directly, by VDR binding to their promoter, or indirectly affecting other pathways, such as Wnt/ β-catenin, related to its antitumoral effects. It has also been reported that Snail, a zinc finger transcription factor involved in migratory processes during embryonic development and in the acquisition of cancer cells movement and invasiveness [184], binds to and represses human VDR gene promoter [185], abolishing the induction of E-cadherin and other target genes normally due to 1α,25-dihydroxyvitamin D_3 [186]. In human colon tumors Snail expression is up-regulated and an inverse correlation exists between the expression of Snail and that of VDR and E-cadherin [185]. These observations suggest that perhaps the loss of VDR expression during colon cancer progression is related to Snail increased levels, which are also responsible for the failure of vitamin D analogous therapy in patients affected by this type of neoplasia [186]. Anyway, in contrast to this vision other studies showed that only in few cases of human colon tumors Snail is over expressed [187]. To clarify the role of VDR in prevention of colonic hyperproliferation and tumorigenesis, several animal models have been used. For example it has been shown that the intra-peritoneal administration of 1α,25-dihydroxyvitamin D_3 suppressed growth of human colon tumor xenografts in nude mice [188]. Also, VDR-knockout mice have been generated [189]. In these mice the complete loss of VDR results in colon cell hyperproliferation, cyclin D1 increase, and in a dramatic increase in DNA damage accumulation in particular in the distal colon [189]. Moreover it has been reported that treatment of $Apc^{Min/+}$ mice with 1α,25-dihydroxyvitamin D_3 results in a significant decrease in total intestinal tumor load [190].

RXR and RAR

RXR and all-trans RAR are NRs that mediate the RA signaling pathway. The two families of receptors consist of three subtypes, α, β and γ, which regulate gene transcription after binding with retinoids (which are natural and synthetic derivatives of vitamin A) [191]. The RAR family is activated by all-trans RA and by 9-cis RA, while the RXR family

is activated exclusively by 9-cis RA [191, 192]. RXR is able to form heterodimers with a wide range of receptors, such as RAR, VDR, TR and PPAR [37, 39, 193]. RXR and RAR bind DNA in the canonical consensus sequence AGGTCA [37]. RXR and RAR can exert their action by binding to this consensus as monomers [194]. The homo- and heterodimeric complexes of RXR, once activated by ligands, bind to their response elements on target genes [191]. RXR homodimers can bind with high affinity and specificity to response elements formed by tandem or direct repeats of the consensus hexamer AGGTCA, but not as a monomer to a single site [193, 195, 196]. Homo- and heterodimeric forms of RXR recognize direct repeats (DRs) with inter-half-site spacing consisting of one to five nucleotides, called DR1 and DR5, respectively [37, 195]. RXR and RAR heterodimerization increases their affinity and selectivity for RAREs (formed by both binding sites arranged in tandem) over the homodimeric form of RXR or RAR [194]. Once associated with agonists, RXRs and RARs undergo conformational changes which lead to the recruitment of coactivators, allowing target gene transcriptional activation [197]. In the RXR-RAR heterodimers, this transcriptional activation not only depends on the binding of the RXR ligand but is in general subordinated to the binding of an agonist ligand to RAR [41, 191]. This effect also holds for other RXR-NR heterodimers, as it does for TRs and VDRs. The binding of these receptors to their cognate ligands could be the required condition for the RXR partner to respond to its agonist ligand. This subordination probably avoids the promiscuous activation of these signaling pathway due to the RXR ligand (9-cis RA) [198]. For several other RXR-NR heterodimers, such as farnesoid X receptor (FXR), liver X receptor (LXR) and PPARs, RXR agonists are able to activate transcription by themselves. For RXR heterodimers, the ligand-binding pocket and the dimerization interface are energetically linked [199, 200], and this allosteric coupling generates a phenomenon termed the phantom ligand effect, which allows ligands of one member of an RXR heterodimer to regulate the activity of its partner LBD [201, 202]. RXR heterodimers exhibit three modes of activation, permissive (RXR-LXR), conditional (RXR-RAR) and non-permissive (RXR-VDR), which reveal the existence of a ligand-mediated allosteric pathway [203]. In the first example, RXR-LXR heterodimer could be activated by rexinoids, LXR agonists or both agonists in a stronger fashion [203]. In the case of RXR-RAR heterodimer, only in the presence of an RAR agonist is there a full response to rexinoids [203]. In the non-permissive example, the RXR-VDR heterodimer cannot be activated by rexinoids in either the presence or absence of VDR ligands [203].

In the absence of ligands, the RAR-RXR target genes are repressed due to the recruitment of complexes containing HDAC bounded through the corepressors (CoRs) to the RAR-RXR dimer. This binding results in histone deacetylation, chromatin condensation and thus silencing of target genes. When ligands bind to the RAR-RXR dimer, the binding of the HDAC complexes is destabilized, favoring the recruitment of the histone acetyltransferase (HAT) complexes. These new complexes lead to chromatin decondensation and consequently to the transcriptional activation of target genes. The response elements for RXRs heterodimers are direct (DR), inverted (IR) or everted (ER) repeat motifs (reviewed in [37]). Due to the asymmetry of the DRs, RXR heterodimers binding to these elements are consequently asymmetric. This was well demonstrated for DR3, DR4 and DR5 where RXR binds at 5′ half-site and the partner (as in the case of VDR or of RAR) binds the 3′ half-site [204–206]. On DR1, RXR can bind as homodimers and as heterodimer with RAR, but in this case with an inverted polarity [207] that renders this heterodimer a potent repressor of the ligand-activated RXR homodimers [208, 209].

Retinoids, which are the natural ligands for RAR and RXR, have potent anticancer functions, and they have been used successfully in the treatment of colon cancer [210, 211]. Interestingly, recent papers show the existence of cross-talk between the Wnt/β-catenin and retinoid-signaling pathways. Some years ago, it was reported that RAR interacts with β-catenin, inhibiting β-catenin-mediated gene transcription in colon cancer cells such as Caco-2 and HT29 [212, 213]. Later, it was also reported that RA and RAR agonists participate together with Wnt signaling in the upregulation of gene transcription [214, 215]. On the other hand, it has been shown that RXR is able to regulate β-catenin degradation via an APC-independent pathway [216]. Indeed, RXR agonists induce the proteasomal degradation of RXRα and of other proteins interacting with RXR, such as RAR, TR and β-catenin through a degradation complex. This APC-independent degradation of β-catenin reduces the activation of gene transcription and cell proliferation [216]. The escape of β-catenin from its 'destruction' mediated by APC or RXR leads to the pathogenic activation of genes involved in tumorigenesis. The regulation of these two pathways is the desired goal of numerous studies that aimed to find a therapeutic approach for cancer due to deregulation of β-catenin turnover. It has been proposed that the RXR-mediated pathway has the potential to become a successful pharmacological approach for the treatment of Wnt/

β-catenin-related cancers. In spite of the complexity of the APC pathway, which would reguire manipulation of a wide range of genes to control, the RXR pathway could be modulated by small hormonal molecules [216].

Among the three subtypes, α, β and γ, it has been demonstrated that the phosphorylation of RXRα protein causes a malfunctioning associated with the carcinogenesis of the liver [217, 218]. The phosphorylated form of RXRα loses its transactivation activity through the RXR-responsive element (RXRE) and acts in a dominant-negative manner, interfering with the function of the normal protein. This effect causes the induction of hepatoma cell growth [218]. In these cells, RXRα natural exogenous ligand, 9-cis RA, induces degradation of the phosphorylated proteins, and restores the function of the NR [218]. These observations suggest that RXRα also plays a role in CRC [219]. In recent years, the ligands for both PPARs and RXRs have been used for the prevention of colon cancer. Studies carried out using the combination of bexarotene and rosiglitazone, which are respectively agonists of RXR and PPARγ, showed that activation of RXR-PPARγ heterodimer leads to growth inhibition and differentiation of Moser cells, which are a human colon cancer model [220]. The same result has been shown in HT29 [221] and in Caco2 [219] cells, where activation of the PPAR-RXR pathway induces apoptosis and inhibits cell growth. Long-term studies are needed to further clarify this potentially successful therapeutic option for modulation of colon cancer progression.

TR

TRs are ligand-dependent transcription factor members of the steroid hormone/RA receptor superfamily. TRs mediate the biological activities of thyroid hormone (T3)-binding DNA as heterodimers with RXR or possibly as homodimers (reviewed in [222]). In the absence of T3, TRs are tightly bound to chromatin [223] on thyroid hormone response elements (TREs) containing two half-sites with the consensus sequence GAGGTCGA arranged in palindrome (P), inverted palindrome (IP) or DR repeat motifs separated by four nucleotides (DR4) (reviewed in [222]). TRs play a pivotal role in intestinal maturation by stimulating intestinal crypt cell proliferation and promoting brush border enzyme expression [224, 225]. Two different genes coding for the two isoforms α and β of TR have been identified. They are located on chromosomes 17 and 3 and give rise to the alternative splicing of the primary transcripts of each gene, producing other TR variants (TRα1, α2, α3, Δα1, Δα2, β1, β2, β3 and Δβ3) (reviewed in [226]). TRα and TRβ share high sequence similarity in the DNA binding and in the hormone-binding domains in spite of a very little similarity among the amino-terminal regions [227, 228]. TRα and TRβ are expressed in most tissues even though with a different tissue-specific abundance. The TR Δα1 and Δα2 isoforms are highly expressed in the small intestine and in a limited number of other tissues [229]. The intestine of $TR\alpha^{-/-}$ mice has been extensively studied. These mice have been generated by disrupting exon 2, which is the first coding exon within the TRα locus. This defect prevents transcription of both TRα1 and TRα2 but has no effect on the expression of TRΔα1 and TRΔα2, which are under the control of an internal promoter in intron 7 of the gene [229, 230]. So these mice express TRΔα1 and TRΔα2 but not TRα1 or TRα2. Their small intestine is consequently smaller, softer and more fragile than in wild-type mice. The jejunum and ileum diameters are reduced, along with the number and size of villi and the overall number of epithelial cells per crypt-villus unit. Circular and smooth-muscle layers are reduced accordingly, with altered motility in the ileum of these mice [229]. All these features indicate a delay in intestinal maturation, since a similar phenotype is characteristic in young mice. Further studies showed that the $TR\alpha^{-/-}$ mice are characterized by a decrease in the proliferation rate of the intestinal crypt cells and in a decreased number of goblet cells in the ileum [231]. Moreover, in these mice the intestinal expression of the intestine-specific Cdx-1 and Cdx-2 homeobox genes is reduced, which is extremely interesting considering that these transcription factors play a key regulatory role in normal intestinal cell proliferation and differentiation [26, 232–234]. An amazing feature is that these $TR\alpha^{-/-}$ mice recover intestinal architecture after a single T3 injection [231]. Follow-up studies have also demonstrated that the expression of TRΔα1 and TRΔα2 in the absence of TRα1 may be deleterious to intestinal development [235]. This was confirmed by the characterization of $TR\alpha^{0/0}$ mice that lack expression of all the products of the TRα locus [236]. These mice are characterized by a phenotype not as severe as in the $TR\alpha^{-/-}$ mice [235]. Moreover, the expression levels of Cdx1and Cdx2 remain unchanged compared to wild-type mice, indicating that TRΔα1 and TRΔα2 mRNAs may exert an inhibitory effect in the regulation of Cdx gene transcription in the absence of TRα1 [235]. These data, and the observation that, on the contrary, TR $\beta^{-/-}$ mice [237] did not show an intestinal phenotype, suggest that the balanced expression of all TRα isoforms is extremely important for normal intestine development [235].

Given the pivotal role of TRs in intestinal development and architecture, it is also plausible to hypothesize a role for these NRs in the alteration of

equilibrium in intestinal epithelium renewal. Indeed, it has been proposed that TRs may exert a role in colon cancer development. TRs may act as tumor suppressors, since in colon cancer cells it has been shown that the ligand-activated form of TRs (T3/TR) strongly suppresses cyclin D1 promoter activity [238]. In particular, it has been reported that the TRα1 receptors directly control the transcription of the β-catenin gene [238]. This finding was supported by the detection *in vivo* of the interaction between TRα1 and a TRE inside the first intron of the β-catenin gene [238]. Thus, cyclin D1 transactivation by β-catenin and Tcf/Lef-1 is abrogated [239] via ligand-dependent TR interaction.

AR

AR, like other members of the steroid receptor superfamily (such as ER), functions as a ligand-dependent transcription factor controlling the expression of genes involved in cell growth, proliferation, differentiation and death, and it has an important role in carcinogenesis and in prostate epithelial cells [240]. Steroid receptors bind DNA as homodimers to repeated palindromic sequences, TGTTCT, spaced by three nucleotides [241–244]. Next to this classical element, AR interacts with other binding motifs that resemble a direct, rather than palindromic, repeat of the TGTTCT hexamer [245, 246]. The physiological activities of AR are largely determined by the presence of androgens and of others cofactors, such as coactivators (CBP, SRC1 and TIF-2) and corepressors, which enhance or repress its activity [247–249]. There is strong evidence that on exposure to its cognate ligands AR shuttles from the cytoplasm to the nucleus [250–252]. It has been reported the existence of a ligand-dependent relationship between the AR and β-catenin [253] and that after ligand binding AR can translocate β-catenin to the nucleus in an APC-independent manner [254]. The ligand-binding domain of AR and the central region containing the armadillo repeats 1–6 of β-catenin are responsible for their direct interactions [255]. Thus, nuclear accumulation of β-catenin correlates with increased AR transcriptional activity [254]. The existence of sex differences in colon cancer incidence was proposed several years ago, due to the observation that this neoplasia occurs more often in men than in women in nearly all countries [256]. The importance of androgens in colorectal cancer is supported by many avenues of research [257]. Moreover, an association between the AR genotype and colorectal cancer has been observed. The AR gene contains two polymorphic trinucleotide repeat segments that encode polyglutamine (CAG) and polyglycine (GGC). The CAG trinucleotide ranges from 6 to 39 repeats, and it has been observed that fewer CAG repeats correspond to higher levels of AR gene transcription [258]. It has been also reported that in colon tumors there is a reduction in the number of CAG repeats in the AR gene [259].

Conclusion and perspectives

The intestinal mucosa represents a dynamic microenvironment in which stem cells and proliferative progenitors in the crypts generate epithelial cells that differentiate during their migration toward the villus compartment. A well-controlled cascade of signals maintains the mucosal architecture by the shedding of senescent and apoptotic cells at the surface of the epithelium. The activity of some NRs seems to play a pivotal role in this process. The identification of a functional interaction between the Wnt/APC pathway and NRs represents a major goal for several laboratories [260]. Table 1 summarizes our current knowledge on nuclear NRs, and on intestine and colon cancer experimental models. What we know today is that β-catenin activates a growing number of NRs, resulting in alterations of cell proliferation and tumorigenesis. On the other hand, Wnt signaling appears to be compromised by the action of some NRs. It is also clear that NRs are regionally compartmentalized along the crypt-villus axis, determining the switching on and off of transcription of particular genes with a strong influence on cell fate. The mechanism for the influence of NRs on cell proliferation, differentiation and apoptosis in the gut is complex and still under investigation. Also, the observed phenotypes after NR activation or inhibition are sometimes contradictory. NR effects depend on the amount of agonists, on the cell type and on the mutational events that predispose cells to cancer development. It is worth noting that the possibility to promote cell differentiation represents a promising new area in cancer research and in particular in mechanism-based strategies to counteract tumor progression. If one considers NRs as a powerful transcriptional link for several nutritional and hormonal signals in the gut, the knowledge of their expression and function in the crypt-villus axis and during tumor formation or progression is of great translational value. Indeed, the generation of an intestinal cancer NR transcriptome will probably be a first step in answering extremely important questions at this stage. Would NR-driven nutritional hits directly protect or predispose cells to somatic mutations that give rise to cancer? Or would NRs be the main force in the regulation of tumor progression by nutritional and hormonal stimuli after cancer initiation by a somatic mutation?

Table 1. Experimental models for nuclear receptor modulation in colon cancer.

Nuclear receptor	Model	Design	Phenotype	Ref.
AR	somatic mutation	CAG repeats in AR gene	↑ colon tumors	[229]
ERβ	ligand activation	estrogen therapy	↓colorectal cancer precursor lesions	[106]
		soy therapy	↓colorectal cancer precursor lesions	[107–109]
		resveratrol therapy	↓colorectal cancer precursor lesions	[117, 118]
	hormone response	ovariectomy of $Apc^{Min/+}$ mice (↑ERβ)	↑intestinal tumor number	[112]
	loss of function	$Erβ^{-/-}$ mice	↓differentiation ↑epithelium proliferation ↓apoptosis	[104]
		ER $β^{-/-}$ $Apc^{Min/+}$ mice	↑ colon tumors	[103]
LRH-1	haploinsufficiency	LRH-$1^{+/-}$ mice	↑ colon inflammation ↓ epithelium regeneration	[67]
		LRH-$1^{+/-}$ $Apc^{Min/+}$ mice	↓ intestinal tumors	[71]
PPARγ	ligand activation	ligand-activated PPARγ in xenograft model	↓ tumor growth	[146]
		troglitazone activated PPARγ	↑ colon tumors	[141]
		BRL-49,653 and troglitazone	↑ colon tumors	[140]
	tumor induction	High-fat diet	↑ colon tumors	[142]
		ligand activation of PPARγ in rats chemically treated with azoxymethane	↓ tumor growth	[147]
	somatic mutations	inactivating somatic mutation of PPARγ gene	↑ colon cancer formation	[137, 146] [138]
PPARβ/δ	tumor induction *in vivo* models	inactivation of APC gene by azoxymethane	↑ PPARβ expression levels	[150, 151]
		xenograft model with PPARβ-null cells	↓ tumor formation	[152]
	ligand activation	GW501516 treatment of $Apc^{Min/+}$ mice	↑ small intestinal adenomas	[153]
		GW501516 treatment of human colon cancer cells HCT116	↓ apoptosis	[153]
		GW0742 and GW501516 treatment of colon cancer cell lines	no increase in cell growth	[169]
		cyclooxygenase-derived prostaglandin E2 treatment	↑ intestinal adenoma formation	[166]
		retinoic acid treatment	↑ tumor growth	[161]
	mouse models	Apc $^{Min/+}$ $PPARβ^{-/-}$ mice	↑ colon tumors	[155]
		$Mlh1^{-/-}PPARβ^{-/-}$ mice	no significant difference in colon tumor growth	[156]
RAR/ RXR	ligand activation	retinoid treatment	↓ colon tumor growth	[210, 211]
		bexarotene and rosiglitazone treatment of colon cancer cells	↓ colon tumor growth ↑ differentiation and apoptosis	[219–221]
TR	mouse models	$TRα^{-/-}$ mice (no expression of TRα1 and TRα2)	↓ intestinal maturation ↓ proliferation of crypt cells	[229] [231]
		$TRα^{0/0}$ mice (no expression of TRα locus)	No severe intestinal phenotype	[236]
		$TRα^{β/β}$ mice (no expression of TRβ locus)	No intestinal phenotype	[237]
	ligand activation	thyroid hormone treatment of colon cancer cells	↓ proliferation	[238]
VDR	ligand activation	vitamin D intake	↓ colon tumors ↑ differentiation and apoptosis	[180] [177–179]
		1α,25-dihydroxyvitamin D_3 treatment of colon cancer cells (SW480)	↑ differentiation and apoptosis	[183]
	in vivo model	intraperitoneal administration of 1α,25-dihydroxyvitamin D_3 in human colon tumor xenograft	↓ colon tumors growth	[188]
	mouse models	VDR knockout mice	↑ colon cell proliferation ↑ DNA damages	[189]
		$Apc^{Min/+}$ treated with 1α,25-dihydroxyvitamin D_3	↓ intestinal tumors	[190]

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