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Potential role of NDRG2 in reprogramming cancer metabolism and epithelial-to-mesenchymal transition

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Running Title: Potential role of NDRG2 in reprogramming cancer metabolism

Summary. Epithelial-to-mesenchymal transition (EMT) allows a cell with epithelial characteristics to transdifferentiate into a cell with mesenchymal characteristics, which is recognized as a key priming event for the initiation and evolvement of cancer metastasis. Accumulating data have shown that aberrant cancer metabolism contributes to the execution of EMT and cancer metastasis through multiple pathological pathways. Recently, the N-MYC downstream-regulated gene 2 (NDRG2), as a tumor suppressor and metabolism-related gene in various cancers, has been widely noted. NDGR2 is associated with energy metabolism, especially glycolysis metabolism. Hence, we propose a hypothesis that EMT is repressed by NDRG2 via cancer metabolic reprogramming, and summarize the pathological processes and molecular pathways related to the regulation of NDRG2.

Key words: NDRG2 (N-MYC downstream-regulated gene 2); Tumor suppressor gene; EMT (Epithelial-to-mesenchymal transition); Metastasis; Metabolic reprogramming.
**Introduction**

In the 1920s, Otto Warburg initially reported that the majority of cancer cells increase glycolysis even in the presence of adequate oxygen (Warburg, 1956). This process was known as the “Warburg effect” and described the way by which cancerous cells utilize aerobic glycolysis from mitochondrial respiration. During the past decades, the metabolic abnormalities that participate in tumorigenesis and tumor progression have been identified as hallmark characteristics of cancer (Cantor et al., 2012). However, the mechanisms of metabolic reprogramming have not been fully described. NDRG2 may be considered a promising target in order to explore the link between metabolism and tumor progression, since there are several reports suggesting that the expression of NDRG2 is downregulated and/or absent in a variety of cancers. In addition, NDRG2 may be considered a metabolism-related gene involved in cellular metabolic processes, including glycolysis, glutaminolysis and fatty acid oxidation metabolism (Xu et al., 2015; Pan et al., 2017). Currently, cancer metastasis is the leading cause of a the majority of cancer-associated mortalities. EMT exerts an essential effect on the occurrence and progression of cancer metastasis. Intriguingly, there is an association between aberrant metabolism and EMT. Therefore, this review aims to investigate the recent reports regarding NDGR2, aberrant metabolism and EMT in cancer. The present study further discusses the molecular mechanism by which NDRG2 regulates EMT via reprogramming of the cancer cell metabolism. The understanding of the explicit carcinogenic pathways may provide new therapeutic targets for cancer.

**NDRG2 acts as a molecular rheostat of EMT**

The NDRG family comprises 4 members, namely NDRG1-4, which are located on chromosomes 8q24.3, 14q11.2, 20q11.21-11.23 and 16q21-q22.1, respectively. The NDRG proteins are characterized by an esterase/lipase/thioesterase active site serine and a α/β hydrolase fold regime, sharing approximately 57-65% amino acid identity (Figure 1) (Hu et al., 2016; Lee et al., 2016). Phylogenetic analyses indicated that NDRG1 and NDRG3 could be classified into one subfamily, whereas NDRG2 and NDRG4 were included in a separate subfamily. Oncogenic and/or tumor suppressive effects have been documented with regard to the low/high expression of NDRG
proteins that impact on key hallmark traits of carcinogenesis, such as proliferation, differentiation, apoptosis, migration, invasion and stress responses (Melotte et al., 2010).

NDRG2 was initially identified and cloned by subtractive hybridization (Deng et al., 2003). NDRG2 is expressed in a wide range of tissues and organs, including heart, brain, liver, kidney, cartilage, gut, skeletal muscle and chorion. The expression of NDRG2 correlated with several human primary tumors, and was down-regulated in breast cancer (Ma et al., 2012; Kim et al., 2014; Kim et al., 2014; Kim et al., 2014), hepatocellular carcinoma (Guo et al., 2013; Cao et al., 2014; Wang et al., 2014), glioblastoma (Deng et al., 2003), lung cancer (Wang et al., 2012), colorectal cancer (Shen et al., 2014), oral squamous cell carcinoma (OSCC) (Tamura et al., 2017), prostate cancer (Gao et al., 2011; Yu et al., 2015), gallbladder carcinoma (Lee et al., 2015) and gastric cancer (Tao et al., 2013) (Table 1). Thus, accumulating evidence indicates that NDRG2 may be a tumor suppressor gene. Furthermore, the down-regulation of NDRG2 is associated with malignant clinical features and increased pathological grade. NDRG2 can act as a biomarker for the prediction of an aggressive phenotype, tumor recurrence, and patient prognosis. The NDRG2 promoter undergoes epigenetic silencing by methylation in the majority of primary tumors, which can give rise to resistance against chemotherapy. Although the biological functions of NDRG2 in tumors have been thoroughly studied, limited information is available with regard to the contribution of NDRG2 in reprogramming metabolism and regulating the EMT.

The novel function of NDRG2: modulators of metabolic reprogramming

Abnormal metabolism is currently regarded as the new malignant phenotype of cancerous cells. The regulatory roles of NDRG2 in tumor inhibition, particularly in metabolic rewiring, remain largely unclear. Thus, the present study notably focused on previous reports regarding the regulation of NDRG2 in the process of energy metabolism in cancer cells. A well-known metabolic abnormality in tumor cells is the Warburg effect that is characterized by increased glycolytic flux from pyruvate to lactate. In addition, aberrant glutamine and lipid metabolism are further involved in the occurrence and development of tumor cells via ATP production (Currie et al., 2013).
The transportation of glucose across the plasma membrane is the first rate-limiting step for glucose metabolism and is executed by glucose transporter proteins (GLUTs). Among the four NDRG members, NDRG2 was the first to be regarded as a metabolic programming protein. NDRG2 inhibits the transportation of glucose by promoting GLUT1 protein degradation without regulating GLUT1 mRNA level. Furthermore, NDRG2 is associated with a better prognosis in breast carcinoma (Ma et al., 2014). Secondly, Xu et al. reported that NDRG2 inhibited the expression of c-MYC by suppressing β-catenin levels, which could activate the transcription of the c-MYC gene in the nucleus. Subsequently, the transcription factor c-MYC directly regulates various glucose and glutamine metabolism genes, namely GLUT1, hexokinase 2 (HK2), pyruvate kinase M2(PKM2), lactate dehydrogenase A (LDHA), glutaminase 1 (GLS1) and glutamine transporter ASC amino-acid transporter 2 (ASCT2). Consequently, NDRG2 can markedly suppress these glycolytic and glutaminolytic targets by the MYC-mediated metabolic reprogramming in colorectal cancer (Xu et al., 2015).

The Wnt/β-catenin and the PI3K-Akt-mTOR pathways are both significant regulatory pathways that can increase the Warburg effect and the anabolic synthesis (Chafey et al., 2009; Ward et al., 2012) in cancer cells. NDRG2 has been shown to participate in the two processes. The reduced expression of NDRG2 was to activate the Wnt signaling pathway, which is a main contributor in the tumorigenesis of hepatoblastoma (Godeke et al., 2016). Moreover, the Wnt/β-catenin pathway directly targets pyruvate dehydrogenase kinase 1 (PDK1) in order to direct the cancer phenotype of the Warburg effect (Pate et al., 2014). Indeed, c-MYC was identified as a downstream target gene of the Wnt/β-catenin pathway, and the expression of this gene was downregulated by inhibition of the Wnt/β-catenin pathway (Sansom et al., 2007). Thus, NDRG2 may attenuate Wnt-driven Warburg metabolism. In contrast to these observations, NDRG2 is capable of recruiting PP2A in order to induce PTEN-Ser380/Thr382/Thr383 dephosphorylation, and subsequently suppress PI3K-AKT activation in the adult T-cell leukemia-lymphoma and OSCC (Nakahata et al., 2014; Tamura et al., 2017). Taken collectively, the studies suggest that NDRG2 functions as a metabolic gene via repression of the PI3K-AKT pathway that in turn inhibits the progression of cancer.

With regard to lipid metabolism, NDRG2 impairs the activation of fatty acid
oxidation (FAO) in hepatoma cells. This supports ATP and NADPH purveyance via suppression of the AMPK/ACC pathway in the absence of glucose (Zhang et al., 2017). NDRG2 overexpression reduces the expression level of peroxisome proliferator-activated receptors alpha (PPARα) – a main transcription factor that synergistically controls the FAO genes, carnitine palmitoyltransferase 1A (CPT1A) - the rate-limiting enzyme translocating acyl-coenzyme A into mitochondria to complete FAO, as well as acyl-CoA dehydrogenase, C-4 to C-12 straight chain (ACADM) - an important enzyme that regulates the initial step of FAO (Pan et al., 2017). However, the molecular mechanisms regarding these processes are not fully explored.

Metabolic rewiring induces EMT activation

EMT acts as the key driver of cancer cell metastasis. This process is orchestrated by a network of transcription factors (EMT-TFs), including Snail, Twist, Zeb, and the Fox family of proteins (Ye et al., 2015). The mechanisms by which EMT-TFs directly or indirectly inhibit the key epithelial marker E-cadherin, have been described in detail in a previous study (Lamouille et al., 2014). Conversely, the metabolic programming that is responsible for the EMT phenotype of an epithelial cell has been poorly understood. Recent evidence indicates that the association between metabolism and EMT is mutual, whereas alterations in the metabolic pathways can further promote the progression of EMT under certain conditions (Sciacovelli., 2017). This part of the review mainly describes how the abnormal levels of glucose, and the deregulated pathways of glutaminolysis and fatty acid metabolism are linked with the induction of EMT.

Glycolysis

Aerobic glycolysis is the main characteristic metabolic reprogramming of cancer cells (Pavlova et al., 2016). HK2 catalyzes the conversion of glucose to glucose-6-phosphate (G-6-P) and is the first rate-limiting enzyme of glycolysis. This enzyme is usually up-regulated in cancer (Palmieri et al., 2009). It has been recently reported that 2-deoxyglucose (2DG), a competitive inhibitor of HK2, can attenuate the pro-metastatic phenotype, reversing angiogenesis and EMT, in a TGFβ-dependent
manner (Bacci et al., 2016; Penny et al., 2016). This process has been reported in pancreatic ductal adenocarcinoma and ER+ breast cancer.

PKM2 controls the last rate-limiting step of glycolysis and catalyzes the final irreversible reaction of the conversion of phosphoenolpyruvate (PEP) to pyruvate that produces ATP. PKM2 has been shown to act as a potent EMT inducer. The overexpression of PKM2 is coupled with malignant clinicopathological features and unsatisfactory patient prognosis in various types of cancer, such as prostate cancer (Giannoni et al., 2015), hepatocellular carcinoma (Fan et al., 2014), colon cancer (Yang et al., 2014) and cervical carcinoma (Cheng et al., 2016; Cheng et al., 2017). Although previous reports suggest that the metabolic function of PKM2 is required for aerobic glycolysis, this enzyme can translocate into the nucleus, playing a role in nonmetabolic transcriptional regulation. Fan et al. demonstrated that nuclear translocation of PKM2 is essential for the EGF (epithelial growth factor)-induced EMT activation, which occurs via the transcription of β-catenin that promotes expression of Snail and Vimentin and reduces expression of E-cadherin (Fan et al., 2014). In addition, PKM2 can bind to TGF-β-induced factor homeobox 2 (TGIF2), which recruits histone deacetylase 3 to the promoter of E-cadherin and subsequently decreases its expression (Hamabe et al., 2014). Moreover, overexpression of PKM2 increases the expression of N-cadherin, Snail2, MMP-2 and MMP-9 and conversely suppresses the expression of E-cadherin by regulating the STAT3-related signaling pathway to facilitate migration (Yang et al., 2014). The inhibition of mTOR/p70s6k signaling downregulated PKM2 expression and abolished TGF-β1-induced EMT (Cheng et al., 2016; Cheng et al., 2017).

LDHA is the main regulator of aerobic glycolysis and catalyzes the irreversible conversion of pyruvate to lactate. A multitude of studies indicated that the attenuation of LDHA inhibits the invasive and metastatic properties of cancer cells (Arseneault et al., 2013; Jin et al., 2017). Initially, Sheng et al. demonstrated that knockdown of LDHA leads to an increase in E-cadherin and a decrease in focal adhesion kinase (FAK), MMP2 and VEGF levels, all of which are involved in EMT (Sheng et al., 2012). In addition, a recent study reported that LDHA silencing in bladder cancer cells can significantly inhibit EMT as demonstrated by the upregulation of the epithelial marker E-cadherin and the downregulation of the mesenchymal markers Snail, N-cadherin, Vimentin and fibronectin at the mRNA and protein levels (Jiang et
al., 2016). Despite several studies demonstrating that LDHA can directly regulate the process of EMT, its product lactate and the formation of reactive oxygen species (ROS) further participate in this phenotype. In contrast to these observations, lactate has been shown to upregulate TGF-β2 expression (Seliger et al., 2013), which subsequently promotes a mesenchymal pro-migration phenotype and elicits MMP-2 expression, ECM remodeling and metastasis in glioma cells (Wick et al., 2006). In addition, LDHA attenuation leads to a redirection of glucose flux to the TCA cycle for OXPHOS subsequent induction of ROS. Enhanced ROS plays an inhibitory role in tropomyosin-mediated cell migration and cytoskeletal remodeling, which suppresses the EMT phenotype and metastasis (Arseneault et al., 2013).

**Glutaminolysis**

Elevated glycolysis is the most well-known feature associated with malignancies. However, glutaminolysis is another indispensable characteristic for cancer cells, and has been frequently correlated with EMT progression. GLS is the pivotal enzyme for the catalysis of glutamine to glutamate in glutaminolysis. This enzyme is encoded by two types of genes in mammalian cells, namely GLS1 and GLS2. GLS1 is up-regulated in cancer development and progression and acts as an oncogene in diverse tumors. Inhibition of glutaminolysis by GLS1 shRNA damages Snail-dependent EMT and metastasis via the inhibition of TGF-β and Wnt3a expression (Lee et al., 2016). In contrast to its oncogenic function, GLS2 further exhibits tumor suppressive activity and is inversely associated with stage, tumor size and prognosis in hepatocellular carcinoma (Liu et al., 2014). A study has highlighted that GLS2 can exert non-glutaminolysis-associated function in order to repress EMT and malignant phenotype through the Dicer-miR-34a-Snail axis (Kuo et al., 2016). Thus, it is speculated that the roles of GLS1 and GLS2 on the process of EMT are context-dependent, and additional work is required to elucidate the specific differences between them. The overexpression of GLS1 decreases the levels of its substrate glutamine and plays a part in the suppression of TGF-β-induced EMT in liver tissues (Shrestha et al., 2016).
Fatty acid metabolism

Although, glucose and glutamine alterations have been extensively studied in the context of cancer metabolism, several reports have recently demonstrated the connection between lipid metabolism and EMT.

For example, the inhibition of the lipogenic enzyme fatty acid synthase (FASN) results in the reversal of the EMT phenotype in breast cancer via the suppression of vimentin, N-cadherin and fibronectin (Gonzalez-Guerrico et al., 2016). In addition, the elevated free fatty acid uptake exacerbates the EMT phenotype via the activation of the Wnt and TGF-β signaling pathways (Nath et al., 2015). It is important to note that the upregulation of acetyl-CoA synthetase (ACSL) and stearoyl-CoA desaturase (SCD) activates AMPK signaling in order to trigger an EMT program which is responsible for cancer invasion and migration (Sanchez-Martinez et al., 2015). Additional enzymes that are involved in lipid metabolism have been identified as EMT regulators. The silencing of acetyl-CoA carboxylase 2 (ACC2) reverses the EMT transition caused by high glucose, triglyceride deposit and accumulation of malonyl CoA content in the kidney (Xu et al., 2014). In addition, ATP citratelyase (ACL) knockdown increases expression of the epithelial markers (E-cadherin, ZO-1) and decreases expression of the mesenchymal marker vimentin in lung cancer cells undergoing a reversal of EMT (Hanai et al., 2012). Furthermore, both arachidonic acid and linoleic acid promote the process of EMT via the activation of FAK, SRC and NF-κB in human mammary non-tumorigenic epithelial cells (Martinez-Orozco et al., 2010; Espinosa-Neira et al., 2011).

CLUT expression and acidic environment

In addition to the aforementioned enzymes, GLUTs contribute a significant role in cancer cell metabolic reprogramming and the development of EMT. GLUTs transport glucose across the plasma membrane and are considered the enzymes responsible for the first rate-limiting step of glucose metabolism. A substantial connection between GLUT1 expression and metastasis has been supported by previous studies. For example, Zuo et al. demonstrated correlations of GLUT1 expression and vimentin, N-cadherin and E-cadherin (Zuo et al., 2016) that are consistent with the study that demonstrated the down-regulation of E-cadherin by
GLUT1 (Mayer et al., 2013). The up-regulated GLUT1 can further increase the expression and activity of MMP-2 to promote invasiveness of cancer (Ito et al., 2004). Interestingly, an additional isoform of glucose transporter family members, GLUT3 augmented glucose consumption and correlated with EMT signatures in the process of lung tumor progression (Masin et al., 2014). Moreover, both GLUT1 and GLUT3 promoted glucose uptake that was shown to induce EMT by stabilization of Snail (Park et al., 2010).

Nevertheless, EMT formation is not only affected by aerobic glycolysis, as the low pH_e environment, which results from the final glycolytic metabolite lactate and a variety of proton exchangers has been shown to be associated with this process. Mounting evidence has revealed that the presence of an acidic environment confers a metastatic advantage to cancer cells (Peppicelli et al., 2014; Suzuki et al., 2014). Silvia et al. highlighted that an acidic pH_e medium in melanoma cells up-regulates EMT markers, including N-cadherin, vimentin and Twist transcription. This phenomenon was proven to be NF-κB-dependent (Peppicelli et al., 2014). The effect of low pH_e in lung carcinoma induced the expression of Zeb2, Twist1 and Twist2 mRNA levels and promoted the invasive and metastatic activities of the cells (Suzuki et al., 2014). Similar findings were reported for human melanoma cells (Suzuki et al., 2014). Accordingly, the studies illustrate that low pH_e generates an acidic microenvironment and elicits EMT in cancer metastasis. Acidosis is also associated with apoptosis, angiogenesis and extracellular matrix (ECM) formation in cancer cells (Huang et al., 2017).

**NDRG2 inhibits EMT via the regulation of cancer metabolism**

With regard to cancer metastasis, a limited number of studies have reported that NDRG2 regulated the process of EMT via GSK-3β-Snail, TGF-β, MMP-19-Slug and STAT3-Snail signaling in colon, colorectal, gallbladder and breast cancer, respectively (Kim et al., 2013; Kim et al., 2014; Shen et al., 2014; Lee et al., 2015; Tamura et al., 2017). Tamura et al. recently highlighted that high expression of NDRG2 induced inactivation of NF-κB and PI3K/AKT signaling pathways via the dephosphorylation of the C-terminal domain of PTEN, and the inhibition of the process of EMT in OSCC (Tamura et al., 2017). Nonetheless, the direct molecular mechanisms by which
NDRG2 inhibits EMT have not yet been fully clarified.

The present study clearly indicates that loss of NDRG2 contributes to induction of metabolic reprogramming, notably the Warburg effect, via a series of signaling pathways (Xu et al., 2015; Lee et al., 2016). Concomitantly, the alteration of the cellular metabolism can intervene with the process of EMT that endows cancer cells with invasive and migratory capacities, and facilitates the tumor dissemination and the metastatic process (Huang et al., 2017; Sciacovelli., 2017). Taken collectively, the study demonstrates that NDRG2 is responsible for the inhibition of EMT via the regulation of cancer cell metabolism. Previous studies have concluded that the deficiency of NDRG2 induces the activation of Wnt/β-catenin, PI3K-Akt-mTOR and c-MYC pathways, which in turn stimulate the Warburg metabolism of cancer cells. However, MYC and HIF-1 cooperatively counterbalance the reprogramming of cancer metabolism. MYC activates the Warburg effect by inducing HK2, phosphofructokinase (PFKM), PKM2, enolase 1 (ENO1), as well as mitochondrial biogenesis (Dang et al., 2009). Like MYC, NDRG2 also could attenuate human renal cancer cell invasion and proliferation by inhibiting HIF-1α mediated processes, which are responsible for upregulating glucose transporters and various glycolytic enzymes to shift oxidative phosphorylation to the glycolytic metabolism (Gao et al., 2013; Semenza et al., 2013). Similarly, NDRG2 restrains the glycolytic metabolic programing, via its metabolic and/or nonenzymatic activity (Sajnani et al., 2017; Xu et al., 2017). This process is responsible for the progression of tumor metastasis and the induction of EMT in various cancer types (Sajnani et al., 2017; Xu et al., 2017). With regard to glutaminolysis and lipid metabolism, NDRG2 can further exert a negative impact on the regulation of GLS1, ASCT2 and fatty acid oxidation, which can trigger the activation of EMT-TFs and promote the EMT process (Xu et al., 2015; Morandi et al., 2017; Pan et al., 2017). Therefore, NDRG2 can play a key role in the occurrence and progression of EMT by targeting the cellular metabolism that determines the energy production of the cell.

Cancer cells adapt to the adverse microenvironment with elevated glucose uptake and glycolysis, thus resulting in the production of an acidic environment. In the present study, loss of NDRG2 was further demonstrated to increase the expression of correlative glycolytic enzymes and GLUTs, which indicates that excessive lactate is produced by immoderate glycolysis. Finally, the acidic microenvironment represents a
direct contributor to the process of EMT. In conclusion, a certain number of studies have suggested that NDRG2 regulates metabolic rewiring and subsequently induces EMT (Figure 2).

Conclusion

A link between NDRG2 and epithelial-mesenchymal transition has not only given us a better comprehension of the role of metabolism reprogramming in cancer metastasis, but also has provided further insight into the tumor-suppressive function of NDRG2 through a novel regulatory mechanism. In this paper, we firstly propose that rewiring energy metabolism connects NDRG2 to the occurrence and development of EMT, which drives the invasive ability of malignant tumors. Deciphering the connection between NDGR2 and EMT may serve as the crucial factor in determining the therapeutic point that exerts maximum drug efficacy. At the same time, metabolic reprogramming has been considered as an emerging target for cancer therapy. Herein, applying NDRG2 alone or in combination with anti-glycolytic agent may validly and synergistically treat metastasis of cancer cells and ameliorate prognosis of patients.

Conflict of interest

No potential conflicts of interest were disclosed.

Acknowledgments

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Zhejiang Cancer Hospital (2013-03-79 and 2015-02-125).

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1853-1862.
Figure Legends

**Figure 1.** Structure of the human NDRG protein sequences. Illustrated are the different domains present in the NDRG family members. Depicted are the NDR domain (as defined by the Pfam database), and regions altered in different isoforms (as defined by UniProt). The NDRG family members are 53-65% homologous to each other and share the conserved NDR domain, which includes the alpha/beta hydrolase motif (Lee et al., 2015; Melotte et al., 2010).

**Figure 2.** The molecular mechanism of NDRG2 regulating the process of EMT though rewiring metabolism. The energy metabolism acts as a crosstalk between NDRG2 and EMT.

**Table 1.** The role of NDGR2 as tumor suppressor gene in cancer