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NON-THEMATIC REVIEW

A new hypothesis for the cancer mechanism

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Abstract Several observations have led us to a new hypothesis for cancer mechanism. First, that cancer appears only on those multicellular organisms with complicated wound-healing capacities. Second, that wounds considered as risk factors can be identified in all cancers in clinics. And finally, that oncogene activation appears not only in cancer, but also in normal physiology and noncancer pathology processes. Our proposed hypothesis is that cancer is a natural wound healing-related process, which includes oncogene activations, cytokine secretions, stem cell recruitment differentiation, and tissue remodeling. Wounds activate oncogenes of some cells and the latter secrete cytokines to recruit stem cells to heal the wounds. However, if the cause of the wound or if the wound persists, such as under the persistent UV and carcinogen exposures, the continuous wound healing process will lead to a clinical cancer mass. There is no system in nature to stop or reverse the wound healing process in the middle stage when the wound exists. The outcome of the cancer mechanism is either healing the wound or exhausting the whole system (death). The logic of this cancer mechanism is consistent with the rationales of the other physiological metabolisms in the body—for survival. This hypothesis helps to understand many cancer mysteries derived from the mutation theory, such as why cancer only exists in a small proportion of multicellular organisms, although they are all under potential mutation risks during DNA replications. The hypothesis can be used to interpret and guide cancer prevention, recurrence, metastasis, *in vitro* and *in vivo* studies, and personalized treatments.

Keywords Wound · Oncogene · Wound healing · Cancer · Mechanism

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1 Background: current cancer theories and questions

Given that cancer has not yet been cured, many hypotheses or theories have been proposed since the beginning of the last century (Fig. 1). These theories include cancer is caused by viruses [1], chromosomal abnormalities [2, 3], somatic mutations [4], accumulated multiple mutations [5], immunological surveillances [6, 7], nonhealing wounds [8], non-mutagenic mechanisms [9], and tissue organization field theories [10].

Current prevalent cancer theories hold that cancer is an uncontrolled somatic cell proliferation caused by the progressive accumulation of random mutations in critical genes that control cell growth and differentiation [11–13]. The immunosurveillance theory plays a supplemental role to the above mutation theory. When the mutation escapes immunosurveillance successfully, a clinical tumor will form

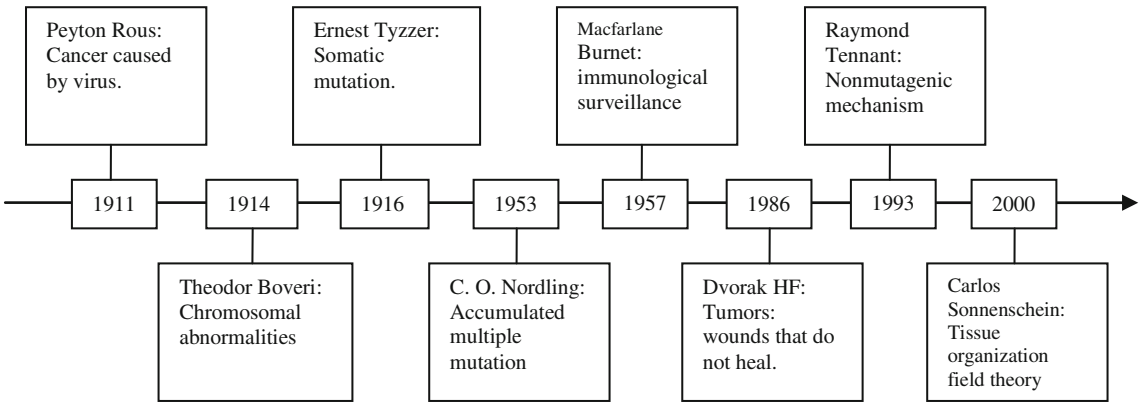

Fig. 1 Timeline of cancer hypothesis or theories

[7]. However, various paradoxes related to the mutation theory have been reported previously, such as a slower proliferation rate of cancer cells than that of normal cells, silent metastatic tumors, normal tissue formation by injecting teratocarcinoma cells into normal blastocysts, cancer formation by transplanting normal murine ovary tissue into the spleen, and spontaneous regression of cancers [10, 14]. In addition, mutation theory cannot explain the following phenomena:

1. If only one mutation causes cancer, the chance for cancers to form is too great. Mutations require cell divisions. There are 10^{12} stem cell divisions per day in the adult human body [12]. If the point mutation rate is 1.1×10^{-8} per cell division [15] and cancer is caused by one point mutation [3, 16], then the theoretical cancer occurrence in everybody would be exceptionally high: 1.1×10^{4} point mutations or cancers daily (10^{12} stem cell divisions $\times 1.1\times 10^{-8}$ point mutation/cell division), meaning everybody would have the chance of 10,000 cancer cells to form daily. This is obviously not the case. Therefore, a multiple step mutation cancer theory (mutation–latent–mutation… to a cancer) [5] and DNA repair theory were developed to match the actual cancer incidence [12].

   Form another perspective, the chance for cancer is too small if multiple specific mutations cause cancer. If cancer forms from five independent point mutations [11], the theoretical cancer occurrence would be $10^{12}\times(1.1\times 10^{-8})^{5}=1.61\times10^{-28}$ daily per person or $10^{12}\times(1.1\times 10^{-8})^{5}\times365\times120=7.05\times10^{-24}$ for a 120-year-old person. It is equivalent to the chance of one cancer case in 1.42×10^{23} people, meaning no one would get cancer in the world. In clinics, 5~10 specific genetic alterations, or even 11,000 genomic alterations per cell were reported for a sporadic colorectal cancer [17–19], leading to the question is mutation the cause or the result of a cancer? Similarly, if the same gene mutation and same expressed proteins are prevalent in a group of cancer patients (e.g., deletions of CDKN2A in bone tumor cell lines [20], p53 and Rb mutations in small cell lung cancer [21]), or in multiple cancer types (e.g., phosphatase and tensin homolog aberrations on various cancers [22]), the chance of random mutation to cause those cancers simultaneously should be impossible in theory.
2. Mutation theory does not explain the time difference to cause cancer in various organisms. More than 50% Sprague–Dawley rats will develop a spontaneous tumor in 2 years [23] and this occurrence is far less than one per million in humans at 2 years old [24]. The doubling times of bone marrow derived stem cells from humans and rats are 25.2 h [25] and 31.5 h [26], respectively. The division rate of human cells is not slower than that of rat cells, indicating that the chance for DNA replication mistake in human cells is not any less than that of a rat's. From the mutation theory alone, humans have no reason to show much lower cancer incidence rate than rats with the same DNA replication time. Similarly, accumulated mutations cannot explain why the cancer occurrences are not correlated with the lifespan among different biological species, e.g., thousands of year old trees without cancer versus a 12-day-old *Drosophila* with cancer, although they have the same DNA replication mechanisms [27, 28] and similar environmental risks that can cause mutations. Furthermore, from the fact that cancer exists in some multicellular organisms but not in the others, mutation should not be the necessary premise of cancer since all multicellular organisms have potential mutation risks during DNA replications, while cancer only exists in a small proportion of them.
3. Multicellular organism cells from two different species in the same potential mutation environment have different outcomes on cancerization. Many schistosome-related human bladder and prostate cancers are reported [29], while no cancers can be found in the schistosome itself, although it has the same potential risk of mutation

from the same cancer environment. If schistosomiasis-associated bladder cancer is caused by the human p53 mutation [30], why does the same environment never hit the schistosome's p53 gene [31] and develop cancer in the schistosome?

4. Cancer recurrence also cannot be explained by mutation theory. Supposing one live cancer cell survives after surgical, chemo, and radiation therapies, another cancer mass with 1×10^{12} cells (about 1 kg) can be formed within 80 days if the cell doubling time is 48 h [32]. If all cancer cells are killed by the above standard therapies and new cancer cells are produced by the accumulated mutation again, according to the mutation theory [11], dozens of years will be needed to develop like the first one. However, this does not match the clinical recurrent cases, e.g., most breast cancers recur in 5 years [33].
5. Neither mutation theory nor immunosurveillance theory can explain the cancer incidence rate turnaround at very old ages in mice (>800 days) [34] and humans (>85 years) [24, 35, 36]. If mutation and failures of immunosurveillance or the DNA repair are the causes of a cancer, the aging cells in very old bodies should have much more chances of developing cancer. One explanation to this incidence turnaround is the natural selection that allows the less cancer-prone population to survive—the survivors at an old age are not susceptible to cancer [36]. However, this mechanism, if it exists, conflicts with why there is no such phenomenon on other aging diseases (such as heart disease) [37].

2 Deduction of a new cancer mechanism

There are two possibilities for the relationship between gene mutation and cancer: first, gene mutation is the cause of a cancer as mutation theory claims, or second instead of being the cause, gene mutation is an intermediate process or a result of a cancerization. Due to many unfit phenomena by the mutation theory, a better cancer etiology should be considered.

2.1 Wounds as risk factors in cancer

Cancer is accompanied by oncogene activations, which are also involved in the wound healing process. If a wound is defined as cellular deaths caused by physical damages (radiation, electromagnetic field, trauma, particles, etc.), chemical damages (carcinogens, toxic chemicals, heavy metals, etc.) and biological damages (inflammations, microorganism infections, free radicals, nutrient deficiency, aging, stress, etc.), wounds considered as risk factors are able to be identified in almost all cancers in clinics. This would include chronic inflammation and prostatitis to prostate cancer; virus infections and trauma to breast cancer; smoke-induced lesions to lung cancer; chronic ulcerative colitis to colon cancer; UV damages to skin cancer; and virus infections, radiation, electromagnetic field to leukemia (Table 1). A study showed that the Rous sarcoma virus induced tumors only at the wound and inflammation sites even though the viruses were circulating in the blood, and the anti-inflammatory agents could inhibit the tumor [38]. Another study even showed that transgenic mice with inflammatory genes, LPA and ATX, would have higher incidence of mastitis followed by breast cancers, which was consistent with clinical situations [39, 40]. These broad correlations between wounds and cancers indicate two possibilities: wounds induce cancer or cancers deal with wounds.

2.2 Oncogenes in wound healing

If oncogenes are defined as the genes that exist in the normal cells [41] and can transform normal cells into cancer cells when over-expressed (or tumor suppressor genes in opposite ways) [42–44], at the molecular level, many oncogenes (if not all) found in cancers are also found to be active in the early wound-healing process to proliferate repair cells. The tumor suppressor genes that are inactivated in cancer are found to be inactive in the early wound healing and active again in the late wound healing process to stop the repair cell proliferation (Table 2). These oncogene activities in the wound healing indicate that oncogene mechanisms also play important roles in the wound healing. If cancer is an outcome of oncogene over-expression, it is possible that a cancer cell is an assembly of activated oncogenes which plays a role to help heal the wound. This hypothesis is supported by the study that the plasma from a tumor-bearing mouse heals the wound much faster than that from a normal mouse [45].

2.3 Cancer appearances in multicellular organisms

Expanding to a broader view, most multicellular organisms on earth are free of cancer, although they all have the same DNA replication mechanisms (Table 3). From simple to complicated species, the wound healing process are also from the simplest (without original wound recovery) to the intermediate complexities (cell migration, differentiation and regeneration), to the most complicated wound healing processes (processes involved in the former plus inflammation responses, stem cell recruitment, and tissue remodeling, etc.). Cancer incidences coincide with the complexities of the wound healing. The more complicated the species, the more functions and specifically differentiated tissues, the more complicated the wound healing process. At a certain level of complexity in wound healing, especially with the process of inflammation and stem cell recruitment (not regeneration), the cancer appears in the creatures whether

Table 1 Cancers and the wounds considered cancer risk factors in humans

Cancer	% of all sites [107]	Wound related
Prostate cancer (M)	25%	Inflammation [108], chronic prostatitis [109], virus infections [110–112]
Breast cancer (F)	27%	Virus infections [113], chronic inflammation [114], electromagnetic field (EMF) [115], breast trauma [116]
Lung and bronchus	14.5%	Chronic inflammation and lesions by smoke [117–119], virus infection [120, 121], trauma predispose to metastasis [122], particles [123]
Colon and rectum	10%	Inflammation [109, 124], Crohn's disease and chronic ulcerative colitis [125]
Urinary bladder (M)	7%	Parasite infection [126], cystitis [125]
Uterine (F)	6%	Cervical erosion [127], chronic inflammations [128]
Skin cancer	4.5%	UV from the sun [129, 130]
Non-Hodgkin lymphoma	4.5%	Hygiene and infections [131], HCV infection [132], mononucleosis [125], EMF [133]
Kidney and renal pelvis	4%	Infection [134]; Increased survival on treatments of inflammation [135]
Thyroid (F)	4%	Thyroiditis [136, 137]
Leukemia (M)	3%	Virus infections [138–141], radiation [142, 143], EMF [133]
Oral cavity and pharynx (M)	3%	Gingivitis, lichen planus [125]
Ovary (F)	3%	Pelvic inflammatory disease, chronic cervicitis [125, 144]
Pancreas	3%	Chronic pancreatitis, hereditary pancreatitis [125]
Brain and nervous system	1.5%	Inflammation [145], infections [146], head trauma on meningioma [147], EMF [133]
Liver cancer	1.5%	Inflammation [108], sarcoidosis [109], parasite infection [126], alcohol intake [126].
Gall bladder cancer	0.7%	Chronic cholecystitis [125]
Gastric cancer	1.4%	Gastric ulcers [148], helicobacter pylori infection [149],
Esophageal cancer	1.1%	Reflux oesophagitis, Barrett's esophagus [125]
Hodgkin lymphoma	0.6%	EBV infection [150], various infections [151]

The percentages were from the estimated new cases in 2009 from reference [107]. *M* male, *F* female, and no indication represent both. The bottom six cancers were calculated from Table 1 and the others were from Fig. 1 of reference [107]

or not their life spans are longer or shorter. This phenomenon implies that nature has selected a common mechanism for wound healing for the complicated species, which is related to cancer.

All of the above relationships between wound healing and cancer at evolution, diseases, and molecular levels strongly indicate one possibility: the wound signaling molecules cause over-expression of the existing oncogenes (and some other genes), leading to the changes of certain chromosomes and cancer cell phenotypes [42], while all the normal cell oncogene (not limited to oncogenes) activities responding to wounds are just a part of the cell's natural metabolism for survival. Therefore, a new cancer theory can be logically speculated: cancer formation is a natural process that organisms have used in wound healing.

2.4 Cancer mechanism on mammals

The following scenario of wound–oncogene–wound healing (WOWH) is described for the cancer mechanism on mammals (Table 4; L1–10). When defined wounds occur in mammals, the body starts the complicated, inflammatory, and stem cell involved wound healing (L1). Molecules such as growth factors, cytokines, and other proteins from the cells in the wound area interrupt the balance of normal molecular metabolism (L2), leading to the activation of corresponding oncogenes (Table 2) and inducing cancerization in some cells (stem cells or actively dividing cells, L3). The cells with activated oncogenes can secrete molecules to recruit stem cells, stimulate stem cell proliferation, and enhance cell differentiation to repair the wound (L3, L4; Fig. 2A). Oncogenes are activated in the early stages of the wound and tumor suppressor genes are activated in the late stages or the healed wound. Mostly, the wound is healed after above efforts. Oncogenes are deactivated and tumor suppressor genes are activated, then the metabolism reverts to normal (L5; Fig. 2B). However, if the wound conditions are still persistent (such as in the situations of constant UV and carcinogen exposures, and chronic inflammations by microorganisms), this WOWH mechanism will not stop. Oncogenes will be activated continuously and more cancer cells (over-activation of the oncogenes transformed normal cells into malignant cells [43, 44]) are divided to secrete more molecules for wound healing, forming a clinical cancer mass (L6; Fig. 2C). After the wound is healed, the molecules of a healed environment initiate cancer cell differentiation (L7) or apoptosis (L8). Subsequently, the clinical cancer mass will be gone (Fig. 2D). However, if a small clinical cancer cannot heal the wound, the cancer mass will

Table 2 Oncogenes and tumor suppressor genes found in cancer and in the wound healing process

Genes	Genes in cancer	Gene functions in wound healing process
Akt1	Breast [152]	Acute skin repair was characterized by an increase of Akt1 phosphorylation in wound margin keratinocytes [153]
Bcl-2	Breast cancer [154]	The expression of Bcl-2 protein decreased as the apoptosis reached a maximum and increased gradually in the process of wound healing [155, 156]
BRCA2	Breast, ovary [157]	A tumor suppressor gene, repaired damaged DNA [158, 159]
β-catenin	Colon [160]	Inhibited keratinocyte migration and activated fibroblast proliferation. The size of the wounds in the mice correlated with the protein level of ß-catenin [161]
EGFR	Lung, colon, glioblastoma, pancreas [162]	Regulated multiple facets of cutaneous wound healing, including inflammation, wound contraction, proliferation, migration, and angiogenesis [163]
Ets-1	Ovarian [164]	Ets-1 accumulated in migrating cells at the wound edge and returned to basal level when reendothelialization was accomplished [165]
c-fos	Prostate [166]	Expressed in epithelia in early stages [167]; involved in the healing of gastric ulcers [168]
FGFR3	Myeloma [162]	FGFRs played crucial roles in the repair of skeletal tissues [169]
GROα	Breast cancer [170]	At day 1 after injury, growth-related oncogene α were maximally expressed in the superficial wound bed and were spatially and temporally associated with neutrophil infiltration. It correlated with keratinocyte migration and subsequently subsided after wound closure at day 4 [171]
Her-2	Breast, lung, ovarian [162]	Depletion of functional Her-2 attenuated the healing of scratch wounds [172]
c-Jun	Prostate [173]	Expressed in epithelia in early stages165; Increased in apoptotic cells of wound healing [174]
c-met	Gastric, lung [162]	c-Met signaling not only controlled cell growth and migration during embryogenesis but was also essential for the generation of the hyperproliferative epithelium in skin wounds, and thus for a fundamental regenerative process in the adult [175]
c-myc	Lymphoma, Leukemia [162]	Deregulation of c-myc depleted the epidermal stem cells, causing the inability of the tissue to react to injury [176]. c-Myc promoted differentiation of human epidermal stem cells [177]
MMP-7	Colon [160]	Involved in intestinal re-epithelialization *in vivo* and upregulated by cytokines relevant in wound repair [178]
p53	Cervical, multiple [162]	A tumor suppressor gene. It was decreased in the first 2 days after wound, increased in 3–5 days and returned to normal after 9 days on the swine skin wound healing process [179]
p63	Invasion and metastasis [180]	A tumor suppressor gene. It was silent in the early days, but activated in later time on wound healing process [181]
PDGFR	Glioma, gastrointestinal [162]	Platelet-derived growth factor (PDGF) isoforms stimulated cell proliferation, migration and survival. The hyperactive PDGFR-ß mainly affected the early proliferative response after injury [182]
PI3K	Breast [183]	The impairment of PI3K/AKT pathway is a key factor contributing to the delayed epithelial wound healing in diabetic corneas [184]
PTEN	Gliomas [162]	A tumor suppressor gene. Injury to the cornea downregulated PTEN expression and contributed significantly to enhance cell migration in wound healing [185]
Raf-1	Ovarian [186]	Raf-1 is required for normal wound healing *in vivo* and for the migration of keratinocytes and fibroblasts *in vitro* [187]
Ras	Pancreatic, thyroid, colon [162]	Activation of Ras led to wound epithelialization [188]
Sox-2	lung and esophageal [189]	Skin-derived precursors derived from Sox2(+) follicle-associated dermal precursors and displayed functional properties predicted of a dermal stem cell, contributing to dermal maintenance, wound-healing, and hair follicle morphogenesis [190]
Src	Breast [191]	Src was activated in cells along the wound edge and blocking this activation with the Src kinase inhibitor, PP1, inhibited wound closure by 85% [192]
VEGF	Tumor angiogenesis [162]	Contributed to neovascularization during wound healing [193]

Table 3 Multicellular species with and without wound healing capacity and cancer

Species	Lifespan	Wound healing	Cancer
Plant, e.g., pine	~1,500 Years [194]	Response to stop further damage only. No recruited cells and no original wound recovery [195]	No[a]
Porifera, e.g., sponge	4 Years [196]	Mesohyl cells infiltrated and proliferated [197]. No cell recruitment found	Hard to find[b]
Cnidaria, e.g., jellyfish	1 Year [198]	Cell migration and differentiation to heal small wounds. No cell proliferation [199]	Hard to find
Hydrozoa, e.g., hydra	~Immortal [200]	Cell proliferation, differentiation and regeneration [201]	Hard to find
Annelid, e.g., earthworm	8 Years [202]	Completele regeneration from amputation by blastema [203]	Yes [204] but scarce
Arthropod, insect, e.g., Drosophila	12 Days [205]	Melanin and hemocyte clot, epithelial cell migration, stem cell proliferation, and tissue reorganization [206–208]	Yes [205, 209]
Chordate, actinopterygius, e.g., Zebrafish	~66 Months [210]	Blood cell migration, recruitment, and inflammation; stem cell proliferation, recruitment, differentiation, and angiogenesis [211–214]	Yes [215]
Amphibia, e.g., newt	30 Years [216]	Stem cell proliferation, recruitment, and differentiation, complement reactions, and regeneration [217, 218]	Yes but difficult [219]
Aves, e.g., chicken	7 Years [220]	Stem cell proliferation, recruitment, differentiation, inflammation, and angiogenesis [38, 221]	Yes [38, 222]
Mammal, e.g., mouse and human	mouse: 2.7 years [34] Human: 110–120 years [24]	Blood coagulation and fibrinolysis; inflammation response; stem cell proliferation, recruitment and differentiation; angiogenesis; extracellular matrix and tissue remodeling [8, 171, 223, 224]	Yes, many

[a] The plant gall (also called "plant tumor") is a parasitic interactions between plants (host) and agrobacteria [225], fungi [226], and insects [227]. The agrobacteria insert a segment of DNA into plant cells [228], which is not like the cancer cells that originate from normal cells in mammals

[b] "Hard to find" means the item is hard to be found on the Internet, indicating the case is rare and hasn't been noticed or studied intensively

Table 4 The logic of hypothesis for cancer mechanism

Logic	Published studies on mammal cells	Indication
L1	Human and mouse wound healing involved reepithelialization, epidermal differentiation, cell migration, proliferation, inflammatory response as well as dermal closure, matrix distribution, and skin remodeling [223] Healing of cutaneous wounds required a complex integrated network of repair mechanisms, including the action of newly recruited leukocytes [171]	Wound healing in mammal is a complicated procedure
L2	Many molecules were highly expressed or secreted, and involved in the process of wound and wound healing, including Bcl-2, Bcl-XL, fas-fas ligand, TNF-TNF receptor, p53, caspases, etc. [229] T lymphocytes infiltrated wounds and tumors, synthesized and exported two well-characterized growth factors, heparin-binding epidermal growth factor-like growth factor (HB-EGF) and basic fibroblast growth factor (bFGF), mediating fibroblasts and smooth muscle cells formations in the angiogenesis associated with wound healing and tumor growth [230] Cytokines produced by or carried within platelets could be released at sites of vascular injury and participate in wound healing [231] Human γδ-T cells secreted connective tissue growth factors during wound healing [232]	Many growth factors, cytokines, and other proteins are highly expressed or secreted during the occurrence of the wound and wound healing. Those molecules also appear in cancer
L3	Wound fluids, especially on early time (day 1) promoted tumor growth on mice [68] Substance–P, SCF, IL–1 and VEGF were markedly induced after alkali burn at mouse eye as well as peripheral blood. Substance–p was the early cytokine induced by alkali burn wound and stimulated cell proliferation and mobilization of mesenchymal stem cells [233] c-Fos- and c-Jun-immunoreactive cells were detected in the epithelial cells and keratocytes around the experimental physical and chemical cornea injuries on rats [234]	Wound activated oncogenes and induced cancerization
L4	In a murine experimental glioblastoma model, endogenous neural precursors migrated from the subventricular zone toward the tumor, surrounded it, and induced glioblastoma cell apoptosis [235] During wound healing, quiescent corneal keratocytes surrounding the injured region differentiated into fibroblast or myofibroblast phenotypes that mediate cell migration, wound contraction, and matrix remodeling. In a 3D culture model of the corneal stroma, TGF-β induced the corneal keratocytes to differentiate into myofibroblasts, and PDGF stimulated significant keratocyte migration [236]	Tumor cells recruit stem cells to the tumor sites. Cytokines migrate and differentiate cells in the wound healing
L5	Fifteen min after the rat cornea epithelial ablation, weak signals for c-fos and c-jun mRNAs were detected in the corneal epithelium surrounding the wound. These signals reached a peak 30–60 min after ablation, but were no longer evident at 120 min [167] p53 expression was decreased to negative in the first 2 days after wound, increased in 3–5 days and returned to normal after 9 days on the swine skin wound healing process. In contrast, the oncogene PDGFR expression was negative before wound and increased 6 h after wound, peak at 1–3 days and returned to normal 9 days after wound [179] In the first day after the human skin wound, there was a dramatic downregulation of p63 expression in wound area. Five days after the injury, induction of p63 in the basal keratinocytes could be detected, followed by a gradual increase of its expression in subsequent days. Several days after complete wound closure, p63 was still strongly expressed not only in the basal keratinocytes but also in the entire spinous layer, whereas the Ki67 expression was restricted to single cells in the basal layer [181]	Oncogenes express in the early stage of a wound. Tumor suppressing genes express in the late stage of a wound. After the wound healing, those genes are back to homeostasis. Cancer secretes molecules with the power to heal wounds in the body

Table 4 (continued)

Logic	Published studies on mammal cells	Indication
	The plasma from tumor-bearing mice healed the wound faster than the plasma from normal mice [45]	
L6	Chronic inflammation and persistent wound healing reactions in large and small bile ducts often lead to liver cancer [237]	Chronic wounds make oncogenes highly expressed. Oncogenes transform some cells into cancer cells. Cancer cells secrete molecules that help to heal wounds
	The level of both c-fos and c-Ha-ras mRNAs were heavily induced in the basal layer of epidermis in chronic wounds when compared to normal skin and acute wounds [238]	
	c-Ki-ras oncogene was frequently activated in mucous cell hyperplasias of pancreas suffering from chronic inflammation [239]	
	The activated Ras oncogene transformed various mammalian cells and had been implicated in development of a high population of malignant human tumors [240]	
	Platelet-rich plasma obtained from healthy (PRP) or tumor-bearing (TPRP) mice was applied to dorsal, full-thickness wounds on diabetic mice. TPRP-treated wounds reached 90% wound closure 5.6–9.5 days earlier than PRP-treated and nontreated wounds, respectively [45]	
L7	After corneal injury, the neurotrophic factor PEDF was increased in the media at a relative late wound stage (48 h) [241]	Some molecules appeared in the wound healing play a potential role in promoting differentiation of cancer cells
	PEDF blocked angiogenesis and induced differentiation in prostate cancer [242]	
	FGF-2 increased after wound closure and inhibited the early increased TGF-β. TGF-β increased the stromal cell migration for wound healing [243]	
	Intracellular FGF-2 significantly inhibited the migratory potential of T-47D breast cancer cells and promoted those cell differentiations [244]	
L8	PEDF induced endothelial HUVEC apoptosis through the sequential induction of PPARgamma and p53 overexpression [245]	Some wound healing molecules induced apoptosis of angiogenesis and cancer cells
	Overexpression of FGF-2 downregulated the oncogene Bcl-2 and promoted apoptosis in MCF-7 human breast cancer cells [246]	
L9	Necrotic cells were characterized by the loss of membrane integrity, organelle swelling, lysosomal leakage, and inducing a significant inflammatory response [229]	Necrosis occurs during the cancer mass expansion due to the nutrient deficiency and hypoxia
	Cancer cell expansion, remodeling and regression induced apoptosis and necrosis due to the nutrient deficiency and hypoxia [247]	
	Hypoxia induced both apoptosis and necrosis through the pathways of HIF-1 and NIP3 [248]	
L10	Spontaneous regression of cancer was reported in virtually all types of human cancer [249]	The existence of spontaneous regression of cancer indicates that cancer, even an advanced one can be a reversible process
	Spontaneous regression was reported on multiple sites of melanoma [250]	
	A complete clinical spontaneous regression was reported on a lung cancer with metastases of abdominal wall, liver, and lung [251]	
	Approximately one half of all cancer patients experienced a complex metabolic status involving progressive exhaustion of adipose and skeletal muscle tissue–cachexia [252]	

grow large and some part of the cancer itself will be necrotic (inducing inflammation—a new wound) due to the lack of nutrients and oxygen (L9). Both the original and new wounds will induce more cancerization and lead to a positive feedback loop until the wounds are healed or the whole system is exhausted (L10; Fig. 2E).

3 Further interpretations of WOWH mechanism

3.1 Dilemma of the cancer mechanism for survival

All of the above WOWH processes are delicately regulated by molecular feedbacks among the wounded cells, inflammation

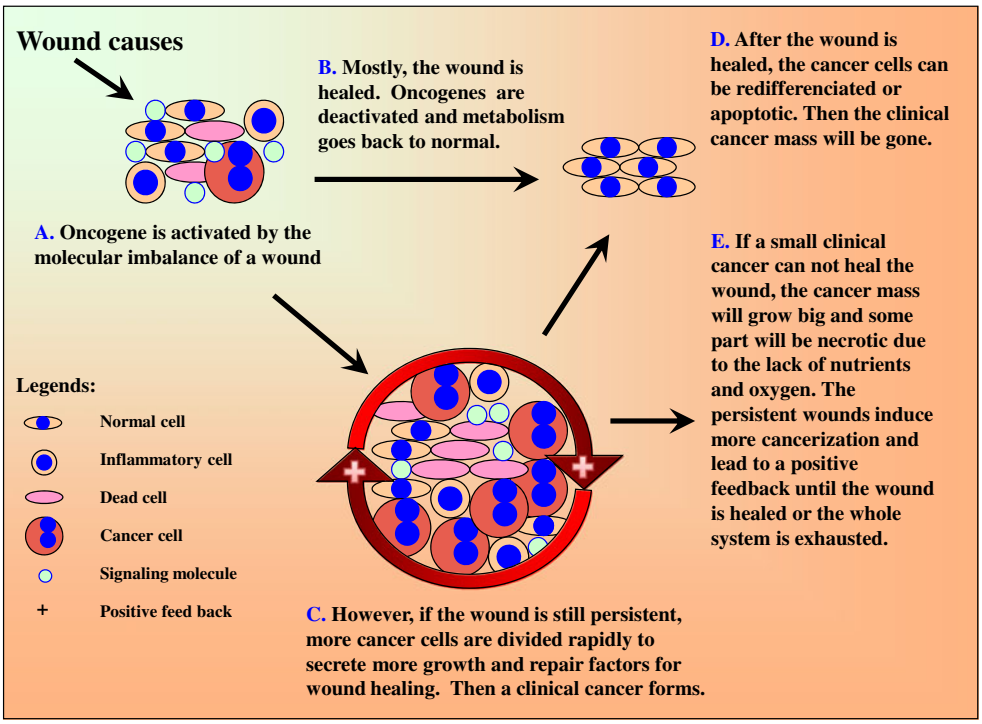

Fig. 2 A scheme of the wound–oncogene–wound healing mechanism

cells, cancer cells, stem cells, extracellular matrix cells, and healed cells. The more signaling molecules secreted from wounded and inflamed cells, the more cancer cells respond. The more signaling molecules secreted from healed wound, the more cancer cells stop working (Table 4, L1–10). Different wounds activate different oncogenes and induce different cancers to produce different molecules for wound healing. This WOWH mechanism is developed incredibly well except for one defect: if wounds persist (such as under chronic microorganism infections, chronic cervical erosion, etc.), the cancer mass will grow larger and larger without a natural mechanism to stop the positive feedback loop in our system until the whole system becomes exhausted (death). The logic that normal cells control themselves on developments, wound healing, and ensuring a homeostasis after the process is understandable [46]. However, if wound causes and wounds persist, then what possible mechanisms could nature use to heal the wound? Continue fighting? Reverse the process? Facing the persistent wounds, natural selection seems to have no better choice in logic besides fighting the wounds until the system becomes exhausted since the chances of the natural regression of late-stage cancer do exist (Table 4; L10). More importantly, breaking this positive feedback loop at some point, e.g., at late stage of a cancer, means all the molecular responses to the wound must be stopped or reversed, leading the logical problems for survival—no response or reversal responses to wounded and aging cells in membranes, skin, liver, blood cells, and the other fast metabolized tissues. A study showed the attempts to generate mice that over-express wild-type p53 gene were unsuccessful on embryo development, while the partial p53 activated mice exhibited enhanced resistance to spontaneous tumors. However, at the same time, they displayed an early onset of aging in their lives, including reduced longevity, osteoporosis, generalized organ and tissue atrophy, retarded wound healing, and less stress tolerance [47].

3.2 Cancer incidence turnover at very old age

When cancer is considered as a functional repair tissue for wound, the mystery of cancer incidence turnaround at very old age can be explained: wound incidence increases along with age due to the accumulation of injuries, inflammations, infections, toxins, and cell aging [48]. The wound healing ability decreases along with age due to cellular aging [49, 50]. Cancer, as a functional wound healing tissue, increases due to the increased wound incidence along with age, but decreases due to the exhausted wound healing ability at very old age (Fig. 3). The lower cancer incidence rate in women versus men [24] can also be explained by the higher wound healing ability in women [51].

3.3 Other unexplainable phenomena above

The other unexplainable phenomena by mutation theory above can be explained by the WOWH mechanism: (1) The chance to have a clinical cancer is not dependent on gene mutation numbers, but on the underlying wounds and the

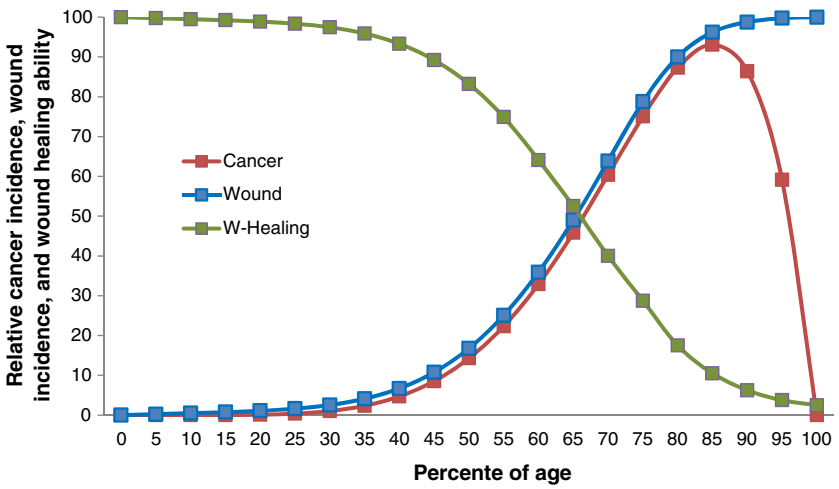

Fig. 3 Relationship of wound incidence (*blue*), wound healing ability (*green*), and cancer incidence (*red*) with age in mammals. Wound incidence increases and wound healing ability decreases along with ages. Cancer, as a functional wound healing tissue, its incidence increases due to the increased wound incidences along with the age, but decreases due to the exhausted wound healing ability at very old ages. All data points are descriptive according to the references of [24, 48–50]

wound healing capacity. Multiple wound causing factors will induce multiple pathways of cancerization to fight the wound. (2) The time difference of cancer incidence among species is due to the different cellular aging time among species. The aging cellular environment is one of the causes of the biological wounds in mammals and the WOWH mechanism will be initiated along with more and more aging cells in the mammal lifespan instead of the accumulated mutation time. (3) The reason different creatures have different outcomes on cancerization in the same potential mutation environment is because they have different wound healing mechanisms. The ones without the WOWH mechanism will not develop a cancer in the mutation environment. (4) The cancer recurrence pace depends on the underlying wounds and the personal wound healing ability. Persistent wounds (induced from stress [51], diet [52], air pollution [53], etc.) will speed up the recurrence pace.

3.4 Healing mechanism other than healing mistake

The commonalities of wound healing and cancer indicate two possibilities: One is that the process approaches the wound incorrectly, leading to wounds that do not heal, or cancer [8, 54]. The other is that nature developed a process to heal the wound—the WOWH mechanism accompanied the wound all the time (Fig. 2). The first possibility fits the situation of the positive feedback loop described above. However, if the oncogene activations are investigated on a broader scale, such as in pregnancy [55, 56], embryonic development [57, 58], menstruation [59], bone and teeth development [60, 61], as well as wound healing (Table 2), the commonalities of the those oncogene activities indicate the molecules with the same functions exist in both normal and cancer states, rather than a mistake programming *de novo* in cancer. Gene mutations were not only in cancer cells (at a higher rate), but also in benign hyperplasia or precancerous diseases (at a lower rate) [19, 62, 63], indicating that gene mutations in cancer should be the result of the tissue adaptations rather than the causes of a cancer. Since cancer only appears in species with relatively complicated wound healing, and overall women have about half cancer incidences less than men [24], this indicates that cancer is not from a simple random mutation or a programming mistake. On all of these aspects, the explanations from WOWH mechanism fit better. The cancer mysteries above and applications below can be understood better and united together only when cancer is considered as an active wound healing tissue. The study that plasma from tumor-bearing mice healed the wound faster than plasma from normal mice [45] is direct evidence that cancer secretes molecules with the power to heal wounds in the body.

4 Applications of WOWH mechanism

4.1 Cancer treatment

The capability to distinguish cancer as functional or a mistake tissue is very important for cancer treatment strategy. If cancer is from a mistake in cellular programming, killing cancer cells is the only choice to treat the disease. However, if cancer is a part of the wound healing procedure, killing cancer cells alone may not lead to a cure. A new cancer mass will grow up after the previous one is removed [64]. A new signaling pathway will be activated after the previous one is inhibited [65]. As long as the underlying wound exists, WOWH mechanism will respond to it until the wound healing power is exhausted. Furthermore, the molecules in signaling pathways are not singly linked to each other. Each of them communicates with many other molecules simultaneously in the signaling networks [66]. Blocking one or two elements of the networks may delay the signal flows for a while but cannot block them completely, as long as wounds exist. In other words, destroying cancer

cells without healing the underlying wounds will allow for an eventual recurrence since the cancer mechanism developed by nature cannot be destroyed in a live mammal. This may be the reason why survivals of cancer patients with metastasis have not changed significantly over the past several decades for the four most common cancers (lung, breast, prostate, and colon cancers) [67]. Therefore, cancer treatment strategies should be focused on the treatments of underlying wound and molecular imbalances after breaking the positive feedback loop by the current standard therapies (surgery, chemo and radiation; Fig. 4). The unknown underlying wounds and personalized molecular differences make the approaches of the cancer cure much more difficult than the traditional standard therapies but it is the only approach to cure cancer. It depends not only on major drug treatments but also on other factors that possibly affect wound healing, such as stress, diet, environment, lifestyle, etc. Cancer curing is a personalized multidimensional homeostatic process at molecular level (Fig. 5). By understanding the WOWH mechanism, the cancer spontaneous regression (Table 4; L10) can be explained and it can be considered as the extreme example of cancer cure by correct overall molecular balances. Treatment with wound fluid at day 10 showed less transplanted tumor formation in mice than that with wound fluid at day 1 [68], indicating the possibility that the molecules from healed wound releases a cancer response to the wound environment. Speculating from that, it is possible that molecules derived from the autologous cancer mass can prevent or treat the recurrence of the original cancer. This hypothesis is supported by the studies that chaperone proteins from tumor cells inhibited tumor growth in several mouse models [69], that second transplanted tumors inhibited the first one on mice [70] and that epidermal growth factor (EGF) cancer vaccine decreased inflammation [71].

4.2 Interpretation of metastasis

Metastasis has been considered as cancer cell migration and proliferation from the primary site to a distant tissue [72]. However, it is not clear why the metastasis did not occur in many cancer cell lines in animal models [72–74]. In addition, how cancer cells pass through the blood–brain barrier on the lung, breast, and skin cancers remains unclear since it seems that only cancer cells can pass the barrier but not the smaller lymphocytes [75]. Based on the WOWH mechanism, another type of "metastasis without cell migration" is possible: the corresponding oncogenes on distant sites can be activated by the persistently circulating wound molecules derived from the wounds and cancer-related necrosis/inflammations. The cells

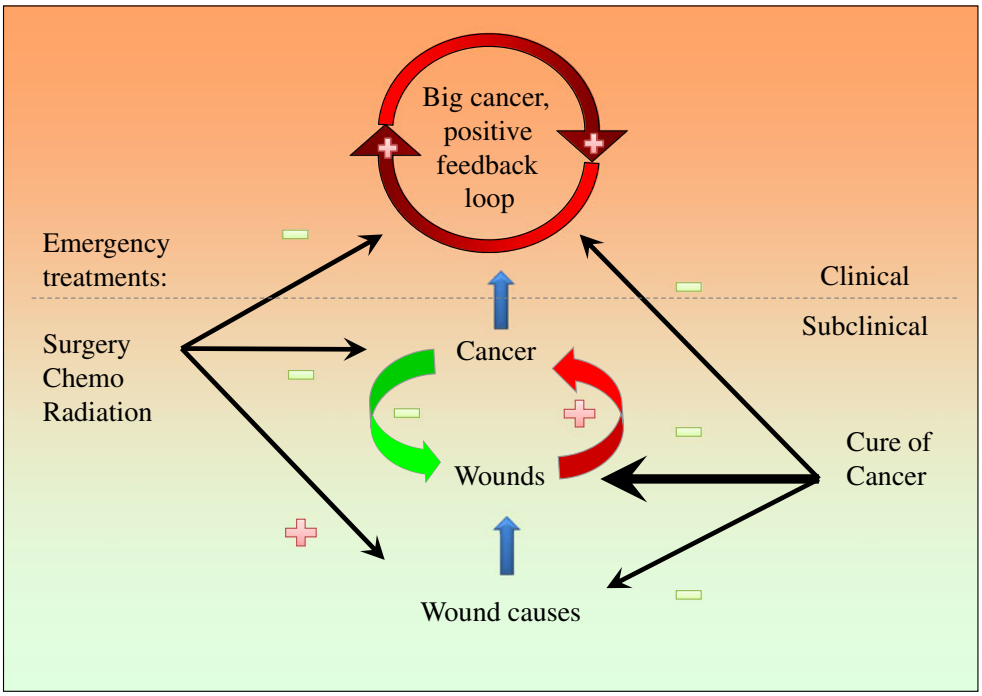

Fig. 4 A scheme of wound, cancer, feedbacks, and treatments. Physical, chemical, or biological factors cause a wound. A cancer responds to the wound to heal it. If the wound stimulation is persistent, a positive feedback loop will be formed till the wound is healed or the whole body exhausted. Surgery, chemo, and radiation therapies can halt the positive feedback loop quickly but the treatments themselves are wound causes. If the wound is persistent, another cancer will reoccur or be induced. To cure the cancer, all three facets, positive feedback loop (caner mass), wounds and wound causes must be covered, although the latter two are more complicated and difficult. *Plus sign* indicates increasing, promotion or positive feedback. *Minus sign* indicates decreasing, reduction, or negative feedback

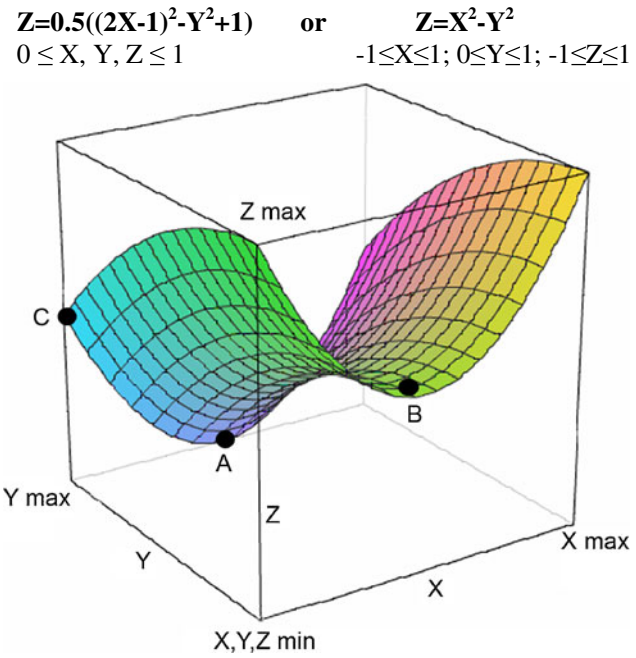

Fig. 5 Molecular regulations for the treatments of diseases including cancer. *X*-axis: doses of major treatment molecules. The optimal doses are between minimum and max (point B). *Y*-axis: the influences of all other possible molecular regulations in cancer treatments, from drugs, diets, life styles to psychological influences. Max *Y* means the best influences. Min *Y* means the worst influences. *Z*-axis: a disease, a cancer mass or cancerization. Min Z means disease free and max means the worst disease stages. *A* Disease (cancer)-free point reached by optimal *X* and max *Y*. Only at this situation, the disease (cancer) can be cured. *B* Partial clinical response point by optimal *X*, but minimal *Y* (correct major treatments but unfortunately with the influences of other wrong life style, etc.). *C* Partial clinical response point by maximal *Y*, but minimal *X* (wrong major treatments with the correct influences of life styles, etc.). $Z=X^2-Y^2$ means that the treatment outcome depends the personalized molecular balances at multiple dimensions. Cancer-spontaneous regression can be considered the extreme example to reach the point *a* in this model

with persistent activated oncogenes will transform and overproliferate, leading to another cancer mass on the remote site —may be considered as "general metastasis" (Fig. 6). For example, PI3K/AKT pathways are activated in both breast cancer [76] and bone remodeling [77]. The circulating molecules that activate PI3K/AKT genes of breast cancer cells will also stimulate those active ones of bone cells, leading to the over expression of PI3K/AKT and abnormal proliferation of bone cells—general metastasis of bone without cell migration. The study of secondary tumor induction [38] is good evidence to support this hypothesis of general metastasis: The Rous sarcoma virus induced a wound tumor in chicks, but did not develop metastasis. However, a wound away from the primary tumor developed a tumor at the wound site without primary tumor cell migration. Even some wound-related molecules (transforming growth factor beta (TGF-β), acidic fibroblast growth factor, and basic fibroblast growth factor) could replace the actual wound in the second tumor development, indicating that the molecules similar to the initiation of the first wound tumor activated the oncogenes of the wound related cells at the second wound site and developed the second tumor—general metastasis without a tumor cell migration. From the concept of general metastasis, it is easier to understand why it is hard to find the continuous cancer cell anchorages on the way from the primary site to the distant metastatic site and how metastatic sites appear in the brain across blood–brain barrier. As long as wounding molecules are circulating in the body, according to the WOWH mechanism, they would promote the oncogene activations in the tissues that have corresponding oncogene activities in their physiological metabolisms, especially if there is wound healing process there.

4.3 Tumor marker fluctuations and its uses

Due to oncogene and other cancer-related gene activations in cancer, many proteins are secreted outside cancer cells and enter the blood circulation. Serum markers for cancer status are being tracked by researchers [78, 79] since the serum samples are easier to be acquired than tissue samples, yet few markers have proved to be clinically useful so far. Some predictable markers in one study may fail to be confirmed in the other study [80, 81]. The difficulty of the clinical use of biomarkers in cancer is due to the problems of understanding them. If a marker is considered a unique label of a cancer cell, no such marker can be found for cancer screening since all markers in the early stages of cancer can be found in other noncancer wounded situations [82] (Table 2). Based on the WOWH mechanism, wound, cancer, and wound healing are interacting. A wound promotes cancer and the cancer heals the wound (Figs. 2 and 4). Wound, cancer, and wound healing will share the most common molecules. Only when the cancer enters the positive feedback loop, might the cancer-based wounds activate some molecular pathways that are rare in the noncancer status. Therefore, it is hard to find a highly specific marker in early cancer stage. One the other hand, the wound, cancer, and wound healing are a dynamic procedure. Wounds stimulate the expressions of cancer-related markers (Table 4; L2, L3), while the cancer may decrease those expressions if the wound status is improved (Table 4; L7, L8). New wounds, cancer treatments, diet, and life style [51–53] affect wound–cancer status (Fig. 5) and further changes the expression of the cancer-related markers, even if in the late stage of cancer. Therefore, it is impossible to use the markers from one cancer status to predict the cancer outcomes in the later stage. That is why there is some discordance of tissue biomarkers between the primary cancer and the later metastatic stage [83]. Furthermore, different wounds activate different oncogenes and induce different cancers to produce different molecules for wound healing, although these different wounds and cancers happen in one organ possibly.

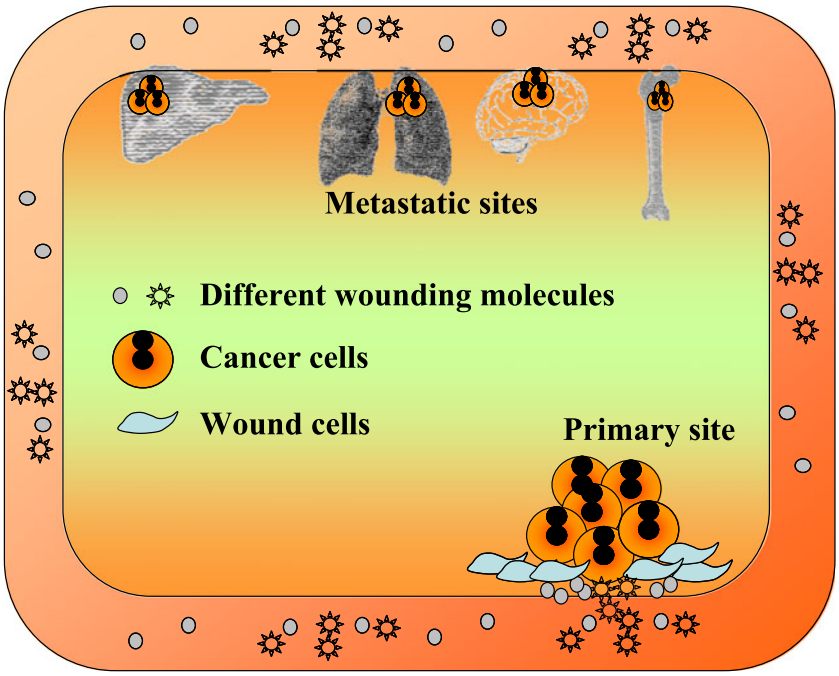

Fig. 6 General metastasis. The corresponding oncogenes that have activities in their physiological metabolisms in the remote tissues can be activated by persistently circulating wound molecules derived from the wounds and cancer related inflammations. The cells with persistent activated oncogenes will transform and over-proliferate, leading to another cancer mass on the remote site without the primary cancer cell migration

Therefore, one marker change cannot cover all wound–cancer situations of the cancer that is named by the tissue or organ, e.g., different expressions of ER±, PR±, and Her-2± in breast cancer [83].

Based on WOWH mechanism, another cancer-related marker change may be speculated and used in clinics (Fig. 7): if each mean±2SD of a cancer-related marker array from a 20-year-old population is set as the puberty range (the reference range with less wounds comparing with older people), older people would have more and more out-puberty ranged (OPR, beyond the mean±2SD of 20 years) markers along with ages since accumulated wounds and aging cells are increasing along with age [48]. However, the OPR marker counts in relatively healthy population (Fig. 7, green line) will

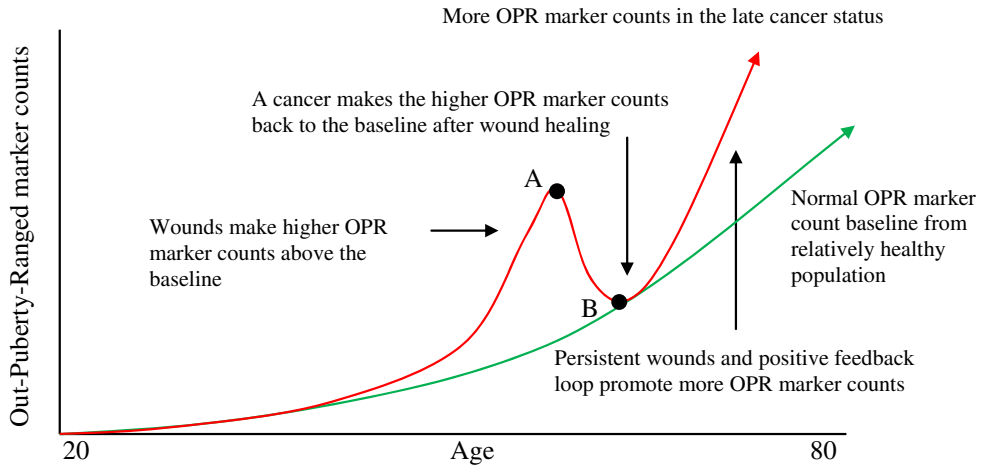

Fig. 7 Interactions of cancer-related biomarkers with age, wounds, and cancer. Each mean±2SD of many cancer-related markers at 20 years old is set to be the puberty range (the reference range for an adult). Beyond this, mean±2SD is set to be out-puberty-range (OPR). The normal OPR marker count baseline from relatively healthy people is increased along with age due to the wound accumulations and cell aging (*green*). Wounds make higher OPR marker counts above the baseline and a cancer makes the higher OPR marker counts towards to the baseline after the wound healing (*red line*). Point *A* is the apex of an abnormal marker count peak and may be a "false positive" point if the pathological and imaging diagnoses fail to find the cancer. Point *B* is the correction point after the wound healing and may be a "false negative or less sensitivity" point if the pathological and imaging diagnoses find the cancer. Different sampling times for populations lead to false positives or false negatives. By monitoring dynamic OPR marker counts, the cancerization status can be seen and personalized treatments can be guided toward the normal baseline till the cure of cancer

be lower than those with precancerous diseases and cancer metastasis (Fig. 7, red line) due to the oncogene activations. The molecules from wound and wound healing interactions, including oncogene activations and the cancer cell activities, will increase the OPR marker counts. When the wound is healed, the increased OPR marker counts will drop back to the normal baseline. That is why in the early stage of a cancer, the markers may or may not be high, e.g., CEA and CA15-3 on colon and breast cancers, respectively [84]. If the wounds are intermittent (such as in the situation of UV exposures in the vacation every year), the OPR marker counts will be up and down. This may make many "false positive and false negative" judgments in the clinic or contradictory results in the studies [85, 86], which is due to the different sampling times of each individual (Fig. 7, points A, B). If the wound is persistent, or the cancer enters the positive feedback loop (such as at the late cancer stage), more wounding molecules and responding genes will be involved [84, 87, 88] and the OPR marker counts will be maintained at a high level. By monitoring the dynamic OPR marker counts of a patient and comparing with the normal baseline, the cancerization status inside the body can be monitored and the personalized treatments can be guided toward the direction of the normal baseline till the cure of cancer.

4.4 Mysteries of transplanted tumor models

It is not easy to transplant cancer cells to form a tumor in a normal mouse. This has been considered due to the inhibition of immunity to tumor formation [89]. However, even in immunodeficient mice, transplanted cancer cells may not form a tumor efficiently [90, 91]. In some situations, the transplanted tumor can be only formed in the presence of functional T lymphocytes [92]. WOWH mechanism gives another explanation for this phenomenon: there is no correct wound molecular environment in the normal mouse for transplanted cancer cells to respond, while nude mice are partial wounded bodies that some cancer cells with the right activated genes may respond to them. Due to the partial wounded bodies, nude mice do not provide molecules that are suitable for all transplanted cancer cell growth, but the tumor growth may be promoted by providing a wound environment [92, 93]. The use of Matrigel (BD Biosciences) in the transplanted tumor model [94] is an example of such a situation since TGF-β [38], FGF [38], EGF [95], insulin-like growth factor-1 [95], platelet-derived growth factor (PDGF) [96], and nerve growth factor [97] in Matrigel are all actively expressed factors in wounds and they all can activate oncogenes, such as Src [98–103], for cancer progress. The receptor themselves of EGF, FGF, and PDGF are oncogenes too (Table 2). Since multiple wound-related cytokines are in the Matrigel, one or more of them will match the pathways that the transplanted cancer cells were previously activated. Therefore, many unsuccessfully transplanted human cell lines are easier to grow in mice in the presence of Matrigel [94] indicating that the host immunodeficiency or not is not the limiting factor for the tumor formation since Matrigel is more like an immunostimulator [104–106] rather than an immunosuppressor. Furthermore, it has been shown that the wounded body (a) requires fewer transplanted cells to form a tumor [68] and (b) forms a bigger tumor [92] than the normal body. It can be speculated that transplanted tumor cells can even grow in heterogenic and immunocompetent mice as long as a corresponding wound existed.

5 Summary

WOWH mechanism is a logic-deduced theory based on the relationships among cancer, precancerous diseases, oncogenes, wound healing, and cancer occurrences in all species of multicellular organisms. Wound triggers the oncogenes to produce cytokines to recruit and differentiate stem cells to heal the wound. If the wound is healed, the process will return to homeostasis. If the wounds are persistent, wounds and the positive feedback molecules will make the cancer mass bigger and bigger until the wounds are healed or the whole system exhausts. The logic of the WOWH mechanism is consistent with the rationales of the other physiological metabolisms in the body—for survival. It helps to understand many cancer mysteries from the mutation theory. It can be used to interpret and guide cancer prevention, recurrence, metastasis, *in vitro* and *in vivo* studies, and personalized treatments.

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