Review Article

Decoding cancer and herbal renaissance

Lan Ko[1,2]^

[1]Research and Development, OnkoTarget LLC, Augusta, GA, USA; [2]Georgia Cancer Center, Medical College of Georgia, Augusta University, Augusta, GA, USA

Correspondence to: Lan Ko, MD, PhD. OnkoTarget LLC, Augusta, GA, USA. Email: lan-ko@outlook.com.

Abstract: The original notion in quest of cancer targets to end cancer still stands, yet the secret of common human cancer was concealed by a chicken-egg paradox. Solid tumors initiate in the tumor microenvironment from rare stem cells, which express a mutant target protein as their specific marker. For decades, the stem cell and target protein cannot paradoxically be found one without first finding the other. With combined evidence from genetics, pathology, stem cell biology, clinical oncology, and herbal medicine in particular, this paradox is resolved. Historical successful anticancer herbs, together with clinical oncology drugs, paved the way to decode cancer. In solid tumors, the liable stem cells are pericyte stem cells on blood vessels in the tumor microenvironment inducing angiogenesis. One identified target protein in pericytes is a DNA repair factor and transcriptional regulator named GT198 (gene symbol *PSMC3IP*, alias name Hop2). Since GT198 is found as a direct drug target of many chemotherapy drugs and clinically successful anticancer herbs, more herbal medicines worldwide can now be screened against this target. In the near future, safer and more effective natural herbal medicines could systematically treat common solid tumors. This review discusses a unified theory of cancer and diseases in which pericyte stem cells are fundamental to both. It also reveals a new approach to identifying multi-functional herbs. Unlocking herbal targets in stem cells enables effective herbal identification and, in turn, awakens the herbal renaissance.

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Introduction

A major challenge in human cancer treatment is that the target proteins responsible for cancer initiation were hidden. The lineage identity of cancer-inducing cells was also unclear. Cellular function changes such as cell cycle, apoptosis, and angiogenesis are all eligible consequences but not the initial cause of cancer. This pitfall hindered the validation of effective anticancer drugs or herbs.

Human cancers are largely grouped into three categories. One is common solid tumors in which cancer initiates from stem cells in the tumor microenvironment (1). This review will focus on this category of solid tumors. The second category is blood cancers without a pathologically defined tumor microenvironment (2). Even so, we speculate that solid and blood cancers potentially share the same stem cell regulators and drug targets. The third category includes sarcomas and rare childhood tumors. In this case, mutant stem cells themselves mature into tumor mass feasible for genetic analysis so that most of their cancer genes, such as Ewing's sarcoma (EWS) or retinoblastoma (Rb) genes, were previously confirmed by cancer genetic studies (3-5). However, they are not involved in human common solid tumors.

In solid tumors, it turned out that a target protein and its associated stem cells were hidden in a chicken-egg paradox, only realized after decoded. Decades ago, our group first

^ ORCID: 0000-0002-0089-9090.

characterized a human transcriptional coactivator named GT198 (gene symbol *PSMC3IP*) (6). Accumulating evidence from us and others has shown that GT198 is mutated in blood vessel pericyte stem cells, which are the primary cancer stem cells causing all human common solid tumors (7). And importantly, GT198 is a direct target of a panel of successful clinical oncology drugs and anticancer herbs (8,9). Based on the logical theory described in this review, few identified protein factors would have an equal functionality in the human genome, leaving GT198 a unique target of anticancer drugs or herbs.

Medicine is a single entity of collective arts for treating illness. Herbal medicine and modern medicine essentially reflect the different angles of view to the same. Thus, an anticancer herb could share an identical target with a chemotherapy drug. With an herbal target available, many anticancer herbs can now be systematically screened, which will strengthen the bridge crossing between modern and herbal medicines.

In this review, the discussion will cover a unified theory of cancer and propose a new concept of multi-active herbs against both cancer and diseases. It explains why decoding cancer could promote an herbal renaissance, which may accelerate a leap forward in biomedicine. Patient survival is proof of the effectiveness of herbs and their target.

Human solid tumors

Cancer genetics

The evidence to reconcile a first-hit cancer gene encompasses broad aspects of biomedicine. I first discuss cancer genetics. The gold standard in cancer genetics to validate a first-hit cancer gene is the presence of recurrent somatic mutations or germline mutations segregated in cancer family pedigrees (10-13). This standard indeed had resulted in most oncogenes in sarcomas or childhood tumors (3,5), but mysteriously not in common solid tumors. Such as the breast cancer gene *BRCA1* is not involved in nonhereditary breast tumors without a family history (14). The lack of valid cancer targets is mainly responsible for insufficient drug identification against common cancer.

However, by analyzing cancer family pedigrees, leading geneticists have indeed previously identified hot cancer gene loci on chromosomes. These include chromosome 11q13 (15), and 17q21 (16), where two hidden solid tumor genes, *RBM14* and *GT198*, are located (*Figure 1*). Early genetic studies of gene copy number gain or loss overlooked compromised genes between gain and loss regions. The *RBM14* (alias name CoAA) gene amplifies its gene body but losses its enhancer (*Figure 1A*) (17,18). The *GT198* gene was shadowed by *BRCA1* nearby (*Figure 1B*) (14,19-22), so that cancer pedigree studies alone missed both solid tumor genes.

This historical failure was also due to another pitfall, in which solid tumor genes are all stem cell regulating genes with an impact on embryonic development. An embryo will not grow up as an adult if its stem cell gene is severely mutated, leaving few families to be analyzed with confidence (*Figure 1C*). In contrast, disease genes or normal variants without stem cell impact have large pedigrees convenient for genetic analysis. Thus, the stem cell impact also hindered the historical discovery of solid tumor genes.

This same reason also causes reciprocal rates between germline and somatic mutation. *BRCA1* has larger pedigrees and rare somatic mutations (23). *GT198* or *TP53* have smaller pedigrees and abundant recurrent somatic mutations in tumors (24-26). *RBM14* is amplified in most solid tumors (17), and may not have any pedigree for analysis (*Figure 1C*). We speculate very few genes in the human genome are first-hit in nonhereditary common solid tumors based on major cancer loci discovered to date.

Hence, somatic rather than germline mutation is critical to validate solid tumor genes. But then, a chicken-egg paradox had prevented. Solid tumors initiate in the tumor microenvironment from rare stem cells, which express a cancer gene itself as a specific marker. One would not find a mutated gene without first finding its affected stem cell or *vice versa*. Our group accidentally bypassed this paradox only because we first cloned the gene (6), before revealing its affected pericyte stem cells (7,27).

Philosophy in stem cells

The cell is a structural and functional unit of humans. The basic scheme in a cell is that extracellular hormone factors send signals through pathways to the nucleus, which controls cell growth and differentiation (*Figure 2A*). Nuclear gene transcriptional machinery is an ultimate target of signal transduction and a molecular switch of subsequent cellular response.

However, within this machinery, a single RNA polymerase II (Pol II) enzyme controls more than 20,000 protein-coding genes in the human genome (*Figure 2B*). It requires Pol II to be tightly controlled by a pyramidal of factors so that the transcription can occur on a specific gene,

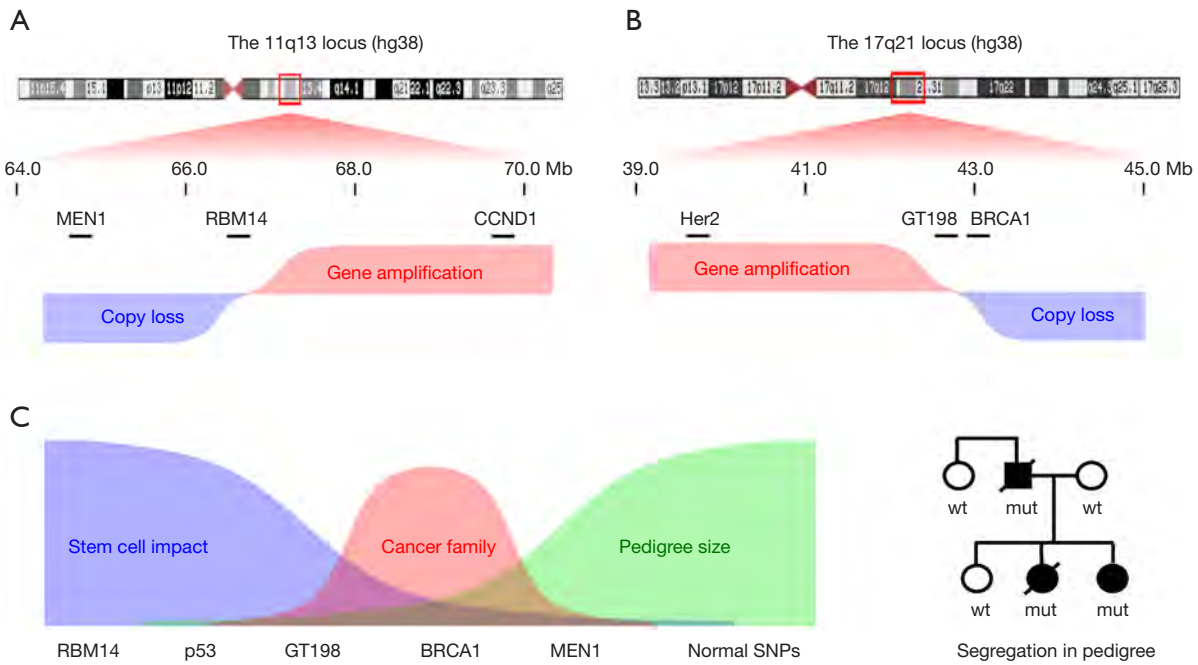

Figure 1 Chromosome 11q13 and 17q21 loci. (A) The *RBM14* gene in cancer has lost its enhancer with the amplified gene body at the 11q13 locus. (B) The *GT198* gene is located near *BRCA1* at the 17q21 locus between the regions of copy number gain and loss. (C) Stem cell impact in oncogenes prevents the existence of large pedigrees in cancer families. At the right is a model of segregation analysis in which affected cancer patients (filled) carry mutations. SNPs, single nucleotide polymorphisms; wt, wild type; mut, mutant.

in a specific cell, and at a specific time. There are at least several thousand transcriptional factors that bind directly to the genes, and several hundred coregulator proteins that bind to transcriptional factors. But there would be only a few proteins, like the cabinet in the government, which can directly connect to the single Pol II molecule with the rest of the gene-regulating machinery. The top secret of cancer genes lies in the Pol II cabinet. Till this day, all first-hit cancer genes are found to either directly bind to Pol II, or within a DNA repair complex that is part of Pol II machinery. For example, RBM14 directly binds to Pol II (28). Sarcoma oncoproteins EWS, TLS, and SYT have sequence homology with RBM14 and directly interact with Pol II (17,29,30). BRCA1, BRCA2, p53, and GT198 are DNA repair factors (31-33). BRCA1 also interacts with Pol II directly (34).

To be an oncoprotein, in addition to serving as a cabinet factor, it must regulate stem cell differentiation at the initial stage (*Figure 2B*). Because cancer is a stem cell disease in which mutant stem cells are unable to terminal differentiate or be eliminated. Otherwise, tumors would be replaced during normal homeostasis, whereas tumors in fact last for decades. This logic indicates that many signaling kinases, growth factors, cell cycle or apoptotic factors, immune cell surface proteins, and transcriptional factors are unlikely to be the first hit of cancer since their changes cannot impact stem cells at the top level of gene control. Similarly, any initial changes in differentiated cells may lead to diseases rather than cancer (*Figure 2B*). Furthermore, when an anticancer drug target is of concern, a cabinet oncoprotein as a drug target has to be highly expressed in cancer but not in normal tissues for manageable low drug toxicity. Thus, cancer target proteins will be very rare indeed.

An in-depth reason for cancer genes encoding stem cell regulators lies in philosophy. A fundamental step of cell differentiation, in normal, cancer, or disease, is the segregation of Yin-Yang transcripts (*Figure 2C*). Yin and Yang are defined as opposite activities or forces that are mutually dependent, mutually inclusive, coexisting, and exchangeable, such as the concepts of hot and cold. In physics, electrons and protons are an example of Yin-Yang. In stem cells, genes transcribe into wildtype and its splice variant transcripts as counter forces. A stem cell is non-polarized. An asymmetrically divided cell represents

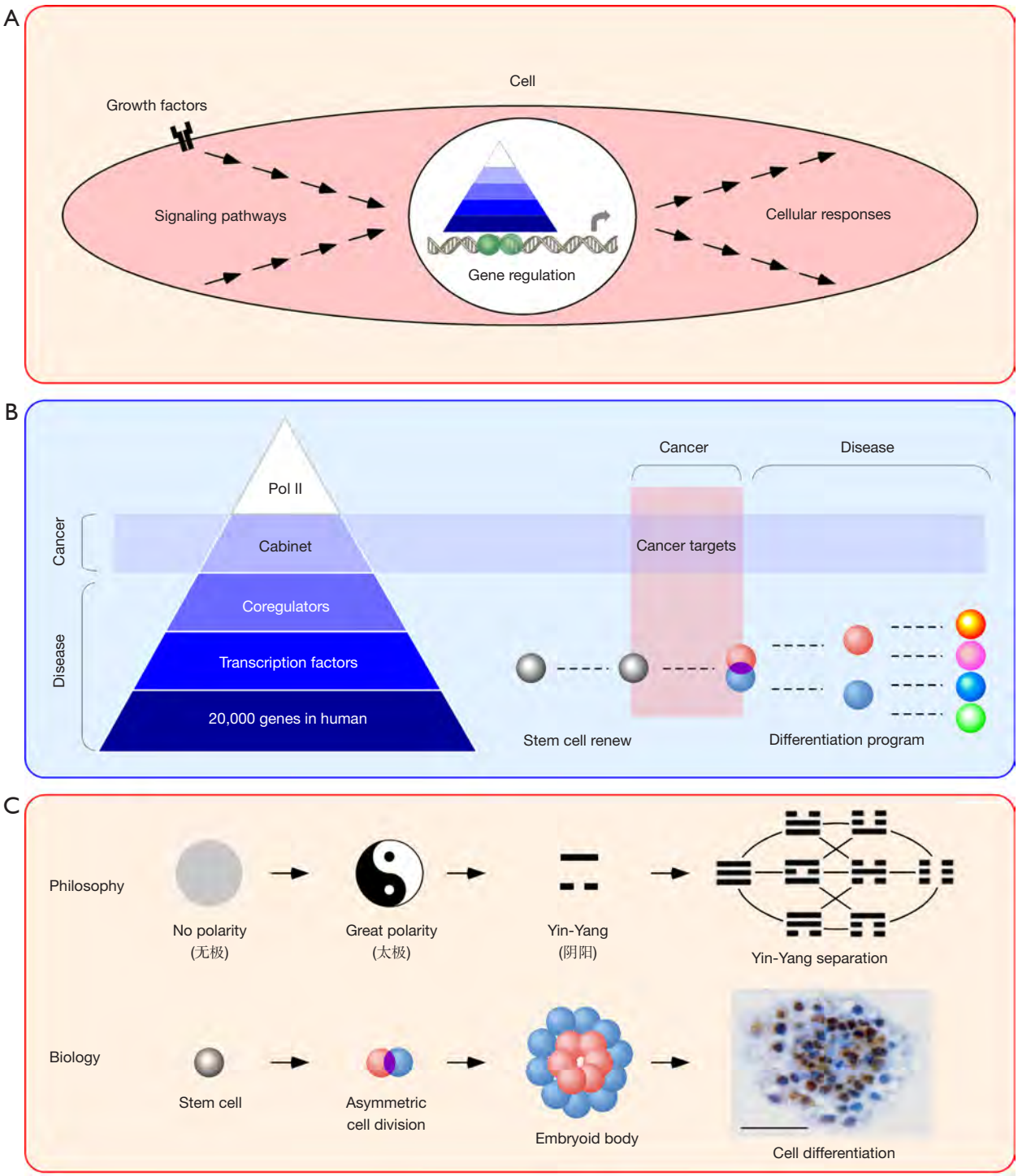

Figure 2 Cancer target proteins control transcription and stem cell differentiation. (A) Nuclear transcription is the target of signaling and molecular switch of subsequent cellular response. (B) Cancer target proteins are Pol II-interacting transcriptional regulators. They control stem cell initial differentiation. (C) Stem cell differentiation in biology shares the same Yin-Yang process in philosophy. A non-polarized stem cell polarizes when counter-forced transcripts segregate during asymmetric cell division to achieve cell differentiation. Combined regulating genes yield diverged cell offspring through Yin-Yang segregations. At day two, immunohistochemical staining of GT198 in a mouse embryoid body shows distinct GT198 expression in differentiating cell layers. Scale bar =50 μm.

polarized (35). Differentiation is then a process of Yin-Yang segregation of counteractive transcripts. The Yang wild type and Yin variant segregate during cell differentiation and produce distinct cell offspring. Often two countered genes work together resembling a classic Tai-Ji image with Yin within Yang and Yang within Yin (*Figure 2C*). The failure of this segregation in stem cells leads to cancer, and in differentiated cells leads to disease. Hence, normal, cancer, and disease unify under one principle. The segregation of counter transcripts with a cascade alternative splicing into daughter cells has been previously documented (36-39), and is a fundamental philosophy in stem cell differentiation. It is also why all first-hit cancer genes have splice variants, such as *RBM14*, *GT198*, *TP53*, *BRCA1*, and *EWS* genes (24,25,40-43). Often their mutations disrupt stem cell differentiation due to their wildtype-variant imbalance.

Oncoprotein GT198 as drug target

History of GT198

In 1995, the first report of GT198 was from a Canadian group screening transcripts in the breast cancer gene locus at 17q21 (44). They found a partial sequence and named gene transcript number 198, which has similar expression patterns to BRCA1. The gene symbol at the time was *HUMGT198A* and later renamed as *PSMC3IP*. Our group first cloned a full-length human GT198 during transcriptional studies and reported it as a transcriptional coactivator (6). Its mouse homolog, named TBPIP, was also found by a Japanese group (45). Later, an NCI group reported it as mammalian Hop2 in meiosis (46), and in DNA repair (47), due to its functional similarities to yeast Hop2. Since the NCBI nomenclature committee was reluctant to modify its incidental gene name *PMSC3IP* decades ago, its various alias names in the literature now include GT198 in cancer, Hop2/ TBPIP in biochemical studies, and *PMSC3IP* in genetic studies.

Even not reconciled early, GT198 functions have now become unified. GT198 is a Pol II cabinet factor activating transcription (6), recombination, DNA repair (47), and meiosis (48). It is because that GT198 is a DNA-binding protein in transcriptional machinery or DNA repair complex. GT198 is also a stem cell regulator whose wild type and splice variant switch expressions during stem cell differentiation at the embryoid body stage (24). Its splice variant is activated in cancer and induces potent apoptosis (24). Using GT198 as a marker in the tumor microenvironment, the cancer stem cells are revealed as blood vessel pericytes stimulating angiogenesis (27,49). The pericyte stem cells produce vascular smooth muscle cell lineages in the tumor microenvironment so that the GT198-effected stromal cells include myoepithelial cells and adipocytes in human breast cancer (27), theca cells in ovarian cancer (50), myofibroblasts in prostate and bladder cancers (49), as well as stromal cells in other common human solid tumors (7). In mouse models, GT198 similarly expresses in the tumor stroma, and the protein vaccine of GT198 reduces mouse tumor growth (51). From a genetics perspective, the human *GT198* gene carries germline mutations in breast and ovarian cancer families (21,22), and in ovarian diseases (52). Recurrent somatic mutations are present in the sporadic breast, ovarian, fallopian tube, prostate, and bladder tumors (24,27,49,50). More importantly, a number of clinical oncology drugs and clinically effective anticancer herbs directly target to GT198 (8,9). All evidence consistently suggests GT198 as a first-hit oncoprotein.

The target-cell paradox is finally unlocked through broad multidisciplinary studies to reveal the target GT198 and its affected pericyte stem cells simultaneously. In particular, oncology drugs and anticancer herbs provided ultimate proof for GT198 as a true target in cancer.

Pericyte stem cells

Small blood vessels consist of endothelial cells lining the inner layer of the vessel wall and pericytes enveloping the surface of the vascular tube (*Figure 3*). If mutated, pericytes become malignant producing vascular smooth muscle cell lineage so that the stroma can be angiogenic even before tumor cells appear. In tumors, pericytes carry mutated GT198 (27), and cause GT198 activation and overexpression (7). These pericytes evolve into tumor cells resembling the local tissue types such as squamous cells in oral cancer (8), or glioma cells in brain cancer (7). The pericyte-derived cells also migrate into tumor-associated lymph nodes suggesting pericyte "cancer stem cells" responsible for tumor metastasis (7). Thus, a metastatic tumor does not necessarily resemble the original tumor as often observed, but is more compatible with its distant home environment. For example, a brain metastasis of breast cancer is due to a mutant pericyte stem cell from the breast circulating to the brain and evolving into mutant neural cells. The finding of GT198-affected pericyte stem cells reconciled the long-standing notions in angiogenesis,

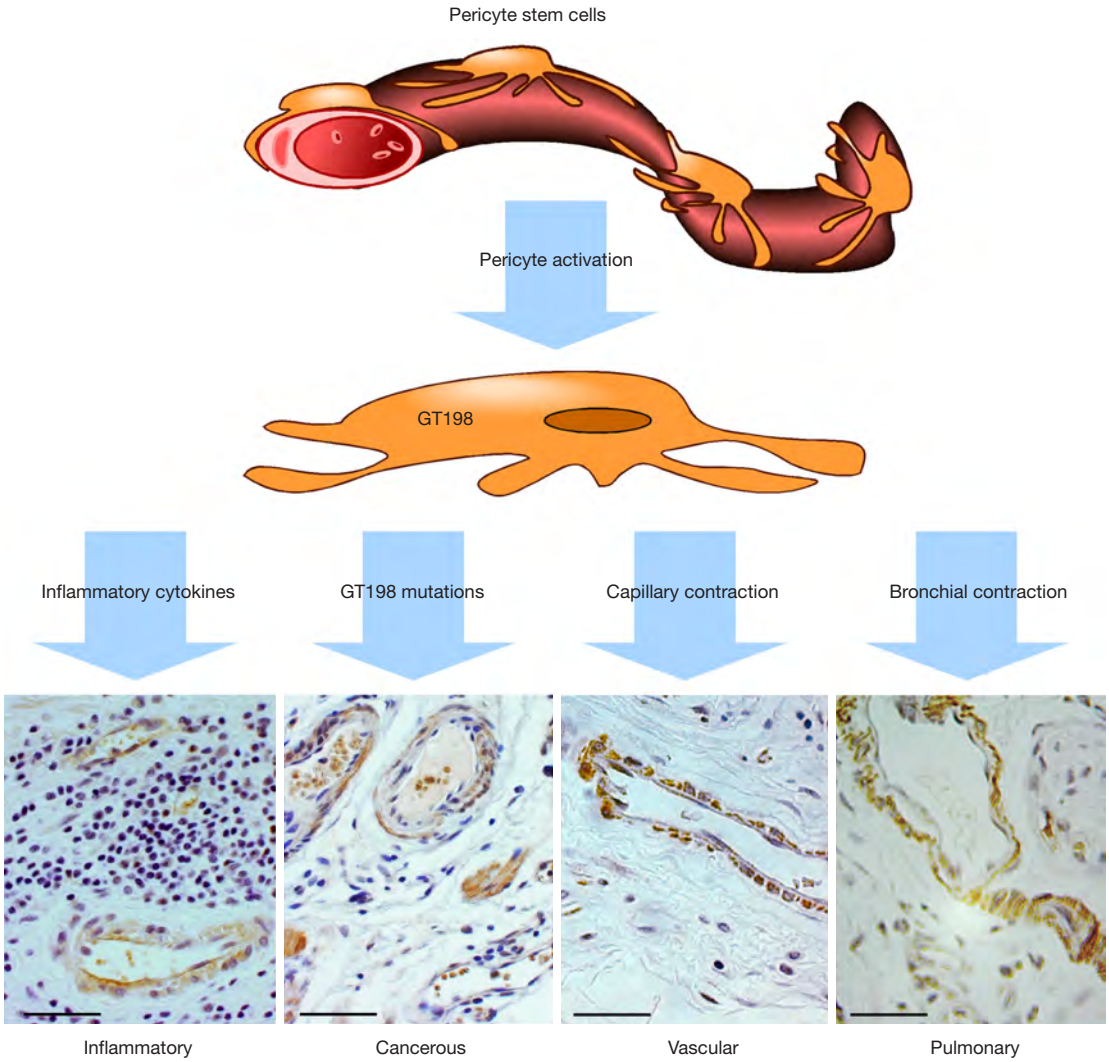

Figure 3 Pericyte stem cells are a common cause of cancer and diseases. Activated pericytes (in orange) expressing GT198 differentiate into vascular smooth muscle cell lineages in cancer and diseases. Immunohistochemical staining of GT198 showing positive blood vessels in infection and cancer; contractile pericytes in the vasculature; and contractile smooth muscle cells in bronchi of the lung. Scale bar =50 μm.

tumor microenvironment, metastasis, and clinical evidence of anticancer drugs and herbs.

The functionalities of pericytes in diseases may parallel that in cancer. In the event of acute inflammation, such as in vascular or pulmonary diseases, pericytes and the descendent smooth muscle cells proliferate and become overly contractile (53). In the event of chronic inflammation in cancer, pericytes may be mutated and cancerous. Consistently, in both acute inflammation in infection and chronic inflammation in cancer, GT198 in pericytes is activated and overexpressed (*Figure 3*). Pathological observations of GT198 show its expression in various human tissues in cancer (7), infection, vasculature, and bronchi of the lung (*Figure 3*). Since GT198 consistently affected pericytes and descendant vascular smooth muscle cell lineages in both cancer and diseases, an intriguing question is whether inhibiting GT198 can treat both cancer and diseases.

Herbs for cancer and diseases

We previously have scanned a panel of common oncology drugs and anticancer herbs and found many of them are GT198 inhibitors (8). Identified oncology drugs include

but are not limited to the well-known mitoxantrone, doxorubicin, paclitaxel, etoposide, and imatinib. The positive anticancer herbs include allspice (*Pimenta Dioica*) from Jamaica, *Gleditsia sinensis* (ZaoJiaoCi) from China, and BIRM from Ecuador (8). Unlike oncology drugs restricted to FDA-approved cancer use only, herbal medicines have accumulated a much broader scope of disease treatment, as evidenced in history. Not surprisingly, all positive herbs identified as GT198 inhibitors have at least four activities in treating cancer, infection, cardiovascular illness, and pulmonary disease (*Table 1*).

Allspice is more well-known for treating viral and bacterial infection than treating human prostate cancer in South America (54-56). It is also a natural antibiotic against various infections in India. Ecuador BIRM treats a long list of ailments including cancer, infection, asthma, and is named Biological Immune Response Modulator (57,58). *Gleditsia sinensis* (alias name ZaoJiaoCi), one of the 50 fundamental Chinese herbs, was described in the ancient Chinese medicinal book BenCaoGangMu for treating various illnesses. Modern research suggests that it has effects on breast and prostate cancer (59,60), cell proliferation and cell cycle (61), and angiogenesis (62-64). It is the most commonly used anticancer herb in China today (65). It was also used to combat COVID-19 during the pandemic and saved lives from severe pulmonary infection due to its multiple pharmacological activities (66). Rosewood and walnut tree branches are also known for their anticancer, anti-inflammatory, antioxidant activities (67,68). In contract, a negative GT198 inhibitor radix isatidis is anti-inflammatory but not anticancer (69) (*Table 1*).

The reason for a given herb having multiple activities in anticancer, anti-inflammation, anti-vascular, and anti-pulmonary diseases, is because it targets the same pericytes and derivative cells affecting multiple diseases and cancer (*Figure 3*). With this idea in mind, a list of herbs can be found as quadruple-effective herbs (*Table 1*). Many of them are predicted to be GT198 inhibitors and can be tested in the future. These include saffron (70,71), pinellia ternate (72), ephedra (73,74), rhubarb (75), pomegranate (76-78), arisaematis rhizome (79), cuttlefish bone (80,81), gardenia (82), houttuynia cordata (83), loquat leave (84), mistletoe (85-87), Nong Ji Li (88), plantain peel (89-91), radix platycodonis (92), snakegourd (93), soursop leave (94,95), turmeric (96,97), Wu Gu Teng (98) (*Table 1*). This collection represents only examples but is far from an inclusive or exhaustive list. The strength of herbal activities in each disease is also relative based on existing evidence. The evidence is derived from a wide variety of sources, including but not limited to the published literature in English or Chinese, medicinal and herbal books, folklores, physician experiences, as well as online herbalist information (99,100). It is foreseeable that more herbs can be identified as quadruple-effective herbs through testing GT198 inhibition as a new approach.

On the other hand, and most importantly, a true anticancer herb targeting GT198 ought to be a quadruple-effective herb with the treatment evidence in both cancer and diseases. This new concept may accelerate the identification of new anticancer herbs, which can be clinically validated in the future.

Herbal renaissance

A unified theory with herb

Medicine is one entity of collective arts for treating human illness. Except, modern medicine is more mechanism-based, whereas herbal medicine is clinical evidence-based. Hence, modern and herbal medicines belong to one unity, only reflecting different views of the same (*Figure 4A*).

However, a major challenge in herbal medicine is the lack of validated molecular drug targets due to divided modern and herbal medicines. In modern medicine, mechanistic drug targets are often unsuccessful without taken herbal treatment into consideration, even though purified chemical drugs and unpurified herbs are supposed to share the same mechanisms or molecular targets. For herbal medicines, without a target, it is challenging to validate disease relevance, standardize dosage, and isolate active components from toxic impurities. Significant existing efforts put into the compatibility of herbal medicines often aim to compensate toxicity via combined herbs. Increased effectiveness and lower toxicity of herbs can be achieved by partial purification using a target that is now available.

In the cancer field, a target validation encompasses multiple disciplines. But scientists are often trained in a particular field and are increasingly more focused when they become seasoned experts. An interdisciplinary study crossing biochemistry, stem cell biology, cancer genetics, pathology, oncology, and herbal medicine is rarely carried out. Like an analogy of the Blind Men and the Elephant (*Figure 4B*), a complete view is limited by the failure to account for other truths as a whole. A unified concept revealing drug targets shall require broadened but simplified studies. Thanks to herbal medicine with its broad-ranging

Table 1 Multi-active herbs against cancer, inflammation, vascular, and pulmonary diseases

Name (Chinese name)	Latin name	Toxicity	Cancer	Inflammation	Vascular	Pulmonary
Positive GT198 inhibitors						
Allspice (多香果)	*Pimenta dioica*	None	+++	+++	++	+
BIRM (免疫增强剂)	*Kalanchoe gastonis-bonnieri*	None	+++	++	++	++
Rosewood (降香)	*Dalbergia odorifera* T. Chen	Low	+++	+++	+++	+
Spina Gleditsiae (皂角刺)	*Gleditsia sinensis* L.	High	+++	+++	+	+
Walnut branch (核桃枝)	*Juglans regia* L.	Low	+++	++	+	–
Negative GT198 inhibitors						
Garden mum (菊花)	*Chrysanthemum x morifolium*	Low	–	++	++	++
Licorice (甘草)	*Glycyrrhiza uralensis* Fisch	Low	–	++	+	+
Radix isatidis (板蓝根)	*Isatis indigotica* Fort	Low	–	+++	–	+++
GT198 inhibition untested						
Arisaematis rhizoma (天南星)	*Arisaema heterophyllum*	High	++	+++	++	+++
Cuttlefish bone (海螵蛸)	*Sepia esculenta* Hoyle	None	+	++	+++	+
Ephedra (麻黄)	*Ephedra sinica*	High	++	+++	+	+++
Gardenia (栀子)	*Gardenia jasminoides* Ellis	Low	++	+++	+++	++
Houttuynia cordata (鱼腥草)	*Houttuynia cordata* Thunb	Low	+	++	+	++
Loquat leave (枇杷叶)	*Eriobotrya japonica*	None	+	++	+	+++
Mistletoe (欧洲槲寄生)	*Viscum album* L.	High	+++	++	+++	++
Nong Ji Li (农吉利)	*Crotalaria sessiliflora* L.	High	++	+	+	+
Plantain peel (芭蕉皮)	*Musa x paradisiaca*	None	+	+++	+	+
Pinellia ternata (半夏)	*Pinellia ternata*	High	+++	+++	+++	+++
Pomegranate (石榴)	*Punica granatum* L.	None	++	+++	+++	+
Radix platycodonis (桔梗)	*Platycodon grandiflorus*	Low	++	+++	++	+++
Rhubarb (大黄)	*Rheum palmatum* L.	Low	+++	+++	+++	+++
Saffron (藏红花)	*Crocus sativus* L.	Low	+++	+++	+++	++
Snakegourd (瓜蒌, 天花粉)	*Trichosanthes kirilowii* Maxim	Low	+++	++	+++	+++
Soursop leave (刺果番荔枝叶)	*Annona muricata* L.	Low	+++	+++	+++	++
Turmeric (姜黄)	*Curcuma longa* L.	None	++	+++	+++	+
Wu Gu Teng (乌骨藤/通光散)	*Marsdenia tenacissima*	Low	++	+	++	+

Herbs are listed in alphabetical order. Herbal treatment evidence in human cancer, inflammation, vascular illness, and pulmonary disease are indicated as: +++, extensive; ++, significant; +, evidence present; –, evidence largely absent.

evidence enabling validations, GT198 has now emerged as an herb target in both cancer and disease. Consequently, a new standard can now be proposed to define solid tumor targets: (I) possess germline or recurrent somatic mutations in their genes; (II) function as Pol II cabinet proteins; (III) regulate stem cells using alternative splice variants; (IV) affect pericytes and descendent lineages in tumor stroma; (V) are inhibited by effective clinical drugs and quadruple-effective herbs.

Identifying an herbal target can be a golden opportunity

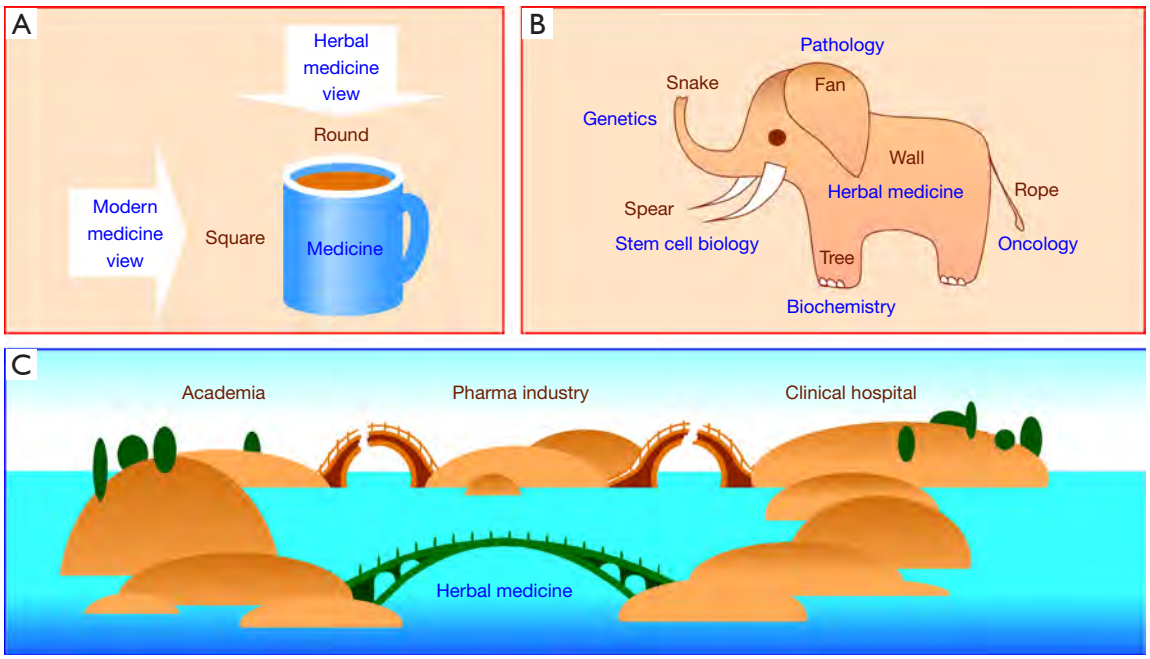

Figure 4 Herbal medicine is a central and integral part of medicine. (A) Herbal and modern medicines reflect distinct views of a single entity of medicine. (B) Biomedical research is an analogy of the Blind Men and the Elephant. Broadened multidisciplinary studies are required to reconcile evidence and to achieve herb target discovery. (C) Herbal medicine is a crossing bridge connecting academia, the pharma industry, and clinical service. The herbal renaissance promotes an advance in biomedicine overall.

to systematically screen, validate, and develop low toxic natural herbal medicines for cancer and diseases. From there, an herbal renaissance may begin.

Reconcile controversies

The finding of GT198 as a target has also explained and reconciled some controversial historical ideas. For example, pathologists traditionally only examined tumor cells but not malignant blood vessels. Geneticists focused on large pedigrees without realizing the impact of stem cells. Cell biologists cultured and analyzed tumor-derived cell lines but not pericyte stem cells. Mouse stem cell biologists did not know that the vulnerable human *GT198* promoter sequence is absent in mice, leaving mice less likely to carry spontaneous tumors with pericyte changes. And finally, clinical oncologists often used cytotoxic drugs resulting in the escape of pericyte stem cells until a metastasis.

Another example is a blurred concept of tumor suppressor versus oncoprotein based initially on their functional gain or loss. Tumor suppressor like p53 has gained in function due to its counter splice variants (25,26). With Yin-Yang balanced transcripts, the two types of tumor suppressor and oncoprotein are actually one. That is unfortunately why no p53 drug has been marketed to date due to unwillingness to inhibit a function thought already lost.

Furthermore, herbal physicians preferred a very low dose of the anticancer herb *Gleditsia sinensis* to avoid toxicity. Our lab observation found a high heat resistance of *Gleditsia sinensis* without activity loss. This is consistent with the ancient description in the book BenCaoGangMu using a high temperature carbonized burn to degrade toxic ingredients in *Gleditsia sinensis* to lower toxicity. Potentially, it could solve more herbal mysteries if we investigate herbal targets in depth.

Crossing bridge with herbs

Herbal medicine is as ancient as humanity itself. It has accumulated an enormous body of clinical evidence throughout the millenarian history of time and from multiple continents of the globe (101). Herbs have been the principal medicine since ancient civilizations, and more than 70,000 plant species have been used during history (102). Herbs contain a great number of beneficial ingredients,

such as phenols, tannins, flavonoids, quinonoids, alkaloids, steroids, peptides, and glycosides. It is possible to find disease-targeting inhibitors within them. Because humans co-evolved together with herbal ingredients in the environment, herbs can be low toxic to humans. In many developing countries today, the herb is the first-line treatment choice for most people (101,103-105).

Despite the long-standing history, after chemical drugs emerged into the market many decades ago, herbal medicine was increasingly disrupted, initially in the West and later in the East (106). Compared to pure chemicals, herbs are hard to study pharmacokinetics and pharmacodynamics. Unpurified natural materials are hard to patent. Unlike synthetic chemicals, raw herbal materials have limits to their natural resources. Modern pharmaceutical giants often shy away from low-profit margin herbal medicines. All increased the challenges of herbal research and development.

Chemical drugs, however, are by no means superior to herbs. Not only chemicals could be toxic to our bodies, and the treatment efficacies are not necessarily better. When we compared a collection of most commonly used anticancer chemotherapy drugs to a few anticancer herbs, we already found none of the chemical drugs perfect (8). They have either poor efficacy like paclitaxel or poor affinity like doxorubicin in inhibiting GT198. In contrast, anticancer herbs allspice and *Gleditsia sinensis* showed both high affinity and high efficacy. They can be developed into effective herbal medicines and purified chemical drugs in the future.

A current major hurdle in herbal medicine may not be a scientific but political one. Our health system has three interconnected sectors: academic institutions, pharma industries, and clinical hospitals. They become increasingly disconnected like three isolated islands (*Figure 4C*). Academia competed on government funding in limited directions often excluding herbal studies. Pharma industries favored chemical drugs for many decades with herbal expertise gradually lost. Clinical services suffered from limited choices of approved drugs. In order to overcome these disconnections and reunite the three sectors again, an herbal crossing bridge is essential and timely needed (*Figure 4C*). Ideally, disease drug targets developed from academia can be first tested in a large number of herbs carrying clinical evidence. Herbs verified by targets will then be further developed into approved herbal medicines. Chemical drugs can further be purified from approved successful herbal medicines with targets available to aid the purification process. Artemisinin, aspirin, and paclitaxel are among many historical examples of success in which chemical drugs were purified from herbs. When herbal targets are systematically investigated, a renaissance in herbal medicine will undoubtedly accelerate the advance of modern medicine.

The herbal target discovery is only an emerging tip of the iceberg. Future herbal target identifications will reunite modern and herbal medicines to achieve greener healthcare.

Summary

Herbal medicine has been a foundation for modern medicine to advance. Its ample clinical evidence is a treasure indispensable to current medical knowledge. For common illnesses, including cancer, cardiovascular, respiratory, inflammatory, neurological diseases, and diabetes, herbal molecular targets could be hidden in stem cells. Through a multidisciplinary approach, a stem cell target of herbs is now found. A unified theory of cancer and disease has emerged. Many historical controversies are reconciled. It also reveals a new concept to explain multi-functional herbs since their target is likely shared. Unlike previously drug target validations with limited scopes in existing molecular mechanisms, future target validations can be conducted using enormous herbs evidenced in clinical success. The validated herbal targets can subsequently aid the future development of herbal medicines and chemical drugs. This strategic approach represents an herbal crossing bridge (*Figure 4C*), to reunite modern academic achievement with traditional herbal wisdom worldwide. It may promote an herbal renaissance and accelerate a leap forward of undivided biomedicine.

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Footnote

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