Austin Journal of Cancer and Clinical Research

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Editorial

NDRG2: On the Path to Cell Stress and Cancer

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Received: January 28, 2015; **Accepted:** February 12, 2015; **Published:** February 16, 2015

The N-Myc downstream-regulated gene (*NDRG*) family is composed of *NDRG*1, *NDRG*2, *NDRG*3 and *NDRG*4, which are important downstream effectors of growth factors, cytokines, and other cellular stimuli in cellular signaling pathway. Aberrant loss or gain of *NDRG* expression underlies the pathophysiological properties of a variety of complex diseases, especially in cancer. Here, we review the molecular properties of *NDRG*2 and the distribution in multiple tissues or cancers. Additionally, in order to introduce its significance and therapeutic potential in anti-cancer research, we will discuss the regulation network of *NDRG*2 in cell signaling pathway which contributes to the diverse cellular roles including cell proliferation, apoptosis, metabolism, stress and migration.

Structure and Tissue Distribution

NDRG was firstly used by Kondoh's group to name a gene repressed by N-myc, which subsequently called *NDRG*1 [1]. Our group identified human *NDRG*2 and described it as a protein containing acyl-carrier protein (ACP)-like domain [2]. We further showed that *NDRG*2 expressed broadly innumerous developing tissues and organs in both human and mouse, and predominantly located in cytoplasm [3,4]. The cell nuclear and membrane locations of *NDRG*2 were also observed in some of the nervous cells, indicating the distinct roles of *NDRG*2 in different tissues [5].

Motif and PROSITE analysis of human *NDRG*2 revealed a "prokaryotic membrane lipoprotein lipid attachment site (PMLA)" motif, which mainly exists in membrane lipoproteins [6]. Further, two domains were recognized in the partial crystal structure of mouse *NDRG*2, an α/β hydrolase catalytic domain and a cap domain [7]. And both the human and mouse NDRG2 proteins showed structural similarity to the α/β hydrolase superfamily, though the key motif of catalytic activity in hydrolase were not observed [8]. The conserved structural features suggest NDRG2 may be involved in molecular interactions.

Molecular functions of *NDRG2*

So far, *NDRG*2 has been reported playing key roles in multiple biological behaviors, such as cell stress [9], cell cycle arrest [10,11], cell apoptosis [12], nervous system formation [13,14], and embryonic development [4,15]. A number of factors were found influencing these behaviors through the regulation of *NDRG*2 expression, including hypoxia-induce factor-1α (HIF-1α), p53 and glucocorticoids etc.

*NDRG*1 was firstly uncovered as an endoplasmic reticulum stress responder in cancer cells [16]. Similarly, we observed the induction of *NDRG*2 in hypoxia conditions and identified *NDRG*2 works as a cell stress responding molecule as well [9]. Further, HIF-1α transcriptionally regulates *NDRG*2 expression through directly binding to HREs of *NDRG*2 promoter. For the physiological significance of *NDRG*2 in cell stress, we elucidated the role of *NDRG*2 in controlling cell apoptosis, tumor angiogenesis and radioresistance [9,17,18]. *NDRG*2 can be translocated from the cytoplasm to the nucleus during hypoxia, and is necessary for hypoxia-induced apoptosis [9]. Furthermore, Both HIF-1 and *NDRG*2 contribute to hypoxia-induced tumor radioresistance [17]. *NDRG*2 acts downstream of HIF-1α and promotes radioresistance through the suppression of radiation-induced Bax expression. Interestingly, it has been shown that there is a feedback loop between HIF-1α and *NDRG*2 [18]. The high level of *NDRG*2 represses the expressions of HIF-1α and other factors, and further inhibits the cell growth and angiogenesis in breast cancer.

In the brain tissue, *NDRG*2 has been shown widely expressed, suggesting the important role of *NDRG*2 in the nervous system [3,19]. A number of disease-related *NDRG*2 gene expression changes were observed in the brains of patients, such as Alzheimer's disease [13], cortical stab injury [20], stroke [21] and depression [14]. Recently, *NDRG*2 was showed mainly expresses in astrocytes within the central nervous system (CNS) and involved in the cell proliferation and activation [21,22]. Estrogen can affect astrocytes by activating the *NDRG*2 promoter and elevating endogenous *NDRG*2 protein expression [22]. Sevoflurane preconditioning inhibits *NDRG*2 up-regulation and nuclear translocation in astrocytes to induce cerebral ischemic tolerance via anti-apoptosis, which represents a new mechanism of neuroprotection induced by sevoflurane preconditioning [23]. Thus, *NDRG*2 could be considered as a marker protein for brain astrocytes [24].

During embryonic development of mouse, *NDRG*2 expression is dynamic, being generally lower in the early stages of development and markedly increasing during later stages, suggesting the important role of *NDRG*2 in histogenesis and organogenesis [4]. Further, *NDRG*2 expression has also been detected at a high frequency in spematogenic cells of the seminiferous tubules in young rats but at a much lower frequency in adult rats, and is associated with germ cell apoptotic status [15]. It may provide the clues of *NDRG*2 in the regulation of testicular development and spermatogenesis in rats, and the involvement in the physiological and pathological apoptosis of germ cells.

NDRG2 on the path to cancer

Given the fact that *NDRG*2 was firstly cloned as a down-regulated gene in glioblastoma, it is reasonable to assume the role of *NDRG*2 in

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Citation: Shen L, Yao L and Zhang J. *NDRG2*: On the Path to Cell Stress and Cancer. Austin J Cancer Clin Res 2015;2(1): 1024.

tumor suppression [2]. Now, *NDRG2* has been found broadly lower expressed in various tumors, such as breast cancer [25], liver cancer [26], colorectal cancer [27], gastrointestinal stromal tumor [28], melanoma [29], and oligodendroglial tumors [30]. The inhibitory effect of *NDRG2* on tumor malignancy has also been full addressed. Reduced expression of *NDRG2* has been implicated in cancer cell proliferation and metastasis [12,27,31,32].

The hypermethylation methylation of *NDRG2* promoter is one of the most important attributes in the loss of *NDRG2* expression various tumors, and significantly associated with the poor prognosis [33,34]. Further, several cancer cells show both the mutation (at -13bp (C>T)) and methylation in *NDRG2* promoter, which can significantly reduce *NDRG2* tumor suppressive activity [35].

Besides the epigenetic regulation, *NDRG2* is also involved in multiple transcriptional factors and signaling pathways during tumorigenesis. Although *NDRG2* was named as N-Myc downstream-regulated gene, the expression of *NDRG2* was not up-regulated in tissues of N-Myc knockout mice [36]. Whereas, our group provided evidence that the expression of human *NDRG2* was down-regulated by c-Myc and N-Myc via transcriptional repression [37]. The ectopic expression of c-Myc dramatically reduces the cellular *NDRG2* protein and mRNA levels through the interaction of c-Myc with the core promoter region of *NDRG2*. Moreover, the c-Myc-mediated repression of *NDRG2* requires association with Miz-1 and possibly the recruitment of other epigenetic factors, such as HDACs, to the promoter. Further studies showed the repression of *NDRG2* is necessary for c-Myc mediated cell cycle control, differentiation, tumor proliferation and metastasis [27,32]. The expressions of *NDRG2* and c-Myc are inversely correlated in tumors, and associated with the patient prognosis [37,38].

The tumor suppressor p53 is another important transcription factor in regulation of cell-cycle arrest and apoptosis. We firstly reported that *NDRG2* is positively regulated by p53 and involved in the p53-mediated apoptosis pathway [39]. The first intron of the *NDRG2* gene contains a site that binds p53 directly and mediates wild-type p53-dependent transactivation. In addition, *NDRG2* enhances p53-mediated apoptosis, whereas overexpression of *NDRG2* suppresses tumor cell growth, regardless of whether p53 is mutated. Recently, we tried to further dig out the related mechanism, and showed that *NDRG2* enhances the p53-mediated apoptosis of hepatocarcinoma cells by downregulating ERCC6 expression which is critical for the nucleotide excision repair capacity [40]. ERCC6 is a *NDRG2*-inducible target gene that is involved in the p53-mediated apoptosis pathway.

Additionally, *NDRG2* has also been found to regulate tumor progression by affecting oncogenic signaling pathways, such as TGF-β pathway and PI3K-Akt pathway. TGF-β serves as a tumor suppressor primarily by inhibiting cell proliferation during early tumor stages, and it behaves as a tumor promoter by stimulating both invasion and metastasis during late tumor stages [41,42]. Our group found *NDRG2* is positively induced by TGF-β through the abrogation of repressive c-Myc/Miz-1 complex on *NDRG2* promoter in normal epithelial cells. However, aberrant hypermethylation of *NDRG2*, which could respond to TGF-β growth inhibition signaling, abrogated the inhibitory effect of *NDRG2* in TGF-β-induced EMT in colon cancer. Reduced *NDRG2* expression was highly correlated with the tumor invasion stage and metastasis. Therefore, *NDRG2* is a new tumor suppressor gene that responds to TGF-β anti-proliferative signaling and tips the balance of oncogenic TGF-β during late-stage colon cancer. Similarly, other group also showed inhibitory role of *NDRG2* in TGF-β-induced tumor metastasis by attenuating active autocrine TGF-β production [43].

Constitutive phosphatidylinositol 3-kinase (PI3K)-Akt activation has a causal role in tumorigenesis and tumor progression. We and other group provided evidences that *NDRG2* is phosphorylated by PI3K-Akt activation and involved in insulin-mediated protection of cardiac cells or pancreatic beta cells [43-45]. In malignant tumors, *NDRG2* overexpression specifically inhibits Akt phosphorylation, implicating the tumor suppressive role of *NDRG2* in PI3K-Akt pathway [46]. The related mechanistic study showed that *NDRG2* can inhibit activation of the PI3K-AKT pathway through the regulation of PTEN activity. *NDRG2* is a PTEN-binding protein that recruits protein phosphatase 2A (PP2A) to PTEN, resulting in the de-phosphorylation of PTEN at the Ser380/Thr382/Thr383 cluster. The loss of *NDRG2* expression activates PI3K-AKT signaling via enhanced PTEN phosphorylation, which may be critical for the development of human cancer.

Cancer cell metabolism is altered compared with normal tissue, which contributes to the initiation and progression of tumors. Therapies that target various aspects of cell metabolism are being developed and primarily focused on glucose metabolism [47]. Currently, *NDRG2* is found involved in glucose-dependent energy metabolism, as well as the nature of its correlation with cancer [48]. *NDRG2* inhibits glucose uptake by promoting glucose transporter 1 (GLUT1) protein degradation without affecting GLUT1 transcription. The colocalization of *NDRG2* and GLUT1 indicates the direct interaction between each other. Further, *NDRG2* is also a negative regulator of AMP-activated protein kinase (AMPK) activity and functions as a sensitizer of glucose deprivation in breast cancer [49]. The broadly role of *NDRG2* in cancer cell metabolism need to be further developed.

The studies on the function and regulation of the *NDRG2* have provided plenty of information on its multiple roles. Especially, *NDRG2* function as a tumor suppressor, suggesting that *NDRG2* may be a useful and functionally relevant biomarker for predicting aggressive forms of human cancer. In this regard, new cancer therapies targeting *NDRG2* may be applied in the future.

Acknowledgments

This work was supported by National Natural Science Foundation of China (NOs. 81230043, 81372390, 81172292, 31401061).

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Austin J Cancer Clin Res - Volume 2 Issue 1 - 2015
ISSN : 2381-909X | www.austinpublishinggroup.com
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Citation: Shen L, Yao L and Zhang J. *NDRG2*: On the Path to Cell Stress and Cancer. Austin J Cancer Clin Res 2015;2(1): 1024.