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REVIEW

NANOG: A promising target for digestive malignant tumors

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Abstract

NANOG has been extensively researched since its discovery by Chambers *et al*. NANOG is a homeodomain transcription factor and an essential regulator of embryonic stem cell (ESC) self-renewal, which inhibits differentiation. Cancer stem cells (CSCs) are a small subset of cells that are thought to drive uncontrolled tumor growth; CSCs retain the tumor capabilities of self-renewal and propagation. The existence of CSCs was recently shown by direct experimental evidence. NANOG is expressed in CSCs and ESCs, although it remains unclear whether ESCs and CSCs share similar mechanisms in the regulation of physical and biological processes. Several studies suggest that the expression level of NANOG is high in cancer tissues and low or absent in normal tissues. High levels of NANOG expression are associated with advanced stages of cancer and a poor prognosis, indicating that it plays a vital role in tumor transformation, tumorigenesis, and tumor metastasis. NANOG is part of a complex regulatory network that controls cell fate determination, proliferation, and apoptosis. NANOG cooperates with other regulators, such as microflora, transcription factors, and kinases, in cancer cells. NANOG might have a promising future in anti-cancer and other therapeutic treatments, which could improve human health.

Key words: NANOG; Cancer stem cells; Gastrointestinal tumor; Anti-cancer

Core tip: This review article differs from previous reviews by concentrating on the relationship between NANOG and cancer. This review contains the following five sections: the structure of *NANOG*, NANOG and cancer stem cells, signal pathways associated with NANOG in cancer, NANOG in specific human tumors, and the role of NANOG in anti-cancer therapy. Each section contains novel insights and comprehensively reviews the current literature, which will be very useful to the journal's readers.

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STRUCTURE OF *NANOG*

NANOG was discovered by Chambers *et al*[1] based on its ability to maintain the self-renewal of mouse embryonic stem cells (ESCs) independently of the cytokine leukemia inhibitory factor (LIF). NANOG was identified by comparing expressed sequence tag libraries from mouse ESCs with various somatic tissues[2]. Research on NANOG has received significant attention since its discovery. As a homeodomain-containing transcription factor, NANOG is a key transcription factor involved in the maintenance of pluripotency and self-renewal in undifferentiated ESCs[1-7]. The NANOG protein is encoded by the only open reading frame of the 2184-nucleotide *NANOG*

cDNA[2]. In addition to the embryonic *NANOG* gene, eleven *NANOG* pseudogenes have been reported in the human genome[8]. However, only the *NANOG* homeobox pseudogene 8 (*NANOGP8*) has a complete open reading frame able to transcribe and translate functional NANOG protein[8-10]. *NANOG* is hypothesized to be an important regulatory factor associated with the pluripotency of ESCs, whereas *NANOGP8* plays a role in tumorigenesis. However, the comprehensive expression patterns of *NANOG* and *NANOGP8* in human cancers have not been fully elucidated. NANOG is expressed from both *NANOG* and *NANOGP8* in colorectal cancers[11]. The human NANOG protein consists of 305 amino acids and could be divided into N-terminal (amino acid 1-95), homeobox domain (amino acid 96-155), and C-terminal (amino acid 156-305) regions[2,12]. The N-terminus is tightly regulated through phosphorylation or other posttranslational modifications of serine, threonine, and proline. The N-terminus also functions as a structural motif for the transcriptional activity of NANOG[12,13]. The C-terminus contains two potent transactivation subdomains[12,13]. The N- and C-terminal regions contain nuclear localization sequences. The homeobox domain in the central region contains a DNA-binding motif and is reported to harbor a potent nuclear export motif[14] that allows the NANOG protein to be transported into and out of the nucleus.

NANOG AND CANCER STEM CELLS

Cancer stem cells (CSCs) are a small subset of cells that are thought to drive uncontrolled tumor growth and retain the potential for tumor self-renewal and propagation. Although the origins of CSCs are debated, the existence of these cells has been proven by direct experimental evidence[15]. Bussolati *et al*[16] found a tumor-initiating stem cell population in renal carcinomas. CSCs possess several stem cell properties, such as clonogenic ability, the expression of NANOG and Oct-4 stem cell markers, and the absence of epithelial differentiation markers. CSCs have been isolated in the following tumor types: glioblastoma, melanoma, prostate carcinoma, colon carcinoma, head and neck squamous cell carcinoma, breast carcinoma, ovarian carcinoma, bladder carcinoma, lung carcinoma, and pancreatic carcinoma[17-29]. Studies have traced the cell lineages within a growing tumor in glioblastomas[30], intestinal adenomas[31], and squamous skin tumors[32]. CSCs are identified as unique cells with the potential to expand the CSC pool and the potential to differentiate into heterogeneous non-tumorigenic cells that constitute the bulk of the tumor[33]. This minority population of cells retains the self-renewal and propagation potential of the tumor, whereas the vast majority of cells are non-tumorigenic daughter cells of CSCs[34]. Singh *et al*[35] isolated CSCs in human brain tumors. Tumors that could be serially transplanted were produced when these authors injected as few as 100 cells into mouse brains. However, injecting as many as 10^5 non-CSCs cells did not result in the development of a tumor. Therefore, the CSC hypothesis provides an attractive cellular mechanism to account for the therapeutic refractoriness and dormant behavior exhibited by many solid tumors.

Liao *et al*[36] determined that *NANOG* regulates the self-renewal of breast CSCs. *Nanog* expression is correlated with aggressiveness in poorly differentiated breast cancer and enhances the tumorigenicity of tumor cells by promoting the self-renewal of CSC subpopulations. The knockdown of *NANOG* significantly inhibited the growth of breast CSCs. Many years of study on cell transplantation suggests that *NANOG* plays a vital role in tumor transformation, tumorigenesis, and tumor metastasis via regulating the CSC population[37]. Several studies have shown that NANOG, in combination with other regulators, modifies chromatin structure and forms a key regulatory network controlling the identity, differentiation, self-renewal, and pluripotency of ESCs[38-40]. Although a deeper understanding of the mechanisms of NANOG circuitry in CSCs is needed, CSCs display preferential overexpression of NANOG normally enriched in ESCs. Thus, similar mechanisms might be involved in the regulation of CSCs[41]. The finding that NANOG might play a crucial role in CSC and ESC signaling networks makes it a potentially ideal target for cancer treatment.

ROLE OF NANOG IN HUMAN TUMORS

Examination of its expression in clinical studies revealed that NANOG is overexpressed in a variety of cancers, including gastrointestinal (GI) tumors. Yang *et al*[42] found that the expression of the NANOG protein was higher in esophageal cancer tissues and was positively correlated with histological grade and lymphatic metastases. Furthermore, when three cell lines were treated with cisplatin to evaluate drug sensitivity, the authors found that sensitivity to cisplatin was decreased by increased NANOG expression. Their study demonstrated that NANOG could promote tumor cell proliferation, invasion, and resistance. Inhibiting NANOG expression inhibits these behaviors by stalling cells in the G0/G1 phase and inducing apoptosis. Using reverse transcription-polymerase chain reaction and real-time quantitative polymerase chain reactions, Chen *et al*[43] demonstrated that the expression of NANOG was higher in gastric cancer tissues than in paracancerous tissues. The expression of NANOG was positively correlated with the histological grade of the tumor, suggesting that NANOG might serve as a novel marker for the diagnosis and prognosis of gastric carcinoma.

Side population (SP) cells are thought to include CSCs with self-renewal capacity and high tumorigenicity[44]. Uchino *et al*[45] found that NANOG was expressed specifically in SP cells of human GI cancer cells. Nucleotide sequencing revealed that NANOGP8 was expressed in GI cancer cells, whereas Nanog was not expressed in these cells. The transfection of NANOGP8 into GI cancer cell lines promoted cell proliferation, whereas its inhibition by anti-NANOG siRNA suppressed the proliferation. These data suggested that NANOGP8 is involved in GI cancer development in a subset of patients and

that it presumably acts by supporting CSC proliferation in these patients.

Zhang *et al*[46] determined that NANOG was expressed in hepatocellular carcinoma (HCC) tissue and paracancerous tissue; however, there was almost no expression of NANOG in normal liver tissue. NANOG expression was positively correlated with the clinical stage and histological grade of the patients, suggesting that NANOG is associated with the development of HCC. A study by Shan *et al*[47] suggested that NANOG plays a crucial role in maintaining the self-renewal of CSCs through the insulin-like growth factor (IGF) 1R-signaling pathway, and NANOG could be a novel biomarker for CSCs in HCC. The authors successfully isolated NANOG-positive cells, using the NANOG promoter as a reporter system, and determined that NANOG-positive cells exhibited enhanced self-renewal ability, clonogenicity, and tumor initiation capacity. Thus, NANOG expression predicts a worse clinical outcome in HCC. In addition, this study showed that NANOG-positive CSCs were resistant to therapeutic agents and had a high capacity for tumor invasion and metastasis. The knockdown of NANOG in NANOG-positive CSCs reduced the self-renewal capacity, decreased the expression of stem cell related genes, and increased the expression of mature hepatocyte-related genes. The overexpression of NANOG in NANOG-negative cells could restore self-renewal. There are many factors and regulatory networks involved in cancer development. Shan *et al*[47] found that IGF2 and IGF-receptor were upregulated in NANOG-positive CSCs. The knockdown of NANOG in NANOG-positive CSCs inhibited the expression of IGF1R, and NANOG overexpression in NANOG-negative cells increased the expression of IGF1R. A specific inhibitor of IGF1R signaling could significantly inhibit self-renewal and NANOG expression in NANOG-positive cells, suggesting that IGF1R signaling participates in NANOG-mediated self-renewal in NANOG-positive cells.

There are a limited number of studies investigating the role of NANOG in pancreatic carcinoma. Pancreatic cancer is well known for being difficult to diagnose at early stages and has a poor recurrence-free prognosis. Lu *et al*[48] isolated pancreatic CSCs from the PANC-1 cell line using flow cytometry. They found that NANOG was highly expressed in human pancreatic cancer tissues, and that NANOG knockdown reduced the proliferation, migration, invasion, chemoresistance, and tumorigenesis of pancreatic CSCs. The authors determined that NANOG affects the biological characteristics of pancreatic CSCs and that its overexpression indicated a worse prognosis. Therefore, NANOG might serve as a potential marker of prognosis and be a novel therapeutic target for pancreatic cancer.

Meng *et al*[49] studied the expression and regulatory effects of NANOG in colorectal cancer (CRC). The authors found that its overexpression was strongly correlated with poor prognoses, lymph node metastases, and Dukes classification for CRC. Univariate and multivariate survival analyses indicated that NANOG expression was a potential prognostic factor for CRC. Studies using gain-of-function approaches revealed that lentivirus-mediated NANOG overexpression promoted the proliferation, motility, and migration of human CRC cells. Previous authors found that NANOG induced the epithelial-mesenchymal transition. Xu *et al*[50] observed that NANOG expression was related to histological grade, lymph node metastases, TNM stage, and liver metastases in CRC. A Spearman correlation analysis showed that NANOG expression is linearly correlated with liver metastases. These results suggest that the NANOG protein might be a potential biomarker for postoperative liver metastases of CRC and could be a potential early liver metastasis screening factor in CRC. Shi *et al*[51] demonstrated that *NANOG* knockdown could suppress proliferation, colony formation, and *in vivo* tumorigenicity in CRC; *NANOG* knockdown could increase the sensitivity of the CRC cell line SW620 to fluorouracil (5-FU). These data suggest that *NANOG* might regulate the aggressiveness of CRC cells.

In addition to its expression in GI tumors, NANOG is expressed in human breast, cervix, oral, kidney, prostate, lung, gastric, brain, and ovarian cancers[52-63]. An elevated expression of NANOG was positively associated with late stage progression and a poorer prognosis in oral cancer patients. The exact role of NANOG in tumor development remains unclear. A recent study showed that the expression of NANOG mRNA did not have any clinical relevance in 79 fresh clinical CRC samples[64]. Although previous studies have demonstrated that NANOG is highly expressed in a variety of tumors and that its increased expression indicates a poor prognosis in patients, comprehensive and systematic studies examining the role of NANOG in human clinical tumor samples are lacking. The role of NANOG in tumor development remains unclear. Whether NANOG is a marker for CSCs in carcinomas or a biomarker representing CSCs requires further study. Additionally, the mechanism of how it participates in CSC biology requires further research.

REGULATORY NETWORKS ASSOCIATED WITH NANOG IN CANCER

NANOG is not an isolated factor in the regulatory process of tumor development, and there are many regulators involved in tumor transformation, tumorigenesis, and tumor metastasis (Figure 1). For example, other transcription factors, microRNAs, and kinases have been reported to mediate the silencing or overexpression of NANOG and to regulate stemness, malignant transformation, and CSC-like phenotypes in cancer cells.

The p53 protein is a key mediator regulating programmed cell apoptosis and cell cycle related pathways; it activates cell-cycle checkpoints and promotes cell senescence. p53 has a well-accepted role in tumor suppression. During the last decade, a direct involvement of p53 in the stemness regulatory network has been investigated in stem cell and cancer research; p53 could reduce self-renewal and enhance differentiation in ESCs and cancer

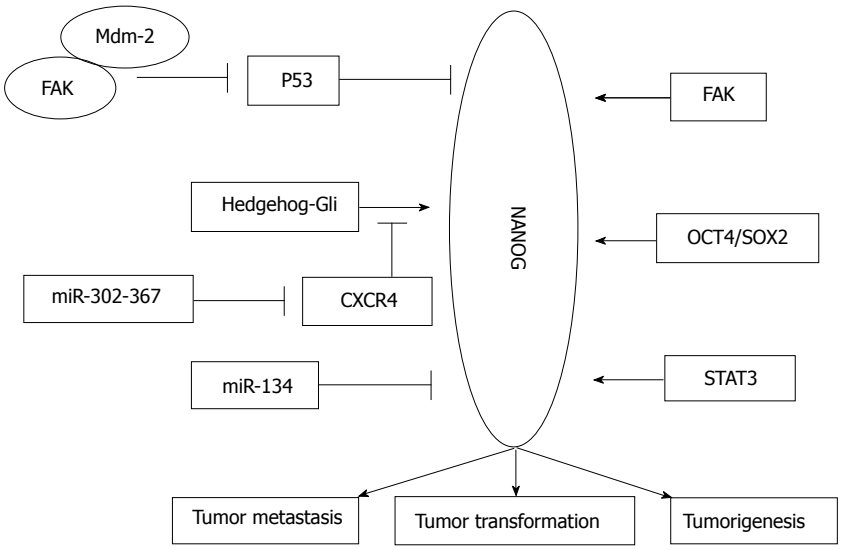

Figure 1 Diagram depicting the regulatory networks of tumor transformation, tumorigenesis, and tumor metastasis associated with NANOG in cancer.

cells. The suppressive effect of p53 on reprogramming and cancer stemness could partially depend on its negative regulation of NANOG[65-68]. It has been reported that p53 could bind to the NANOG promoter and suppresses its expression after DNA damage[66]. Hedgehog is another essential regulator of stemness properties; hedgehog promotes self-renewal in ESCs and promotes cancer progression. Po *et al*[69] showed that the loss of p53 activated the Hedgehog-Gli pathway; the Hedgehog-Gli pathway was responsible for NANOG upregulation through p53-independent signaling by the binding of Gli transcription factors to the NANOG promoter. The growth and tumorigenicity of glioma stem cells was regulated by the p53-independent Hedgehog-Gli pathway. Zbinden *et al*[70] demonstrated a positive regulatory loop between *NANOG* and sonic hedgehog signaling. The knockdown of *NANOG* decreased the endogenous activity of Gli1, and NANOG mRNA levels were modulated by the hedgehog pathway. Their research showed that the Hedgehog and p53 pathways are cross-linked and could cross-regulate NANOG expression since p53 directly suppresses NANOG and Hedgehog[66,69].

Focal adhesion kinase (FAK) is a tyrosine kinase that plays a significant role in tumor survival[71]. Many tumors overexpress FAK mRNA and protein[72]. FAK is important for cell adhesion, proliferation, motility, invasion, and angiogenesis[73]. FAK and p53 are involved in the regulation of survival/apoptotic signaling in cancer cells through p53-regulated FAK promoter activity and through FAK-p53 protein binding[74-78]. Golubovskaya[65] reported that NANOG binds the FAK promoter and upregulates FAK expression. Additionally, FAK could bind and phosphorylate NANOG. FAK could bind Mdm-2 and activate p53 degradation[77], and p53 negatively regulates both NANOG and FAK.

The LIF/STAT3 pathway is critical for NANOG function in the maintenance of ESC pluripotency. It was reported that 14 of the 22 STAT3 target genes contributing to the maintenance of an undifferentiated state were also regulated by *NANOG* in mouse ESCs. Torres *et al*[79] examined the functional interactions of NANOG with the Stat3 and NF-κB pathways and found that NANOG and Stat3 bind to and synergistically activate Stat3-dependent promoters. NANOG could bind to NF-κB proteins and inhibit the transcriptional activity of NF-κB proteins to increase the expression of pluripotency markers. Bourguignon *et al*[80] found that NANOG-STAT3 could activate common targets in head and neck squamous cell carcinomas. Additionally, the LIF-induced phosphorylation of STAT3 directs the binding of STAT3 to the *NANOG* gene enhancer and upregulates NANOG expression. Zhou *et al*[81] found that the hepatitis C virus (HCV) core protein could upregulate *NANOG* expression by enforced expression of the phosphorylated Stat3 protein. The phosphorylated Stat3 directly binds to the *NANOG* promoter and enhances cell growth and cell cycle progression. The knockdown of *NANOG* blocked the cell cycle at the G0/G1 phases. These findings provide insight into the mechanism of hepatocarcinogenesis by HCV infection. The finding that the LIF/STAT3 pathway promotes NANOG expression in ESCs and cancer cells suggests that NANOG is an important mediator of the LIF-dependent pathway. STAT3 might also regulate *NANOG* expression through epigenetic modifications[82]. Nettersheim *et al*[83] showed that the OCT3/4-SOX2-mediated expression of *NANOG* could be silenced by methylation of promoter CpG-sites in testicular germ cell tumors. The global methylation of DNA decreases from fetal spermatogonia to mature sperm. CpGs in the *NANOG* promoter were hypomethylated in spermatogonia and hypermethylated in sperm. The selective repression of NANOG suggested that pluripotency must be suppressed to prevent malignant transformation. The methylation of CpGs in the *NANOG* promoter of germ cell tumors and derived cell lines are correlated to the differentiation state.

MicroRNAs are associated with the pathogenesis of many cancers. There are reports identifying microRNAs that target *NANOG* and mediate the malignant progression in cancer cells or CSCs. MicroRNA-21 (miR-21) appears to play a critical role in tumor cell survival, chemoresistance, and progression. Bourguignon LY found that NANOG and Stat-3 signaling promote miR-21 expression in CD44-activated head and neck squamous cell carcinoma cells by downregulating tumor suppressor proteins and upregulating proteins that inhibit apoptosis[80]. Fareh *et al*[84] showed that the miR302-367 cluster is strongly induced during serum-mediated stemness suppression in glioma-initiating cells. The stable expression of the miR302-367 cluster is sufficient to suppress the stemness characteristics, self-renewal, and cell infiltration into host brain tissue through inhibition of the CXCR4 pathway. The inhibition of CXCR4 leads to disruption of the sonic hedgehog-GLI-*NANOG* network, which is involved in self-renewal and the expression of the embryonic stem cell-like signature. Their research demonstrated that the miR302-367 cluster could efficiently trigger a cascade of inhibitory events leading to the disruption of glioma-initiating stem-like cells with tumorigenic properties. MiR-134 was first found to directly target NANOG in mouse ESCs and glioblastoma cells. The overexpression of miR-134 reduced proliferation, invasiveness, and migration capability, and promoted apoptosis of glioblastoma cell lines by directly suppressing NANOG expression[85]. A global gene expression profile screen of NANOG siRNA-transfected embryonal carcinoma cells suggested that NANOG is involved in the cell cycle-signaling pathway[86]. Several cell cycle- and p53-related signaling pathway genes were downregulated by *NANOG* knockdown. These results suggest a role of NANOG in the cell cycle and in survival[87].

The majority of the regulatory mechanisms related to NANOG are focused on transcription; however, there are accumulating data showing the importance of post-transcriptional and translational regulation of NANOG. Moretto-Zita *et al*[88] first reported that the stability of NANOG in mouse and human ESCs is regulated by an evolutionarily conserved post-translational mechanism. The mechanisms through which NANOG regulates cell proliferation and tumor growth require further investigation.

DISCUSSION

The overexpression of *NANOG* predicts tumor progression and a poor prognosis in several cancers. *NANOG* is associated with tumor development[89], and *NANOG*/*NANOGP8* expression is associated with gastric carcinogenesis[90]. Moreover, extensive loss-of-function analyses revealed that RNAi-mediated NANOG knockdown inhibits tumor development[91]. The low expression level of *NANOG* is a promising survival prognosis marker in oral squamous cell carcinoma patients. NANOG is an important factor that affects the biological behavior of CSCs. There is evidence showing that the elimination of CSCs with the potential for self-renewal and tumor propagation should be a target of cancer drug development. However, CSCs are particularly resistant to conventional chemotherapy and radiotherapy compared with non-CSCs. Previous studies demonstrated the important contribution of pluripotent transcription factors to CSC function. NANOG exhibits significant clinical potential because it serves as a valuable marker of tumorigenesis[92]. Therefore, NANOG might have a promising future in anti-cancer and other therapeutic treatments, which could improve human health. Drugs targeting NANOG activity might be efficacious. However, further work is needed to design individualized therapies for cancer patients. These therapies should focus on functional analyses that define the transcription factors determining CSC phenotypes. Such studies might reveal precise regulatory mechanisms and identify new components of the transcriptional regulatory networks relevant to tumor transformation, tumorigenesis, and metastasis.

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