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Expression and role of nuclear receptor coregulators in colorectal cancer

Mouna Triki, Marion Lapierre, Vincent Cavailles, Raja Mokdad-Gargouri

Mouna Triki, Marion Lapierre, Vincent Cavailles, RIRCM, Institut de Recherche en Cancérologie de Montpellier, INSERM U1194, Université de Montpellier, Institut régional du Cancer de Montpellier, 34298 Montpellier, France

Mouna Triki, Raja Mokdad-Gargouri, Centre de Biotechnologie de Sfax, Université de Sfax, Sfax 3072, Tunisie

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Correspondence to: Vincent Cavailles, PhD, IRCM, Institut de Recherche en Cancérologie de Montpellier, INSERM U1194, Université de Montpellier, Institut régional du Cancer de Montpellier, 208 rue des apothicaires, 34298 Montpellier, France. vincent.cavailles@inserm.fr
Telephone: +33-4-67612405
Fax: +33-4-67613787
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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/β-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-α, p300, CREBBP and MED1) and corepressors (N-CoR1 and 2, NRIP1 and MTA1) of nuclear receptors and summarize their links with the WNT/β-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/β-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/β-catenin signaling cascade, their expression in CRC and their role in intestinal physiopathology.


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[11]. 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[2].

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[3]. At least three molecular pathways have been identified as involved in CRC pathogenesis[4]. The most common is the chromosomal instability (CIN) pathway, characterized by inactivation of tumor suppressor genes (APC, TP53, SMAD4) and activation of oncogenes (KRAS)[5]. 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[6]. Finally, the third molecular mechanism involves gene silencing via aberrant hypermethylation of promoter CpG islands (CpG island methylator phenotype, or CIMP)[7]. 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)[8].

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-β. The WNT/β-catenin signaling pathway is the most studied in CRC[9]. 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 β-catenin in the cytoplasm and to its translocation into the nucleus. There, β-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, β-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 β-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[10]. NR signaling dysregulation contributes to various human diseases, including cancer[11]. 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[10,12]. Members of the hormone receptor subfamily generally bind to DNA as homodimers and include estrogen (ERα and ERβ), 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[10]. 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[13].

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...
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[18]. 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), PPARβ/δ and thyroid hormone receptor alpha (TRα), are detected mostly in the proliferative compartment of the crypt, suggesting that they might be involved in cell proliferation regulation. Other NRs (including VDR, ERβ, GR, MR and FXR) are mostly expressed in the differentiated compartment of the intestinal epithelium. The last group includes the NRs LXRβ, PPARα, RARα and RXRβ that are ubiquitously expressed in the intestinal mucosal epithelium[19].

Differently from what observed in the normal intestine, the expression of most NRs is downregulated in patients with familial adenomatous polyposis (FAP) and in ApcMIN mice (an animal model of CRC), while only few are upregulated[20]. For instance, loss of ERβ and VDR in mice results in colon cell hyper-proliferation[21,22]. On the other hand, the expression of other NRs, such as ER-2, is induced in CRC models and is downregulated in HT29 colon cancer cells upon restoration of the activity of wild type APC[19]. 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[18].

The canonical WNT/β-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[23]. Components of the WNT pathway can modulate NR function through transcriptional activation or repression[18]. Similarly, NRs can exert dynamic changes in the WNT signaling pathway. For instance, it has been reported that after association with β-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[24]. By contrast, β-catenin activity is repressed when associated with VDR, RAR and AR[25-27]. Moreover, components of the WNT pathway can interact with PPARβ/δ. Specifically, PPARβ/δ levels increase in CRC in response to inactivation of the APC gene or after treatment with the potent carcinogen azoxymethane[28]. This suggests that loss of APC expression leads to increased PPARβ/δ expression through the β-catenin/TCF-4 transcriptional pathway[29].

Besides the WNT pathway, NR cross-talk with the Notch pathway that plays a role in both intestinal development and cancer[30,31]. For instance, TRα1 controls several components of the Notch pathway[32,33]. 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[34]. 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[35]. Several NRs are regulated by NCoA-1, including PR, GR, ERα, TR, RXR and PPAR[36,37]. Interestingly, GST pull-down and coimmunoprecipitation assays showed that NCoA-1 binds directly to β-catenin, the key mediator of the canonical WNT signaling pathway[38,39]. 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 β-catenin[39,40]. Upon binding to β-catenin, NCoA-1 specifically enhances β-catenin transactivation activity, as indicated by transient transfection experiments using the TOP-Flash reporter plasmid[39]. 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 β-catenin and increase TCF-4 mediated transactivation[40].
In the colon mucosa, NCOA1 expression is confined mostly to the crypts\(^{[41]}\). 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\(^{[42]}\), to our knowledge, no other study reported data on NCOA1 expression and role in CRC.

**NCOA2**

NCOA-2, also referred to as TIF2/GRIP-1/SRC-2, was identified soon after the discovery of NCOA-1\(^{[43]}\). NCOA-2 is involved in mammary gland morphogenesis, energy balance and lipid metabolism\(^{[44,45]}\). Indeed, the NCOA2 gene is expressed in many tissues\(^{[43,46]}\), including colon\(^{[47]}\). Conversely, there are discrepancies about NCOA-2 expression in CRC. Indeed, by immunohistochemistry, Grivas et al\(^{[48]}\) 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\(^{[47,49]}\).

In agreement, NCOA2 knock-down using siRNA in normal colonocytes (NCM460 cells) promotes cell proliferation and reduces apoptosis\(^{[49]}\). Previous studies also reported that NCOA-2 can bind to β-catenin\(^{[38,50]}\). Yu et al\(^{[49]}\) 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.

**NCOA3**

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\(^{[51]}\). Amplifications in the 20q11-13 region that includes the NCOA3 gene are detected in 10% to 32% of CRC\(^{[52,53]}\). Moreover, the NCOA-3 protein is overexpressed in 35% of human CRC samples\(^{[53]}\). 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\(^{[51,54]}\). Furthermore, NCOA-3 overexpression has been correlated with clinicopathological features, such as advanced clinical stage, lymph node and liver metastases\(^{[53,54]}\). However, NCOA-3 overexpression has been also associated with lower risk of death (43.5% vs 19.3%) and prolonged overall survival\(^{[55]}\). 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\(^{[55]}\). Few reports have investigated NCOA-3 interactions with components of other pathways that have a critical role in CRC. Xie et al\(^{[55]}\) associated NCOA3 molecular abundance with inhibition of the p53 pathway. Moreover, Mo et al\(^{[56]}\) demonstrated that NCOA-3 directly interacts with the adjacent normal mucosa and is expressed in many tissues, including colon. Conversely, there are discrepancies about NCOA-2 expression in CRC. Indeed, by immunohistochemistry, Grivas et al\(^{[48]}\) 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\(^{[47,49]}\).

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Description and aliases</th>
<th>Gene ID</th>
<th>MIM</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCOA1</td>
<td>Nuclear receptor coactivator 1</td>
<td>8648</td>
<td>602691</td>
<td>2p23.3</td>
</tr>
<tr>
<td>NCOA2</td>
<td>Nuclear receptor coactivator 2</td>
<td>10499</td>
<td>601993</td>
<td>8q13.3</td>
</tr>
<tr>
<td>NCOA3</td>
<td>Nuclear receptor coactivator 3</td>
<td>8202</td>
<td>601937</td>
<td>20q13.12</td>
</tr>
<tr>
<td>NCOA4</td>
<td>Nuclear receptor coactivator 6</td>
<td>23054</td>
<td>605299</td>
<td>20q11.22</td>
</tr>
<tr>
<td>PPARC1A</td>
<td>PPAR gamma, coactivator 1 alpha</td>
<td>10891</td>
<td>604517</td>
<td>4p15.2</td>
</tr>
<tr>
<td>EP300</td>
<td>E1A binding protein p300</td>
<td>2033</td>
<td>602700</td>
<td>22q13.2</td>
</tr>
<tr>
<td>CREBBP</td>
<td>CREB-binding protein CREBBP, KAT3A, RITS</td>
<td>1387</td>
<td>600140</td>
<td>16p13.3</td>
</tr>
<tr>
<td>MEDI</td>
<td>Mediator of RNA polymerase II transcription subunit 1</td>
<td>5469</td>
<td>604311</td>
<td>17q12</td>
</tr>
<tr>
<td>NCOA1</td>
<td>Nuclear receptor coactivator 1</td>
<td>9611</td>
<td>600849</td>
<td>17p12-p11</td>
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<tr>
<td>NCOA2</td>
<td>Nuclear receptor coactivator 2</td>
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<td>600848</td>
<td>12q24.31</td>
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<tr>
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<td>Nuclear receptor coactivator 3</td>
<td>8204</td>
<td>602490</td>
<td>21q11.2-q21.1</td>
</tr>
<tr>
<td>MTA1</td>
<td>Metastasis associated 1</td>
<td>9112</td>
<td>603526</td>
<td>14q32.33</td>
</tr>
</tbody>
</table>

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triKi M et al. Nuclear receptor corepressors in CRC

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 NCaA-3 might be a potential
target for CRC treatment.

NCaA-6
NCaA-6, also referred to as NRC, ASC-2, TRBP, PRIP
and RAP250, was originally isolated as a ligand-dependent
NR-interacting protein[56]. The NCaA6 gene is amplified
and overexpressed in breast, colon and lung cancer[57].
Recently, NCaA-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[58].

Peroxisome proliferator-activated receptor-γ coactivator
1-α
PPARGC1A encodes a transcriptional coactivator
(PGC1-α) that regulates mitochondrial biogenesis and
function[59]. PGC1-α enhances the activity of PPARγ[60]
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[10,61,62].
In the normal intestinal epithelium, PGC1-α 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 Apcmin/+ mice, compared with the
adjacent healthy intestinal mucosa[63].

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

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[64,65]. p300 plays a role in many cellular
activities, including cell differentiation, growth and
DNA repair[66]. 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[67]. In addition, p300
loss in HCT116 cells results in a more aggressive
phenotype characterized by increased cell migration
and reduced cell adhesion[68]. Finally, low p300
expression is associated with CRC aggressiveness (for
instance, lymph node invasiveness)[69]. 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[70].

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

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[76] and a coactivator of PPARγ[77]. MED1
mRNA levels are lower in CRC tissues than in the
adjacent normal mucosa[47]. Moreover, absence of
MED1 expression in CRC is correlated with lymph node
metastasis and with advanced TNM stage[78]. 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[79].

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[80,81].
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 (CoRNR) and harbor
the consensus sequence L/I-X-X-I/V-I or LXXXI/
LXXXI/L[82]. 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[83]. Interestingly, HDAC3 is overexpressed in
human colorectal adenocarcinomas and in CRC cell
lines[84,85]. Moreover, HDAC3 plays a central role in
regulating CRC cell proliferation and differentiation,
particularly through the regulation of p21[84].

In CRC, N-CoR2 is aberrantly expressed in all tested
primary tumors\textsuperscript{[87]}. Moreover, increased IKK\textsubscript{α} 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\textsuperscript{[88]}. IKK\textsubscript{α} 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\textsuperscript{[87]}. On the other hand, NCOR1 expression level is higher in human CRC tissues than in normal mucosa\textsuperscript{[47]}. IKK\textsubscript{α} also phosphorylates N-CoR1 and aberrant N-CoR1 cytoplasmic localization is a general feature of CRC\textsuperscript{[89]}. 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\textsubscript{α} activity\textsuperscript{[90]}. Subsequently, it was reported to interact and inhibit other transcription factors, including NRs and E2F transcription factors\textsuperscript{[91]}. 2-Nuclear receptor-interacting protein 1 (NRIP1) exerts its repressive activity via four inhibitory domains that recruit histone deacetylases or C-terminal binding proteins\textsuperscript{[92]}. Several post-translational modifications, such as acetylation and sumoylation, play important roles in controlling NRIP1 subcellular localization and repressive activity\textsuperscript{[93]}. 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\textsuperscript{[94]}. 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\textsuperscript{[95]}. Similarly, MTA1 mRNA overexpression in CRC has been correlated with deeper invasion through the intestine wall and higher lymph node metastasis rate\textsuperscript{[96]}. MTA1 overexpression is closely correlated with an aggressive course in several human carcinoma types. Aberrant MTA1 expression has been observed in CRC\textsuperscript{[47]}. 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\textsuperscript{[103]}.

**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 pathway, including nuclear receptor coregulators in CRC.
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 develop better prognostic tools for CRC.

Table 2  Copy number variation and expression levels of nuclear receptor coregulators in human colorectal cancer

<table>
<thead>
<tr>
<th>Coregulator</th>
<th>CNV (%)</th>
<th>Expression</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCOA1</td>
<td>Gain (5.5)</td>
<td>ND</td>
<td>Giannini 2005, Grivas 2009, Yu 2016</td>
</tr>
<tr>
<td>NCOA2</td>
<td>Gain (30.1)</td>
<td>↑ or ↓</td>
<td>Anzick 1997, Aust 2004, Xie 2005</td>
</tr>
<tr>
<td>NCOA3</td>
<td>Gain (40.6)</td>
<td>↑</td>
<td>Lee 1999</td>
</tr>
<tr>
<td>NCOA6</td>
<td>Gain (42.7)</td>
<td>↑</td>
<td>D’Errico 2011</td>
</tr>
<tr>
<td>PPARC1A</td>
<td>Loss (8.4)</td>
<td>↓</td>
<td>Ishihama 2007</td>
</tr>
<tr>
<td>EP300</td>
<td>Loss (19.3)</td>
<td>↑</td>
<td>Ishihama 2007</td>
</tr>
<tr>
<td>CREBBP</td>
<td>Gain (5.3)</td>
<td>↓</td>
<td>Giannini 2005</td>
</tr>
<tr>
<td>MED1</td>
<td>Gain (11.8)</td>
<td>↓</td>
<td>Fernández-Majada 2007</td>
</tr>
<tr>
<td>NCOR1</td>
<td>Loss (40.4)</td>
<td>↑</td>
<td>Lapiere 2014</td>
</tr>
<tr>
<td>NCOR2</td>
<td>Gain (9.8)</td>
<td>↑</td>
<td>Fernandez-Majada 2007</td>
</tr>
<tr>
<td>NRIP1</td>
<td>Loss (17.2)</td>
<td>↓</td>
<td>Toh 1997</td>
</tr>
<tr>
<td>MTA1</td>
<td>Loss (15.0)</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

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.

Table 3  Mutations identified in the different nuclear receptor coregulator genes in human colorectal cancer n (%) 216 United States patients (COAD-US) 187 Chinese patients (COCA-CN)

<table>
<thead>
<tr>
<th>Coregulator</th>
<th>Patients affected</th>
<th>Mutations</th>
<th>Patients affected</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCOA1</td>
<td>6 (2.78)</td>
<td>7</td>
<td>9 (4.81)</td>
<td>14</td>
</tr>
<tr>
<td>NCOA2</td>
<td>10 (4.63)</td>
<td>10</td>
<td>26 (13.90)</td>
<td>32</td>
</tr>
<tr>
<td>NCOA3</td>
<td>21 (9.72)</td>
<td>17</td>
<td>9 (4.81)</td>
<td>10</td>
</tr>
<tr>
<td>NCOA6</td>
<td>19 (8.80)</td>
<td>21</td>
<td>8 (4.28)</td>
<td>10</td>
</tr>
<tr>
<td>PPARC1A</td>
<td>10 (4.63)</td>
<td>12</td>
<td>5 (2.67)</td>
<td>6</td>
</tr>
<tr>
<td>EP300</td>
<td>13 (6.02)</td>
<td>15</td>
<td>14 (7.49)</td>
<td>21</td>
</tr>
<tr>
<td>CREBBP</td>
<td>18 (8.33)</td>
<td>20</td>
<td>7 (3.74)</td>
<td>11</td>
</tr>
<tr>
<td>MED1</td>
<td>3 (1.39)</td>
<td>4</td>
<td>6 (3.21)</td>
<td>6</td>
</tr>
<tr>
<td>NCOR1</td>
<td>21 (9.72)</td>
<td>25</td>
<td>23 (12.30)</td>
<td>48</td>
</tr>
<tr>
<td>NCOR2</td>
<td>41 (18.98)</td>
<td>43</td>
<td>30 (16.04)</td>
<td>40</td>
</tr>
<tr>
<td>NRIP1</td>
<td>5 (2.31)</td>
<td>5</td>
<td>6 (3.21)</td>
<td>10</td>
</tr>
<tr>
<td>MTA1</td>
<td>11 (5.09)</td>
<td>13</td>
<td>12 (6.42)</td>
<td>13</td>
</tr>
</tbody>
</table>

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

Table 4  Effects of the different nuclear receptors coregulators on the WNT signaling pathway

<table>
<thead>
<tr>
<th>Coregulator</th>
<th>Effect</th>
<th>Assay</th>
<th>Domains on β-catenin</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCoA-1</td>
<td>↑</td>
<td>GPD CoIP</td>
<td>aa 234-585</td>
<td>Li 2004, Tong 2015</td>
</tr>
<tr>
<td>CREBBP</td>
<td>↑</td>
<td>Y2H GPD CoIP</td>
<td>AR10 to C-ter</td>
<td>Takemaru 2000</td>
</tr>
<tr>
<td>N-CoR1</td>
<td>↑</td>
<td>GPD</td>
<td>aa 120-683</td>
<td>Song 2008</td>
</tr>
<tr>
<td>N-CoR2</td>
<td>↑</td>
<td>GPD</td>
<td>aa 120-683</td>
<td>Song 2008</td>
</tr>
<tr>
<td>NRIP1</td>
<td>↓</td>
<td>CoIP</td>
<td></td>
<td>Zhang 2014</td>
</tr>
</tbody>
</table>

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