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Perspective

Tumor suppressive actions of the nuclear receptor corepressor 1

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ABSTRACT

Nuclear Receptor Corepressor 1 (NCoR) is an important transcriptional regulator that interacts with nuclear receptors and other transcription factors. Recent results have shown the presence of inactivating mutations or deletions of the *NCoR* gene in human tumors. NCoR has a strong tumor suppressor activity, inhibiting invasion, metastasis formation and tumor growth in xenograft mouse models. These changes are associated to transcriptional inhibition of genes linked to bad prognosis and increased metastasis in cancer patients. NCoR loss causes a long-term repression of *NCoR* gene transcription, suggesting that NCoR deficiency in the cancer cell could be propagated playing a role in tumor progression in the absence of *NCoR* gene mutations. The thyroid hormone receptor TRβ increases NCoR expression and this induction is essential in mediating the anti-metastatic and tumor suppressive actions of the receptor. Since metastasis is the main cause of cancer-related deaths, these results define NCoR as a potential target for cancer therapy.

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1. Introduction

Gene transcription is dependent on post-translational modifications of the histone tails that regulate the accessibility of nucleosomal DNA. Among these modifications, histone acetylation is one of the best studied and has been correlated with an open chromatin conformation and transcriptional activity, while histone hypoacetylation is associated with a more compact chromatin and transcriptional inhibition [1]. The relative levels of histone acetylation are determined by the enzymatic activities of both histone acetyltransferases and histone deacetylases (HDACs). Transcriptional repression of gene expression by a sequence specific transcription factor can be mediated by the recruitment of HDACs to the gene regulatory region. These enzymes are found in the cells in large multiprotein complexes that contain corepressors with the function of bridging chromatin-modifying enzymes and transcription factors [2].

One of the best-studied corepressors is NCoR (or Nuclear Receptor Corepressor 1). NCoR and the homologous protein SMRT (Silencing Mediator of Retinoic and Thyroid Hormone Receptors or NCoR2) were first identified by their interaction with the unliganded thyroid hormone receptors (TRs) and retinoic acid receptors [3,4]. However, later studies demonstrated that NCoR and SMRT also associate with other transcription factors [5,6]. Both corepressors share approximately 50% of amino acid identity and contain similar functional domains. The N-terminal region of the corepressors contains three strong repressor domains that function as binding sites for HDACs [2]. Initially, NCoR was thought to act through the indirect recruitment of HDAC1 or 2, via the adaptor mSin3 protein. However, it can also directly recruit other deacetylases, including HDAC3, HDAC4, HDAC5 and HDAC7. Among these enzymes, HDAC3 appears to be the main responsible for the repressive activity of NCoR [7–9]. In fact, the catalytic activity of HDAC3 requires interaction with NCoR or SMRT [7,10] and this deacetylase has been shown to be essential for repression by TRs *in vivo* [11].

2. Physiological functions of NCoR

As expected from their important role in gene transcription, NCoR and HDAC3 affect numerous developmental and homeostatic processes [12]. In mammals, germline mutations of the NCoR gene are embryonic-lethal, causing development arrest and impairing CNS development and erythropoiesis [13]. Not surprisingly, HDAC3 knockout mice are also not viable [14]. An important function of NCoR is to control cell fate determination and differentiation of neural stem cells [15], thus influencing the development of neural lineages. In adult mice, NCoR also controls cell fate decisions regulating adipocyte and muscle cell differentiation and is also essential for metabolic homeostasis, modulating lipid metabolism, fat accumulation, glucose homeostasis, energy expenditure and oxidative metabolism [16–18]. The regulation of clock genes and circa-

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dian rhythms [19,20] is other major function of NCoR, which also represses expression of proinflammatory genes in macrophages [21], being a key inhibitor of chronic inflammation and atherosclerosis [22].

3. NCoR in cancer

Given the variety of the physiological actions of NCoR and its regulatory role in the control of metabolism and inflammation, it is no surprising that NCoR could play a prevalent role in various diseases including cancer. Alterations in NCoR expression have been linked to various solid tumors in humans. A list summarizing the status of NCoR in different human tumors is shown in Table 1. Analysis of public database demonstrates that inactivating NCoR mutations, including missense, synonymous and truncating mutations are highly prevalent in many types of tumors, showing features of driver mutations [23]. Although in most cases these mutations cause loss of NCoR expression, aberrant cytoplasmic localization of NCoR leading to loss of its corepressor function appears to be a general trait in colorectal cancer [24]. Bi-allelic frameshift mutations in the *NCoR* gene have been found in cancer colon cell lines, suggesting that mutational inactivation of this gene could play a role in colon cancer as well [25]. Cytoplasmic NCoR mislocalization is also significantly associated with malignant melanoma progression, worse clinical outcome and upregulation of a specific cancer-related genetic signature [23]. Additionally, NCoR expression decreases during bladder tumor progression [26], and recurrent truncating mutations in the NCoR gene, together with other non-silent mutations in genes involved in chromatin remodeling, are frequently found in these tumors [27].

In addition, results from independent studies have shown that reduced NCoR expression could play a role in hormone-dependent endometrial, prostatic and breast cancer initiation and progression. In endometrial carcinomas, NCoR expression is significantly lower than in endometrial hyperplasia [28] and progestin treatment is associated with increased expression of NCoR, suggesting that induction of the corepressor may be an important component of the progesterone-induced growth suppression of endometrial cancer [29]. However, increased NCoR levels were found in prostate cancer cell lines compared with non-malignant cells [30]. Although NCoR is recruited to the androgen receptors in response to antagonist ligands, the treatment of choice in androgen-dependent prostate tumors, the contribution of the corepressor to disease progression and tumor recurrence awaits further investigations [31]. A tumor suppressor role for NCoR appears to be clear in the case of breast carcinomas. Low NCoR expression has been associated with invasive tumors [32] bad prognosis and insensitivity to tamoxifen treatment [33,34], suggesting that NCoR deficiency could be relevant for breast cancer progression. Loss of components of corepressor complexes has been found in breast tumors [35], reinforcing the idea that NCoR could suppress breast cancer. Large-scale genomic analysis has confirmed the existence of NCoR mutations in these tumors [36,37], with frame-shift or nonsense inactivating mutations having been identified among the novel driver mutations in breast cancer [38].

The gene for NCoR maps to chromosome 17p11.2 in humans. This band is frequently deleted in malignant disorders, and particularly in hepatocarcinomas (HCC) [39,40], suggesting that loss of this corepressor could also drive liver cancer. Accordingly, one homozygous mutations of *NCoR* has been detected in HCC [40] and reduced NCoR expression was found in a significant number of these tumors, which is consistent with the reduced mRNA levels of the corepressor revealed upon examination of large HCC data sets [14]. In agreement with the human data, liver-specific deletion of HDAC3 resulted in the spontaneous growth of HCC in mice, showing the essential role of the enzyme in the maintenance of chromatin structure and genome stability [14]. Given that HDAC3 is inactive until its association with corepressors, development of these tumors is most likely due to the lack of NCoR transcriptional repression. All of the above results suggest that NCoR could play a role as an important suppressor of cancer initiation or progression, but the mechanisms by which the corepressor exerts their tumor suppressor role are not yet well understood.

4. An autoregulatory loop of NCoR expression controls invasion, tumor growth and metastasis

To test a possible role of NCoR in tumor growth, we have recently analyzed the effects of NCoR depletion in breast and liver cancer cell lines and found that NCoR deficiency increases significantly the size of xenografts formed in immunodeficient mice. NCoR acts not only as a suppressor of tumor growth but also as an inhibitor of tumor invasion. NCoR deficient cells showed enhanced invasive capacity *in vitro* and increased extravasation to the lungs when they were inoculated in the tail vein of immunodeficient mice. The incidence of metastasis as well as the number of metastatic lesions was also significantly enhanced in the absence of the corepressor, showing that NCoR can also suppress the metastatic potential of cancer cells *in vivo* [41]. Therefore, the corepressor inhibits the ability of cancer cells to grow as invasive tumors, to pass into the circulation, and to form metastasis. These findings agree with the role of NCoR as a tumor supressor, providing an explanation for its loss of expression in human tumors and defining NCoR as a potential target for cancer therapy.

Genes that are relevant for metastatic progression have been identified. Among them, high levels of expression in primary tumors of the prostaglandin-synthesizing enzyme cyclooxygenase 2, the transcriptional inhibitor ID1, the chemokine receptors CXCR4, CCR6 and CCR1, the protooncogene c-Met, or some metalloproteases are associated with high risk of metastasis and poor prognosis in patients [42–48]. We found that many of these genes are NCoR targets [41]. NCoR and HDAC3 are recruited to their regulatory regions, repressing histone acetylation and silencing their expression. The inhibitory effect of NCoR on tumor invasion and formation of metastasis observed in the mouse models is compatible with the silencing of pro-metastatic genes observed in the cultured cells.

In the course of these studies, we made the unexpected observation that transient NCoR silencing with siRNA lasted for a very long time, showing the existence of an autoregulatory loop that mantains *NCoR* gene transcription. Thus, *NCoR* gene expression was significantly lower in tumors and metastasis originated from cells transfected with NCoR siRNA even one month before, and prometastatic genes were still derepressed at this time. Moreover, there was a significant inverse correlation between transcript levels of the corepressor and prometastatic genes, indicating again the crucial role of NCoR in the silencing of these bad prognostic genes. Examination of the molecular mechanism responsible for long-term repression of the *NCoR* gene after siRNA knockdown demonstrated that this repression occurs via an epigenetic mechanism that involves the recruitment of SMRT and HDAC3 and the increase of repressive chromatin marks such as trimethylation of histone H3 in lysines 9 and 27 at the promoter region of the silenced *NCoR* gene. Histone methylation enables binding of the heterochromatin protein 1 (HP1) and facilitates local heterochromatinization [49]. We found that heterochromatinization leads to exclusion of transcription factors such as SP1 from the promoter and creates a stably silenced chromatin state. This finding has the valuable implication that a reduction of NCoR levels could represent an important mechanism for tumor progression when no *NCoR* gene mutations

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