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## Expression and role of nuclear receptor coregulators in colorectal cancer

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### Abstract

Colorectal cancer (CRC) is one of the most common human cancers and the cause of about 700000 deaths per year worldwide. Deregulation of the WNT/ $\beta$ -catenin pathway is a key event in CRC initiation. This pathway interacts with other nuclear signaling pathways, including members of the nuclear receptor superfamily and their transcription coregulators. In this review, we provide an overview of the literature dealing with the main coactivators (NCoA-1 to 3, NCoA-6, PGC1- $\alpha$ , p300, CREBBP and MED1) and corepressors (N-CoR1 and 2, NRIP1 and MTA1) of nuclear receptors and summarize their links with the WNT/ $\beta$ -catenin signaling cascade, their expression in CRC and their role in intestinal physiopathology.

**Key words:** Immunohistochemistry; Colon cancer; Nuclear receptors; Transcription coregulators; WNT signaling

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**Core tip:** Colorectal cancer (CRC) is one of the most common human cancers worldwide. Deregulation of the WNT/ $\beta$ -catenin pathway is a key event in CRC initiation. This pathway interacts with other nuclear signaling pathways, including members of the nuclear receptor superfamily and their transcription coregulators. In this review, we provide an overview of the literature dealing with the main coactivators and corepressors of nuclear receptors, and summarize their links with the

WNT/ $\beta$ -catenin signaling cascade, their expression in CRC and their role in intestinal physiopathology.

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## INTRODUCTION

### Colorectal cancer

Colorectal cancer (CRC) is the third most common human cancer with more than 1.3 million recorded cases in 2012. Patients are generally treated with surgery, chemotherapy and radiotherapy that are associated with several side effects. Despite important advances in CRC prognosis, diagnosis and treatment during the last decade, it remains the cause of about 700000 deaths per year worldwide<sup>[1]</sup>. Although CRC can be sporadic or hereditary, in both cases, environmental factors contribute to its development. The main risk factor is age; however, diet, sedentary lifestyle and tobacco smoking also increase the risk of developing CRC<sup>[2]</sup>.

CRCs are complex and heterogeneous epithelial tumors that involve various genetic and epigenetic alterations. The progressive accumulation of these molecular changes contributes to the transformation of normal mucosa into neoplasia<sup>[3]</sup>. At least three molecular pathways have been identified as involved in CRC pathogenesis<sup>[4]</sup>. The most common is the chromosomal instability (CIN) pathway, characterized by inactivation of tumor suppressor genes (*APC*, *TP53*, *SMAD4*) and activation of oncogenes (*KRAS*)<sup>[5]</sup>. The hallmark of the second molecular pathway is microsatellite instability (MSI) that results from the deregulation of DNA mismatch repair (MMR) genes, leading to genetic hypermutability<sup>[6]</sup>. Finally, the third molecular mechanism involves gene silencing *via* aberrant hypermethylation of promoter CpG islands (CpG island methylator phenotype, or CIMP)<sup>[7]</sup>. A recent study has proposed a unique molecular classification of CRC based on gene expression with four consensus molecular subtypes (CMS): MSI immune (CMS1), canonical (CMS2), metabolic (CMS3) and mesenchymal (CMS4)<sup>[8]</sup>.

### WNT signaling pathway

Large-scale investigations have identified several critical genes and multiple signaling pathways that are important for CRC initiation and progression, including WNT, Notch, p53, RAS-MAPK, PI3K and TGF- $\beta$ . The WNT/ $\beta$ -catenin signaling pathway is the most studied

in CRC<sup>[9]</sup>. In normal intestinal cells, WNT expression is detected in cells at the crypt base and is essential for the maintenance of stem cell compartmentalization and, ultimately, for the intestinal tract organization and patterning. The WNT canonical pathway is activated upon binding of the WNT ligands to the Frizzled/LRP receptor. This interaction induces a signaling cascade, leading to the stabilization of  $\beta$ -catenin in the cytoplasm and to its translocation into the nucleus. There,  $\beta$ -catenin interacts with the TCF/LEF transcription factors to modulate specific target genes that are involved in cell proliferation and differentiation, such as *MYC*, which encodes the Myc proto-oncogene, and *CCND1*, which encodes the cyclin D1 protein. In the absence of WNT ligands,  $\beta$ -catenin is targeted for proteasomal degradation upon phosphorylation through its association with a destruction complex composed of various scaffold proteins, such as adenomatous polyposis coli (APC), Axin 2, glycogen synthase kinase 3 (GSK3) and casein kinase 1 (CK1). Approximately 70%-80% of sporadic CRCs involve somatic mutations that inactivate APC, leading to  $\beta$ -catenin accumulation and activation of its target genes.

### Nuclear receptor signaling

Nuclear receptors (NRs) are ligand-activated transcription factors that directly regulate genes and are involved in several physiological processes, such as growth, homeostasis, differentiation, development and metabolism<sup>[10]</sup>. NR signaling dysregulation contributes to various human diseases, including cancer<sup>[11]</sup>. Currently, NRs represent one of the largest families of transcription factors (48 members in humans) that can be classified in three groups (hormone, metabolic and orphan NRs), based on their ligand properties<sup>[10,12]</sup>. Members of the hormone receptor subfamily generally bind to DNA as homodimers and include estrogen (ER $\alpha$  and ER $\beta$ ), androgen (AR), progesterone (PR), glucocorticoid (GR) and mineralocorticoid receptors (MR). Metabolic receptors, such as farnesoid X (FXR), liver X (LXR) and peroxisome proliferator-activated receptors (PPARs), bind to DNA as heterodimers with their obligate partner retinoid X receptor (RXR). Orphan receptors include all NRs for which ligands were (or are still) unknown<sup>[10]</sup>. NRs share a modular structure composed of an N-terminal activation domain, which is important for interactions with coregulators (activators and repressors), a DNA-binding domain, a small hinge region and a C-terminal ligand binding domain that interacts with the ligands and transcriptional coregulators<sup>[13]</sup>.

NRs promote gene transcription mainly through classical gene transactivation and transrepression. These activities are modulated by transcriptional coregulators that allow NRs to target gene promoters and to coordinate transcription. Additionally, NRs can modulate also other nuclear signaling pathways that

rely on various transcription factors, such as SP1, AP-1, p53 or NF- $\kappa$ B<sup>[14-17]</sup>. Moreover, NR activities can be influenced by post-translational modifications whereby they are targeted by other cellular pathways, leading, for instance, to activation of kinases in response to growth factors. Recent investigations have highlighted the role of some NRs, such as ER, PPAR, nuclear vitamin D receptor (VDR), RXR and retinoic acid receptor (RAR), in the regulation of intestinal cell growth and differentiation and also in CRC.

### NRs in the gut and in CRC

Various NRs regulate the cell cycle, proliferation and apoptosis of intestinal epithelial cells and are now considered as factors that might also modulate CRC development and progression<sup>[18]</sup>. The characterization of NR localization and expression in normal and tumoral gut epithelium led to a better understanding of their potential role in CRC. On the basis of their expression profile in the normal intestinal epithelium, NRs can be divided in three subgroups. Some NRs, such as NR5A2 (LRH1), PPAR $\beta/\delta$  and thyroid hormone receptor alpha (TR $\alpha$ ), are detected mostly in the proliferative compartment of the crypt, suggesting that they might be involved in cell proliferation regulation. Other NRs (including VDR, ER $\beta$ , GR, MR and FXR $\alpha$ ) are mostly expressed in the differentiated compartment of the intestinal epithelium. The last group includes the NRs LXR $\beta$ , PPAR $\alpha$ , RAR $\alpha$  and RXR $\beta$  that are ubiquitously expressed in the intestinal mucosal epithelium<sup>[19]</sup>.

Differently from what observed in the normal intestine, the expression of most NRs is downregulated in patients with familial adenomatous polyposis (FAP) and in *Apc*<sup>Min/+</sup> mice (an animal model of CRC), while only few are upregulated<sup>[20]</sup>. For instance, loss of ER $\beta$  and VDR in mice results in colon cell hyperproliferation<sup>[21,22]</sup>. On the other hand, the expression of other NRs, such as ESR-2, is induced in CRC models and is downregulated in HT29 colon cancer cells upon restoration of the activity of wild type APC<sup>[19]</sup>. In both cases, variations in NR expression/activity seem to be directly related to the WNT signaling pathway and indeed, many NRs cross-talk with the WNT signaling pathway<sup>[18]</sup>.

The canonical WNT/ $\beta$ -catenin pathway is one of the major signaling pathways involved in the establishment of intestinal homeostasis. WNT signaling is fundamental for the maintenance of the intestine proliferative compartment<sup>[23]</sup>. Components of the WNT pathway can modulate NR function through transcriptional activation or repression<sup>[18]</sup>. Similarly, NRs can exert dynamic changes in the WNT signaling pathway. For instance, it has been reported that after association with  $\beta$ -catenin, NR5A2 (LRH1) is activated to promote *CCND1* transcriptional activation and governs the self-renewal of intestinal crypt cells. Consequently, proliferation of epithelial cells is enhanced, contributing

to CRC development<sup>[24]</sup>. By contrast,  $\beta$ -catenin activity is repressed when associated with VDR, RAR and AR<sup>[25-27]</sup>. Moreover, components of the WNT pathway can interact with PPAR $\beta/\sigma$ . Specifically, PPAR $\beta/\sigma$  levels increase in CRC in response to inactivation of the APC gene or after treatment with the potent carcinogen azoxymethane<sup>[28]</sup>. This suggests that loss of APC expression leads to increased PPAR $\beta/\sigma$  expression through the  $\beta$ -catenin/TCF-4 transcriptional pathway<sup>[29]</sup>.

Besides the WNT pathway, NR cross-talk with the Notch pathway that plays a role in both intestinal development and cancer<sup>[30,31]</sup>. For instance, TR $\alpha$ 1 controls several components of the Notch pathway<sup>[32,33]</sup>. Deciphering the mechanisms underlying NR cross-talk with different signaling pathways could eventually lead to the identification of targets for clinical interventions in CRC and for diagnostic/prognostic purposes.

### NR coregulators in CRC

The expression of NR target genes is modulated by a large set of transcription coregulators that can act as NR activators and repressors. This review focuses on several of these transcription factors (Table 1) that may play a role in intestinal homeostasis and tumorigenesis.

## TRANSCRIPTIONAL COACTIVATORS

### Nuclear receptor coactivator 1

Nuclear receptor coactivator 1 (NCoA-1), also known as SRC-1/RIP160, was the first identified member of the SRC family. It belongs to the structurally homologous p160 family of coactivators<sup>[34]</sup>. This family includes three members (SRC-1, -2 and -3) characterized by the presence of three distinct structural domains: (1) the bHLH-PAS domain that facilitates the interaction with several transcription factors; (2) the central NR-interacting domain; and (3) two C-terminal activation domains<sup>[35]</sup>. Several NRs are regulated by NCoA-1, including PR, GR, ER $\alpha$ , TR, RXR and PPAR $\gamma$ <sup>[34,36,37]</sup>. Interestingly, GST pull-down and coimmunoprecipitation assays showed that NCoA-1 binds directly to  $\beta$ -catenin, the key mediator of the canonical WNT signaling pathway<sup>[38,39]</sup>. The bHLH-S/T domain (amino acids 1 to 580) and the domain required for NCoA-1 histone acetyltransferase (HAT) activity (amino acids 1080 to 1442) appear to be involved in this interaction, together with the Arm3-10 domains of  $\beta$ -catenin (amino acids 234 to 585). Upon binding to  $\beta$ -catenin, NCoA-1 specifically enhances  $\beta$ -catenin transactivation activity, as indicated by transient transfection experiments using the TOP-Flash reporter plasmid<sup>[39]</sup>. It should be mentioned that coactivator-associated arginine methyltransferase 1 (CARM1), which is associated with the different p160 family members and participates in their coactivator function, also can bind to  $\beta$ -catenin and increase TCF-4 mediated transactivation<sup>[40]</sup>.

**Table 1** Description of the genes analyzed in the review

Name	Description and aliases	Gene ID	MIM	Location
NCOA1	Nuclear receptor coactivator 1 F-SRC-1, KAT13A, RIP160, SRC1, bHLHe42, bHLHe74	8648	602691	2p23.3
NCOA2	Nuclear receptor coactivator 2 GRIP1, KAT13C, NCoA-2, SRC2, TIF2, bHLHe75	10499	601993	8q13.3
NCOA3	Nuclear receptor coactivator 3 ACTR, AIB-1, AIB1, CAGH16, CTG26, KAT13B, RAC3, SRC-3, SRC3, TNRC14, TNRC16, TRAM-1, bHLHe42, pCIP	8202	601937	20q13.12
NCOA6	Nuclear receptor coactivator 6 AIB3, ASC2, NRC, PRIP, RAP250, TRBP	23054	605299	20q11.22
PPARGC1A	PPAR gamma, coactivator 1 alpha LEM6, PGC-1 (alpha), PGC-1v, PGC1, PGC1A, PPARGC1	10891	604517	4p15.2
EP300	E1A binding protein p300 histone acetyltransferase p300, KAT3B, p300	2033	602700	22q13.2
CREBBP	CREB-binding protein CREBBP, KAT3A, RTS	1387	600140	16p13.3
MED1	Mediator of RNA polymerase II transcription subunit 1 TRIP2, MED1, PBP, PPARBP, PPARGBP, CRSP1, CRSP200, DRIP230, RB18A	5469	604311	17q12
NCOR1	Nuclear receptor corepressor 1 N-CoR, N-CoR1, PPP1R109, TRAC1, hN-CoR	9611	600849	17p12-p11
NCOR2	Nuclear receptor corepressor 2 CTG26, N-CoR2, SMAP270, SMRT, SMRTE, SMRTE-tau, TNRC14, TRAC, TRAC-1, TRAC1	9612	600848	12q24.31
NRIP1	Nuclear receptor interacting protein 1 RIP140	8204	602490	21q11.2-q21.1
MTA1	Metastasis associated 1	9112	603526	14q32.33

In the colon mucosa, *NCOA1* expression is confined mostly to the crypts<sup>[41]</sup>. Although, the *NCOA1* gene (with *NCOA2*) was identified by a ChIP-seq based genome-wide analysis as a possible TCF-4 target in SW620 CRC cells<sup>[42]</sup>, to our knowledge, no other study reported data on *NCOA1* expression and role in CRC.

### NCoA-2

NCoA-2, also referred to as TIF2/GRIP-1/SRC-2, was identified soon after the discovery of NCoA-1<sup>[43]</sup>. NCoA-2 is involved in mammary gland morphogenesis, energy balance and lipid metabolism<sup>[44,45]</sup>. Indeed, the *NCOA2* gene is expressed in many tissues<sup>[43,46]</sup>, including colon<sup>[47]</sup>. Conversely, there are discrepancies about NCoA-2 expression in CRC. Indeed, by immunohistochemistry, Grivas *et al.*<sup>[48]</sup> found that NCoA-2 expression is significantly higher in carcinoma than in normal colorectal tissues. Moreover, they reported that NCoA-2 overexpression is associated with more advanced disease. Conversely, two other studies suggested that NCoA-2 expression (both mRNA and protein) is downregulated in cancer tissues compared with the adjacent normal mucosa<sup>[47,49]</sup>.

In agreement, *NCOA2* knock-down using siRNA in normal colonocytes (NCM460 cells) promotes cell proliferation and reduces apoptosis<sup>[49]</sup>. Previous studies also reported that NCoA-2 can bind to  $\beta$ -catenin<sup>[38,50]</sup>. Yu *et al.*<sup>[49]</sup> confirmed these data by demonstrating that NCoA-2 exerts an inhibitory effect on the WNT signaling pathway. Altogether, these findings suggest a potential tumor-suppressor activity of NCoA-2 in CRC.

### NCoA-3

NCoA-3, also known as amplified in breast cancer 1 (AIB1) or SRC-3/RAC3/ACTR/TRAM1, is the third member of the p160 family of NR transcriptional coactivators. It was first described in breast adenocarcinoma where it is amplified and strongly expressed<sup>[51]</sup>. Amplifications in the 20q11-13 region that includes the *NCOA3* gene are detected in 10% to 32% of CRC<sup>[52,53]</sup>. Moreover, the NCoA-3 protein is overexpressed in 35% of human CRC samples<sup>[53]</sup>. Interestingly, NCoA-3 overexpression does not always correlate with gene amplification, suggesting that it might also be regulated by other molecular mechanisms, such as post-translational modifications<sup>[51,54]</sup>. Furthermore, NCoA-3 overexpression has been correlated with clinicopathological features, such as advanced clinical stage, lymph node and liver metastases<sup>[53,54]</sup>. However, NCoA-3 overexpression has been also associated with lower risk of death (43.5% vs 19.3%) and prolonged overall survival<sup>[48]</sup>. In support of these observations, comparison of normal intestine and CRC cell lines showed that NCoA-3 expression is significantly higher in CRC cell lines. Furthermore, *NCOA3* knock-down decreases the proliferation of RKO, HCT116 and CT26 cells and the ability of CT26 cells to form tumors after grafting in BALB/c mice<sup>[55]</sup>. Few reports have investigated NCoA-3 interactions with components of other pathways that have a critical role in CRC. Xie *et al.*<sup>[53]</sup> associated *NCOA3* molecular abundance with inhibition of the p53 pathway. Moreover, Mo *et al.*<sup>[55]</sup> demonstrated that NCoA-3 directly interacts



with Notch intracellular domain and is recruited to the *HES1* promoter to enhance Notch signaling and, subsequently, CRC cell proliferation. Collectively, these findings suggest that NCoA-3 might be a potential target for CRC treatment.

### NCoA-6

NCoA-6, also referred to as NRC, ASC-2, TRBP, PRIP and RAP250, was originally isolated as a ligand-dependent NR-interacting protein<sup>[56]</sup>. The *NCOA6* gene is amplified and overexpressed in breast, colon and lung cancer<sup>[57]</sup>. Recently, NCoA-6 has emerged as an important coactivator not only of NRs, but also of a number of other well-known transcription factors involved in CRC, such as c-Jun and p53<sup>[58]</sup>.

### Peroxisome proliferator-activated receptor- $\gamma$ coactivator 1- $\alpha$

*PPARGC1A* encodes a transcriptional coactivator (PGC1- $\alpha$ ) that regulates mitochondrial biogenesis and function<sup>[59]</sup>. PGC1- $\alpha$  enhances the activity of PPAR $\gamma$ <sup>[60]</sup> and also of other members of the NR superfamily (e.g., RXR, FXR and RAR) that are involved in the modulation of intestinal cell differentiation and apoptosis<sup>[19,61,62]</sup>. In the normal intestinal epithelium, PGC1- $\alpha$  is highly expressed in differentiated enterocytes at the surface where cells produce and accumulate reactive oxygen species. Conversely, its expression is reduced in crypts and in colorectal tumors. Indeed, the mRNA levels of *PPARGC1A* and its target genes are reduced by 70%-90% in colon tumor samples from patients with FAP and from *Apc*<sup>Min/+</sup> mice, compared with the adjacent healthy intestinal mucosa<sup>[63]</sup>.

Furthermore, PGC1- $\alpha$  ectopic expression in CRC cells leads to a reduction of their proliferative rate and to a proapoptotic effect. In agreement, mice that overexpress PGC1- $\alpha$  in the intestinal epithelium are protected against tumors, whereas the opposite is observed in *Ppargc1a*<sup>-/-</sup> mice. Altogether, these data suggest that by regulating the intestinal cell fate, PGC1- $\alpha$  could play a role in protecting against CRC formation and mitochondria-mediated apoptosis<sup>[63]</sup>.

### p300 and CREB-binding protein

CREB-binding protein and p300 are two closely homologous proteins involved in multiple biological processes. They function as coregulators and also as HATs<sup>[64,65]</sup>. p300 plays a role in many cellular activities, including cell differentiation, growth and DNA repair<sup>[66]</sup>. A study performed on 27 primary colon adenocarcinoma samples showed that p300 inactivation due to a missense point mutation could be involved in CRC development<sup>[67]</sup>. In addition, p300 loss in HCT116 cells results in a more aggressive phenotype characterized by increased cell migration and reduced cell adhesion<sup>[68]</sup>. Finally, low p300 expression is associated with CRC aggressiveness (for

instance, lymph node invasiveness)<sup>[69]</sup>. Comparison of colon adenocarcinoma and normal tissue samples showed that both p300 and CREB-binding protein are overexpressed in tumors. However, while increased CREB-binding protein tumor expression is associated with overall good patient survival, p300 overexpression is associated with poor patient survival<sup>[70]</sup>.

p300 and CREB-binding protein have a key role in the regulation of the WNT/ $\beta$ -catenin signaling pathway<sup>[71,72]</sup> and several studies connected them to CRC<sup>[73]</sup>. Specifically, p300-mediated WNT signaling has been associated with embryonic stem cell (ESC) differentiation, while CREB-binding protein-mediated WNT activity promotes cell proliferation<sup>[71]</sup>. Finally, selectively blocking the association between  $\beta$ -catenin and CREB-binding protein with ICG-001 downregulates WNT transcriptional activity in CRC cells<sup>[74,75]</sup>.

### Mediator of RNA polymerase II transcription subunit 1

Mediator of RNA polymerase II transcription subunit 1 (also known as mediator complex subunit 1, MED1, or TRAP220) is the main subunit of the TRAP/Mediator complex<sup>[76]</sup> and a coactivator of PPAR $\gamma$ <sup>[77]</sup>. MED1 mRNA levels are lower in CRC tissues than in the adjacent normal mucosa<sup>[47]</sup>. Moreover, absence of MED1 expression in CRC is correlated with lymph node metastasis and with advanced TNM stage<sup>[78]</sup>. It has been reported that the *MED1* gene is hypermethylated in CRC tumors and also in the matched normal mucosa. This indicates that *MED1* silencing occurs early in CRC formation and is associated with cancer initiation rather than cancer progression<sup>[79]</sup>.

## TRANSCRIPTIONAL COREPRESSORS

### Nuclear receptor corepressor 1 and 2

Nuclear receptor corepressor (N-CoR or N-CoR1) and the highly similar silencing mediator of retinoic and thyroid receptor (N-CoR2 or SMRT) were the first identified NR corepressors, based on their ability to mediate transcriptional repression of TR and RARs<sup>[80,81]</sup>. Additional studies revealed that N-CoR1 and N-CoR2 mediate the ligand-independent interaction with other NRs. The NR interaction domains located in the C-terminus of N-CoR1 and N-CoR2 correspond to the so-called corepressor NR boxes (CoNR) and harbor the consensus sequence L/I-X-X-I/V-I or LXXXI/LXXXI/L<sup>[82]</sup>. Both corepressors exert their function by recruiting various proteins to specific promoters, particularly histone deacetylases 3 (HDAC3), one of the main actors responsible for their repressive activity<sup>[83]</sup>. Interestingly, HDAC3 is overexpressed in human colorectal adenocarcinomas and in CRC cell lines<sup>[84-86]</sup>. Moreover, HDAC3 plays a central role in regulating CRC cell proliferation and differentiation, particularly through the regulation of p21<sup>[84]</sup>.

In CRC, N-CoR2 is aberrantly expressed in all tested

primary tumors<sup>[87]</sup>. Moreover, increased IKK $\alpha$  activity in CRC has been correlated with the specific phosphorylation of Ser-2410 in N-CoR2. This phosphorylation event also leads to N-CoR2 cytoplasmic translocation and degradation<sup>[88]</sup>. IKK $\alpha$  recruitment to chromatin is associated with the transcriptional activation of different Notch target genes (including HES1 and HES5) and with N-CoR2 release from the corresponding promoters<sup>[87]</sup>.

On the other hand, *NCOR1* expression level is higher in human CRC tissues than in normal mucosa<sup>[47]</sup>. IKK $\alpha$  also phosphorylates N-CoR1 and aberrant N-CoR1 cytoplasmic localization is a general feature of CRC<sup>[89]</sup>. Specifically, N-CoR1 is excluded from the nucleus of 98% of tested tumor samples, whereas it is mainly nuclear in the normal mucosa. These results indicate that N-CoR1 nuclear export might be associated with intestinal tumorigenesis.

### Nuclear receptor-interacting protein 1

This transcription coregulator, also known as receptor-interacting protein of 140 kDa (RIP140), was originally identified in breast cancer as a modulator of ER $\alpha$  activity<sup>[90]</sup>. Subsequently, it was reported to interact and inhibit other transcription factors, including NRs and E2F transcription factors<sup>[91]</sup>. 2-Nuclear receptor-interacting protein 1 (NRIP1) exerts its repressive activity *via* four inhibitory domains that recruit histone deacetylases or C-terminal binding proteins<sup>[92]</sup>. Several post-translational modifications, such as acetylation and sumoylation, play important roles in controlling NRIP1 subcellular localization and repressive activity<sup>[93]</sup>.

In a recent study, we showed that NRIP1 plays a major role in normal and malignant development of the intestinal epithelium by exerting a negative control on the WNT/ $\beta$ -catenin signaling pathway through regulation of APC transcription<sup>[94]</sup>. Furthermore, NRIP1 expression (both mRNA and protein) is lower in CRC samples than in the adjacent healthy tissue. Interestingly, NRIP1 is considered a marker of good prognosis in CRC. Overall survival is better in patients with a CRC that strongly expresses NRIP1 than in patients whose tumor shows low NRIP1 expression.

Nevertheless, NRIP1 cross-talk with the WNT/ $\beta$ -catenin signaling pathway is complex because another study using co-immunoprecipitation assays in human hepatocellular MHCC97 cells showed that NRIP1 can also interact directly with  $\beta$ -catenin<sup>[95]</sup>.

We recently identified the transcription coregulator ligand-dependent corepressor (LCoR)<sup>[96]</sup> as a partner and transcriptional target of NRIP1 (Jalaguier *et al.*<sup>[97]</sup> submitted for publication). Similar to NRIP1, LCoR was first discovered thanks to its ligand-dependent interaction with ER $\alpha$ , and subsequently was found to interact with many other NRs. The *LCOR* gene is widely expressed in embryonic and adult tissues. LCoR is expressed also in many human cell lines, and this expression is particularly high in Caco2 cells.

Moreover, immunoprecipitation experiments in Caco2 cells showed that the tumor suppressor KLF6 interacts with LCoR<sup>[98]</sup>. Interestingly, KLF6 is inactivated in CRC, suggesting that it might play an important role in CRC development<sup>[99]</sup>. As consequence, LCoR interaction with KLF6 could have potential implications in CRC initiation and development.

### Metastasis-associated protein 1

3-Metastasis-associated protein 1 (MTA1) is a component of the nuclear remodeling and deacetylation (NuRD) complex that is associated with adenosine triphosphate-dependent chromatin remodeling and transcriptional regulation (for reviews, see<sup>[100,101]</sup>). MTA1 overexpression is closely correlated with an aggressive course in several human carcinoma types. Aberrant MTA1 expression has been observed in CRC<sup>[47]</sup>. MTA1 mRNA overexpression in CRC has been correlated with deeper invasion through the intestine wall and higher lymph node metastasis rate<sup>[102]</sup>. Similarly, MTA1 protein expression is significantly higher in moderately and poorly differentiated CRC specimens and liver metastatic tumors compared with normal colon tissues. Moreover, MTA1 overexpression in HCT116 cells enhances cell proliferation, migration and adhesion, while *MTA1* silencing inhibits these functions<sup>[103]</sup>.

## CONCLUSION

NR coregulators (coactivators and corepressors) represent a family of key regulatory transcription factors that control major steps in gene expression, including not only transcriptional initiation but also elongation, splicing and translation. These molecules are both targets and depositors of a huge number of post-translational modification marks that could play a key role in intestinal pathogenesis. By cross-talking with factors that are part of other signaling pathways, these transcription coregulators are centrally positioned to finely tune major physiopathological processes, such as development, energy storage and utilization, as well as tumor initiation and progression. In this review, we summarized how the expression of the main NR coregulators is dysregulated in CRC (see Table 2 for a synthetic summary). In most of the cases, the molecular mechanisms responsible for the expression deregulation in intestinal tumors are not fully known. One major mechanism could involve variation in gene copy number. As shown in Table 2, this is a relevant explanation in several cases, but other levels of regulation (transcriptional or post-transcriptional) could also be involved. In addition, the multiple qualitative alterations of these genes (*i.e.*, mutations affecting their coding sequence) that have been identified in CRC (Table 3) could play a major role in controlling their biological activity. We also discussed the links between NR coregulators and the WNT/ $\beta$ -catenin

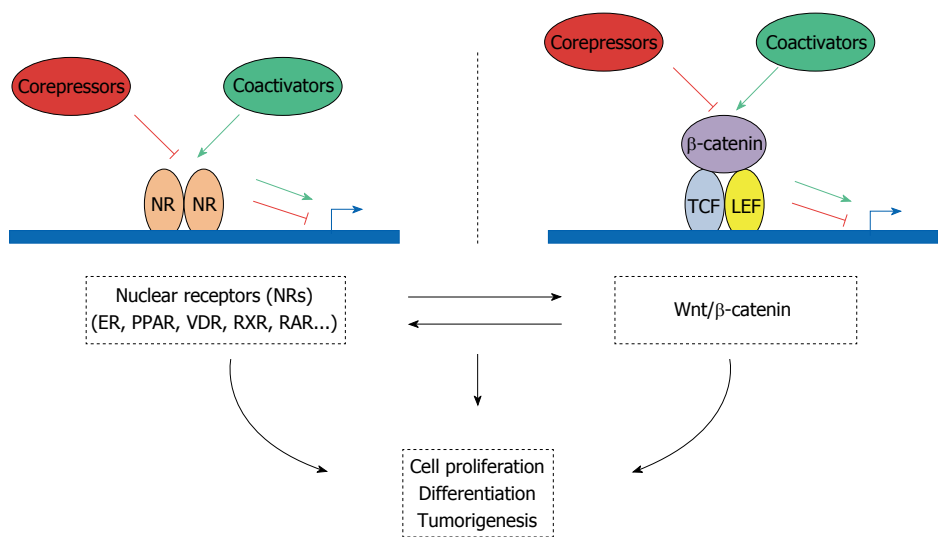


Figure 1 Overall scheme integrating the different pathways and actors involved. NR: Nuclear receptor.

Table 2 Copy number variation and expression levels of nuclear receptor coregulators in human colorectal cancer			
Coregulator	CNV (%)	Expression	Ref.
NCOA1	Gain (5.5)	ND	Giannini 2005, Grivas 2009, Yu 2016
NCOA2	Gain (30.1)	↑ or ↓	
NCOA3	Gain (40.6)	↑	Anzick 1997, Aust 2004, Xie 2005
NCOA6	Gain (42.7)	↑	Lee 1999
PPARGC1A	Loss (8.4)	↓	D'Errico 2011
EP300	Loss (19.3)	↑	Ishihama 2007
CREBBP	Gain (5.3)	↑	Ishihama 2007
MED1	Gain (11.8)	↓	Giannini 2005
NCOR1	Loss (40.4)	↑	Fernández-Majada 2007
NCOR2	Gain (9.8)	↑	Giannini 2005, Fernández-Majada 2007
NRIP1	Loss (17.2)	↓	Lapierre 2014
MTA1	Loss (15.0)	↑	Toh 1997

Gene copy number analysis was performed in 379 CRC samples from the “Carte d’Identité des Tumeurs de la Ligue contre le Cancer” using the Nexus Copy Number software (BioDiscovery, CA, United States). The percentage of CRC specimens showing chromosomal gains and losses are indicated (B. Orsetti, personal communication). Variations in the expression level were determined using the data extracted from the indicated references. ND: Not determined; CRC: Colorectal cancer.

signaling pathway that involve, in several cases, a direct interaction with β-catenin (Table 4). Finally, we summarized what is known about the biological relevance of these different cross-talks in intestinal physiopathology (Figure 1 for an overall scheme integrating the different pathways and actors that are involved). Often, their effects have been assessed only using *in vitro* experimental approaches. Therefore, additional work using transgenic mouse models is required to precisely determine their role in CRC. This will certainly lead to useful information that may help clinicians to improve therapeutic interventions and to

Table 3 Mutations identified in the different nuclear receptor coregulator genes in human colorectal cancer <i>n</i> (%)				
Coregulator	216 United States patients (COAD-US)		187 Chinese patients (COCA-CN)	
	Patients affected	Mutations	Patients affected	Mutations
NCOA1	6 (2.78)	7	9 (4.81)	14
NCOA2	10 (4.63)	10	26 (13.90) <sup>1</sup>	32
NCOA3	21 (9.72) <sup>1</sup>	17	9 (4.81)	10
NCOA6	19 (8.80) <sup>1</sup>	21	8 (4.28)	10
PPARGC1A	10 (4.63)	12	5 (2.67)	6
EP300	13 (6.02) <sup>1</sup>	15	14 (7.49) <sup>1</sup>	21
CREBBP	18 (8.33) <sup>1</sup>	20	7 (3.74)	11
MED1	3 (1.39)	4	6 (3.21)	6
NCOR1	21 (9.72) <sup>1</sup>	25	23 (12.30) <sup>1</sup>	48
NCOR2	41 (18.98) <sup>1</sup>	43	30 (16.04) <sup>1</sup>	40
NRIP1	5 (2.31)	5	6 (3.21)	10
MTA1	11 (5.09) <sup>1</sup>	11	12 (6.42) <sup>1</sup>	13

Data from the ICGC Data Portal (<https://dcc.icgc.org>). <sup>1</sup>Indicated genes with mutations detected in more than 5% of patients.

Table 4 Effects of the different nuclear receptors coregulators on the WNT signaling pathway				
Coregulator	Effect	Assay	Domains on β-catenin	Ref.
NCoA-1	↑	GPD CoIP	aa 234-585	Li 2004, Tong 2015
NCoA-2	↓	GPD	C-terminal part (aa)	Li 2004, Song 2005, Yu 2016
CREBBP	↑	Y2H GPD CoIP	AR10 to C-ter	Takemaru 2000
N-CoR1		GPD	aa 120-683	Song 2008
N-CoR2		GPD	aa 120-683	Song 2008
NRIP1	↓	CoIP		Zhang 2014

Y2H: Yeast two-hybrid assay; CoIP: Coimmunoprecipitation assay; GPD: GST-pull down assay; AR: Armadillo repeat.

develop better prognostic tools for CRC.



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