Review

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Yin-yang regulating effects of cancer-associated genes, proteins, and cells: An ancient Chinese concept in vogue in modern cancer research

Shuyong Wei*

College of Animal Science, Southwest University, Chongqing, China.

Summary **Great achievements have been made in human cancer research, but most of this research is focused on conditions at the microscopic rather than the systemic level. Recent studies have increasingly cited the ancient Chinese theory of yin-yang in an effort to expand beyond the microscopic level. Various cancer-associated genes and proteins such as mitogen-activated protein kinase (MAPK), p38, p53, c-Myc, tumor necrosis factor (TNF)-α, NF-κB, Cyclin D1, and cyclin-dependent kinase (CDK) and cells such as T cells, B cells, macrophages, neutrophils, and fibroblasts have been reported to regulate various types of cancers in a yin-yang manner. These studies have brought the theory of yin-yang into vogue in cancer research worldwide.**

Keywords: Yin-yang, cancer, gene, protein, cell

1. Introduction

As molecular biology and technology develop, cancer research has increasingly focused on conditions at the microscopic level. Therefore, gathering detailed information to fully depict an organism remains a major challenge (*1*). The theory of yin-yang originated from ancient Chinese philosophy and was incorporated into traditional Chinese medicine after Huangdi's Internal Classic. Yin-yang is increasingly cited by modern researchers in an effort to expand beyond the microscopic focus of cancer research and to view biological phenomena from a macroscopic level.

The theory of yin-yang was introduced to Western medical journals more than 60 years ago (*2*). The relationship between disease and yin-yang was first described in 1971 (*3*), and the hypothesis of yin-yang regulation of cell function based on cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) was first reported in 1975 (*4*). This ancient Chinese theory has been increasingly cited by recent authors and it has been adopted by researchers around the world (*5-7*). Various genes, proteins, and cells are reported to have yin-yang effects by promoting, inhibiting, and eradicating cancer. These studies provide a more comprehensive and systematic understanding of this complicated disease (Figure 1).

2. Yin-yang effect of cancer-associated genes and proteins

The yin-yang relationship between proliferation and differentiation of cells plays a pivotal role in the development of cancer. A yin-yang balance has been highlighted as a feature of cells (*7,8*), and some yin-yang regulating genes and proteins associated with cancer have been found over the last 30 years. MAPK, p53, c-Myc, and CDK are particularly important, and Bcl-2/Bcl-X1, c-JUN, hepatocyte nuclear factor (HNF) 4a, and miR-145 are also included in these pathways (Figure 2).

2.1. *MAPKs*

The MAPK family includes p38, jun nuclear kinases (JNKs), and extracellular signal-regulated kinases (ERKs), and the family plays important roles in cellular proliferation, differentiation, and apoptosis (*9*). Ordinarily, JNKs and p38 MAPK, which share several

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**Address correspondence to:*
Dr. Shuyong Wei, College of Animal Science, Southwest University, Chongqing 402460, China.
E-mail: shuyongwei013@163.com

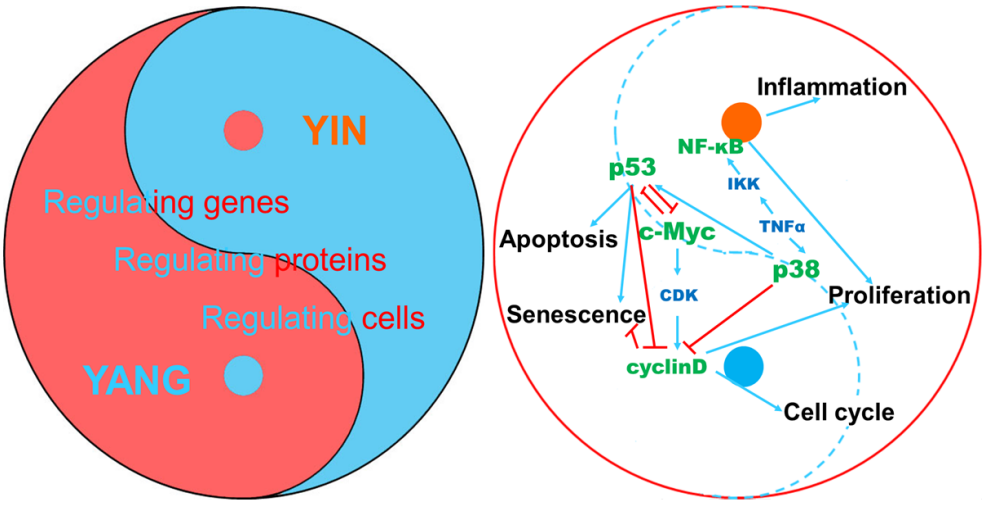

Figure 1. The yin-yang effects of cancer-associated genes and proteins. Yin represents the senescence and apoptosis of cancer cells; Yang represents cancer cells' life processes such as the cell cycle, proliferation, and suppression of senescence. Cancer-associated genes, proteins, and cells all have yin-yang effects on cancer development. The genes p38, p53, c-Myc, CDK, TNFα, and NF- κB play a particularly important role in cancer.

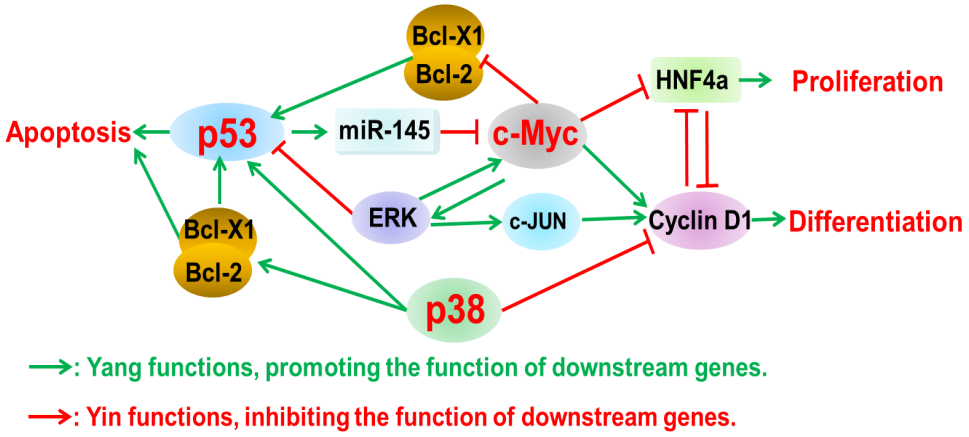

Figure 2. Effects of p38, c-Myc, p53, and Cyclin D1 on cancer cells. p38 MAPK can induce the apoptosis of cancer cells by activating p53 or Bcl-2/Bcl-X1, while p38 inhibits the differentiation of cells by inhibiting Cyclin D1. c-MYC and p53 can inhibit each other. c-MYC promotes cell differentiation by activating Cyclin D1 but it inhibits p53 activity through ERK or the Bcl-2/Bcl-X1 pathway and it inhibits cell proliferation through HNF4a. In contrast, p53 inhibits c-MYC by activating miR-145. ERK promotes Cyclin D1 and the differentiation of cells through the c-MYC and c-JUN pathways. HNF4a and Cyclin D1 can inhibit each other; the former regulates cell proliferation while the latter regulates cell differentiation.

upstream regulators such as MAPK kinase (MKK) 4, are considered to be cancer suppressors (*10*). However, the two stress-activated signaling pathways may promote cancer development. A study in p38MAPK knock-in mouse indicated that p38MAPK is a key component of human lung cancer, that it provides an early and pro-tumorigenic signal in the tissue microenvironment that is reprogrammed by p38MAPK-hyaluronan, and that it plays a critical role in driving lung tumorigenesis (*11*). A recent study on JNK1$^{-/-}$ mouse intestinal epithelial cells and Caco-2 cells reported that the interaction of JNK1 with the vitamin D receptor physically and functionally attenuates the calcitriol-mediated inhibition of cancer cell proliferation (*12*). In human vestibular schwannoma cells, JNK can enhance cell survival by suppressing the accumulation of mitochondrial superoxides (*13*). Activated ERK1/2 kinases can up-regulate various transcription factors such as c-Myc, and subsequently promote cancer cell survival (*14*). However, another study has indicated that ERK can increase the transcription and stability of c-Jun and cyclinD1 and its receptor and that ERK can activate C kinase 1 (RACK1), enabling protein kinase C to enhance JNK activity (*15*). Furthermore, this signaling axis plays a central process in melanoma tumorigenesis.

2.2. *p38 and p53*

Both p38 and p53 are generally considered to be cancer suppressors, but they have both negative and

positive effects on cancer cells (*11,16-20*). p38 acts as a regulator in inflammation but as a suppressor in tumors. p38α, a prototypic p38 MAPK, was originally identified as an essential signaling kinase for the production of many inflammatory cytokines (*16*). p38 inactivation supports cell transformation *in vitro* and promotes experimental cancer development *in vivo*. By activating p53, phosphorylating Bcl2s, decreasing cyclin D expression, and inhibiting Cdc25 phosphatase, activated p38 mediates apoptosis induced by DNA damage (*17*). p38 is involved in oncogene-induced senescence, which is a mechanism of cancer suppression (*18*). p53 is considered to be a potent suppressor of tumorigenesis in mammals, and it is a multifunctional transcriptional regulator causing cells to stop growing or die when stressed or damaged (*19*). In organisms, the activity of p53 is optimally balanced, preventing the development of cancer as well as the premature occurrence of aging phenotypes. Tyner *et al*. reported that some tissues show delayed aging in $p53^{-/-}$ or $p53^{+/-}$ mice and that hyperactive p53 expression in mice induced substantial resistance to spontaneous tumorigenesis (*20*).

2.3. *c-Myc and p53*

c-Myc is important to the proliferation and growth of normal cells. The activated c-Myc oncogene contributes to the development of various human cancers, such as leukemia, lymphoma, and solid tumors. However, the deregulation of c-Myc also mediates intrinsic cancer suppression including apoptosis, cellular senescence, and DNA damage (*21*). The balance of p53 and c-Myc is important to cell proliferation, so Dai *et al*. (*22*) describe p53 as yin and c-Myc as yang. There is an inverse relationship between p53 and c-Myc in controlling cell growth and proliferation, and balanced regulation of the two genes is crucial to cells. A study revealed the networks of p53 and c-Myc regulation in cells (*23*). In brief, p53 induces miR-145 expression and subsequently suppresses c-Myc expression, and c-Myc can counterbalance the action of p53 action to a great degree.

2.4. *Cyclin D1 and CDK*

The proliferation and differentiation of cells, which are driven by cyclins and CDK, play a yin-yang role in cancer. Cyclin D1 is overexpressed in many tumors and can activate CDK4/6, and then phosphorylate and inactivate the tumor suppressor Rb. Rb suppresses tumor growth by inhibiting E2F, which is a transcription factor that regulates DNA synthesis. The action of Cyclin D1 on cell proliferation and differentiation is associated with HNF4α, c-Myc, CKip21, and p53 (*24,25*). HNF4α and cyclin D1 negatively regulate each other and are in turn regulated by other modulators, such as p53, c-Myc, and CKip21. Cyclin D1 can inhibit the differentiation factor ChREBP in a CDK-independent fashion, decrease ChREBP gene transcription and protein function, and result in decreased expression of genes involved in differentiation (*24*).

2.5. *TNF-α and NF-κB*

An important prototypic pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-α) binds to and activates its receptor TNFR. TNF-α is a key regulator of inflammation, cell survival, and cell apoptosis (*26,27*), and TNF-α has yin-yang effects on cancer. The combination of TNF and TNFR can activate downstream cell survival pathways through TNF receptor-associated factor (TRAF) and nuclear factor κB (NF-κB) and also caspase 8 and associated apoptotic pathways through fas-associated death domain (FADD) (*26*). TNFα acts as either a tumor-promoting or tumor-destructive factor (*28*). At a high dose, TNFα can selectively destroy tumor blood vessels and activate T cells that attack and eliminate cancer cells. However, a low dose of TNFα is found in several types of cancers and is important to the development of all stages of cancer (*26*). Activation of NF-κB is detected in various types of cancers (*29*). Signaling pathways mediated by Toll-like receptors (TLRs), TNFα, and interleukin (IL)-1β are involved in this activation (*30*). In some cancers, the essential activity of NF-κB is usually caused by genetic alterations in NF-κBs or their inhibitors IκBs. However, the deregulation of NF-κB activity is attributed to the regulation of the IKK/ NF-κB signal pathway (*31*). IKKβ-deleted mice have decreased expression of many genes including IL-1β, IL-6, TNFα, and COX-2, resulting in a significant reduction in tumor size and number (*32*).

3. Yin-yang effect of the tumor microenvironment and cells

3.1. *The tumor microenvironment and cancer*

Both tumor cells and neighboring normal cells play a role in establishing the tumor microenvironment. They serve as a passive medium for tumor cell growth and also as an arena for interaction of both microenvironmental components and tumor cells. Tumor cells can regulate gene expression in normal cells and vice versa, thereby influencing their phenotype (*33,34*). Specialized variants of hematopoietic and mesenchymal cells such as macrophages, granulocytes, and monocytes are recruited from the bone marrow or bloodstream during cancer development, and some of these cells can become tumor-associated cells. Such cells substantially contribute to the development of cancer.

Cancer-associated inflammation is a double-edged sword. By secreting cytokines and chemokines,

inflammatory cells can express both pro-tumorigenic (yang) and anti-tumorigenic (yin) effects on the proliferation, migration, and differentiation of many types of cancer cells based upon their level of expression in the tumor microenvironment (Figure 3). Pro-tumorigenic effects include releasing survival factors, growth factors, and promoting angiogenesis and lymphangiogenesis. Anti-tumorigenic effects include releasing NK cells, activating apoptosis, and reducing tumorigenicity. Various inflammation-associated cells, including T cells, B cells, macrophages, neutrophils, and fibroblasts, have yin-yang effects on cancer (Table 1).

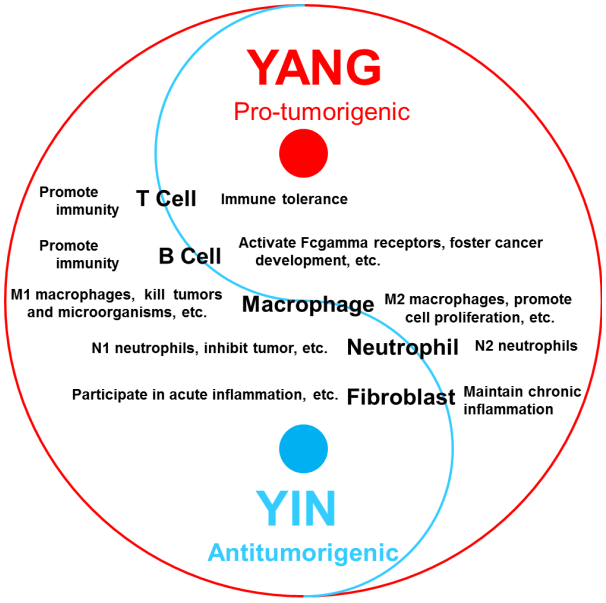

Figure 3. Yin-yang effects of tumor-associated cells. Yin represents antitumorigenic effects, including promoting immunity, killing microorganisms and tumors, and inhibiting tumor growth. Yang represents pro-tumorigenic effects, including immune tolerance, fostering cancer development, promoting cell proliferation, and maintaining chronic inflammation.

3.2. *T cells and B cells*

Tumor-related inflammation is an important component of the tumor microenvironment. Subpopulations of regulatory T cells (Tregs), which promote or inhibit the immune response, display yin-yang characteristics under certain conditions (*35*). The depletion of Tregs leads to the lack of suppression of immune cells, causing an excessive immune response and autoimmunity and promoting anti-tumor responses, while the expansion of Tregs can counteract autoimmunity and inhibit anti-tumor responses (*36*). As an example, inflammatory bowel disease can be induced by syngeneic CD4+CD45RB^{high} T cells but prevented by CD4+CD45RB^{low} T cells in mice (*37*). Furthermore, the costimulation of T cells also plays a crucial role in controlling immune function (as yang) and tolerance (as yin) (*38*). As the most prominent costimulatory receptors for T-cell activation, some proteins of the CD28 family seem to dampen T cell activation and regulate the induction of T cell tolerance (39).

B cells also play a role in inflammation and tumors. During carcinogenesis, B cells can produce antibodies, activate Fcgamma receptors (FcgammaRs) on resident and recruited myeloid cells, and foster cancer development (*40*). In transplanted B16 melanomas, B cells can drive M2-like polarization of macrophages and promote the growth of the melanoma by producing IL-10 (*41*). Mantovani *et al*. describes B cells as yin and macrophages as yang in the development of cancer (*42*).

3.3. *Macrophages*

Based on differences in activation and function, macrophages can be divided into classically activated macrophages such as M1 macrophages and alternatively activated macrophages such as M2 macrophages (*43,44*). These two types of macrophages regulate

Table 1. Yin-yang effects of inflammatory cells on cancer

Inflammatory cells	Effects on cancer		*Ref.*
	Yin (Antitumorigenic)	Yang (Pro-tumorigenic)	
T cells	Promote immunity	Immune tolerance	(*37-39*)
B cells	Promote immunity	Activate Fcgamma receptors, drive M2-like polarization of macrophages, and foster cancer development	(*41,42*)
Macrophages	M1 macrophages, kill microorganisms and tumors	M2 macrophages, promote cell proliferation, produce growth factors, active the arginase pathway and angiogenesis, and scavenge debris	(*45-47, 49-54*)
Neutrophils	N1 neutrophils, kill cells and inhibit tumor growth, regulate adaptive immune responses by interacting with dendritic cells	N2 neutrophils, secrete angiogenic factors and matrix-degrading enzymes, support metastatic phenotype acquisition, and suppress antitumor immunoreaction	(*56-63*)
Fibroblasts	Participate in acute inflammation, enable infiltrating immune cells to undergo apoptosis or exit the site through the lymphatic system	Maintain chronic inflammation	(*64-67*)

neoplastic progression and immune surveillance in a yin-yang manner (*45*). M1 macrophages are potent effector cells that kill microorganisms and tumors (*46-49*). However, M2 macrophages play roles in regulating inflammation and adaptive immunity (*50*), promoting cell proliferation by producing growth factors (*51*), activating the arginase pathway (52) and angiogenesis (*53*), and scavenging debris by expressing scavenger receptors (*54*).

3.4. *Neutrophils*

Neutrophils are short-lived white blood cells derived from bone marrow myeloid precursors, and these cells can promote or inhibit cancer under particular conditions. By polarizing to either the "N1" or "N2" phenotype, tumor-associated neutrophils can respectively inhibit or promote the development of lung cancer (*55*). The functions of tumor-associated neutrophils are described as antitumorigenic (N1 phenotype) and pro-tumorigenic (N2 phenotype), and which phenotype they express is defined by transforming growth factor (TGF)-β, an immunosuppressive cytokine that can affect tumor progression (*56*). Consistent with this "N1-N2" hypothesis, TGF-β can inhibit the activity and cytotoxicity of neutrophils *in vitro* (*57*). The pro-tumorigenic function of neutrophils may be associated with secretion of angiogenic factors and matrix-degrading enzymes (*58,59*), facilitation of the acquisition of a metastatic phenotype (*60*), and suppression of an antitumor immunoreaction (*61*). Nonetheless, neutrophils can kill tumor cells and inhibit tumor growth (*62*) as well as regulating adaptive immune responses by interacting with dendritic cells (*63*).

3.5. *Fibroblasts*

In the tumor microenvironment, cancer-associated fibroblasts (CAFs) play an important role in the maintenance of chronic inflammation (*64*). In the normal inflammatory process, stromal fibroblasts dictate the type and duration of leukocyte infiltrates, enabling the infiltrating immune cells to undergo apoptosis or exit the site through the lymphatic system (*65*). When these regulatory circuits are damaged, however, inflammation becomes persistent and chronic (*66*). CAFs can both directly and indirectly contribute to the inflammatory process in tumors. They do so directly by recruiting immune cells to respond to the cytokines and chemokines they secrete, and they do so indirectly by modifying the extracellular matrix to favor different immune cells (*67*).

4. Conclusion

In conclusion, modern biological science and cancer research has consistently focused on phenomena at the cellular and molecular level, such as gene suppression and activation, promotion and suppression of apoptosis, protein degradation and synthesis, counteraction of inflammation and inflammation, and tumor suppression and oncogenic processes. This means that the theoretical framework is becoming more complex but less unified. A macroscopic theory is needed to integrate key concepts or the framework will lack important components or falter. The theory of yin-yang provides a macroscopic view on biological phenomena. As Dutt *et al*. said (*68*), the concepts of yin-yang provided the intellectual framework for Chinese scientific thinking, especially in biology and medicine.

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