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Abnormal Methylation Enzymes as the Most Critical Issue of Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The objective of this study is to present convincing evidence to show that abnormal methylation enzymes (MEs) are the most critical issue of cancer, and to call for the acceptance of cell differentiation agent (CDA) formulations as the right medicines for cancer therapy. CDA formulations are the creation of the nature to function as allosteric regulators to keep abnormal MEs under control. Cancer is a disease caused by multiple factors. Toxic insults inducing cachexia symptoms to trigger a cascade of events resulting in the collapse of chemo-surveillance, which is an important allosteric mechanism to prevent the build up of cells with abnormal MEs; evolution of cancer stem cells (CSCs) from progenitor stem cells (PSCs) due to wound unhealing; and the activation of oncogenes and/or the inactivation of suppressor genes to play important roles to cause cancer. Among these multiple factors, abnormal MEs are the most critical issue of cancer. MEs play an important role on the regulation of cell replication and differentiation. This biological role is so important, so that MEs are subject to double allosteric regulations, one at the individual enzyme level and another at the enzyme complex level. When MEs become abnormal, cells are locked in perpetual state of proliferation which is the most outstanding feature of cancer. The solution of perpetual proliferation of cancer cells (CCs) is a very important issue of cancer. Killing of replicating cells and induction of terminal differentiation of replicating cells are two options to stop perpetual proliferations. The strategy based on killing of replicating cells displays the features as anti-wound

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healing and contra-indication of cancer therapy, whereas the strategy based on the induction of terminal differentiation displays the features as pro-wound healing and the right indication of cancer therapy. Evidently, the pro-wound healing strategy is the right approach of cancer therapy. A right approach is a golden rule to dictate the success to solve difficult challenges. Destabilization of abnormal MEs is the critical mechanism to achieve terminal differentiation of cells with abnormal MEs. Since abnormal MEs are most critical issue of cancer, the solution of cancer is best achieved by CDA formulations, the creation of the nature on allosteric regulation to take care of the issue of abnormal MEs.

Keywords: Allosteric regulation; cancer therapy; CSCs; MEs; PSCs; wound healing.

1. INTRODUCTIOON

President Biden brought up cancer moonshot initiative on Sept. 12, 2022, the 60th anniversary of the moonshot speech of President Kennedy, urging health profession to save 50% of cancer patients in the following 25 years [1]. NCI experts predicted in 2019 that both cancer incidence and cancer mortality were on the way up by an annual increment of 5% [2]. Obviously, the goal of President Biden cannot be fulfilled by the practices based on the killing of cancer cells (CCs) [3]. Cytotoxic chemotherapy was established when we did not have full knowledge of cancer. Perpetual proliferation of cancer cells was recognized as the most outstanding feature of cancer. "Killing of cancer cells became the accepted standard treatment, and disappearance of tumor became the accepted criterion on the evaluation of therapeutic efficacy. Cytotoxic chemotherapy was the major therapeutic modality employed in the war on cancer declared by President Nixon as a presidential project during 1971-1976, which did not significantly reduce cancer mortality" [4]. If a therapeutic modality has been drilled through as a presidential project and failed to achieve the goal, it was only fair to conclude that this treatment modality was not good for cancer therapy. Apparently, cancer establishments agreed on this conclusion to shift the search of new cancer drugs away from cytotoxic drugs to gene and targeted therapeutic drugs during 1976-1996, to anti-angiogenesis drugs during 1996-2016, and now to immunotherapeutic drugs [5]. "Reduction of tumor size remains the standard criterion on the judgement of effective cancer drugs. Since cytotoxic drugs are the most effective drugs to achieve reduction of tumor size, cytotoxic drugs remain major cancer drugs despite ineffective to save cancer patients" [6,7]. A drastic change of cancer leaderships is definitely needed to correct the mistakes of past leaderships directing us to combat cancer with wrong medicines [8].

Now we have a better knowledge of cancer. Cancer is caused by wound unhealing, and multiple factors are involved in the process of carcinogenesis. Wound healing is a process requiring the proliferation and the terminal differentiation of progenitor stem cells (PSCs) [9]. PSCs are the most primitive stem cells to give rise to organs or tissues during embryonic development of fetus. A small % of these cells. usually less than 2%, are reserved in the organs or tissues for the growth or repair of the organs or tissues. Methylation enzymes (MEs) play an important role on the regulation of cell replication and differentiation [10]. Methylation enzymes are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [11]. Important enzymes involved in biological regulation are subject to allosteric regulation. Methylation enzymes are exceptionally important to subject to double allosteric regulations, one on the individual enzymes and one on the enzyme complex. On individual enzymes, SAHH is the receptor of steroid hormones or related allosteric factors [11], and on the enzyme complex, it is allosterically regulated by telomerase and chemo-surveillance [12,13]. An enzyme system subject to double allosteric regulations certainly is an indication of an exceptional importance of this enzyme system in biological regulation. The association of ternary MEs with telomerase tilts the regulation in favor of cell replication. The build up of cell mass is obviously important for the development of fetus and the healing of wound. Pre-mature induction of differentiation by thalidomide may result in malformation of the fetus. Abnormal MEs are important for the normal development of the fetus and wound healing. But abnormal MEs if gets out of control can be disastrous. Contact inhibition, TET-1 enzyme and chemo-surveillance are the mechanisms to keep cells

with abnormal MEs under control. If such safety mechanisms become dysfunctional, then the disastrous consequences may ensue. Cancer is the result of abnormal MEs getting out of control. Abnormal MEs are the most important issue of cancer. Accumulating evidence demonstrates that cancer cells show largely different DNA methylation patterns from normal cells. In general, DNA methylation levels are reduced in regions of low CpG density compared with normal cell, while a subset of CpG islands are hypermethylated in cancer [14,15]. Aberrant epigenetic modifications occur at a very early stage in neoplastic development and they are widely described as essential players in cancer progression. The capable cancer leaderships must be able to identify the most critical issues of cancer, and take the right approaches to put away cancer. The most critical issue of cancer is abnormal MEs, and the best solution of cancer is CDA formulations, which are the nature's prescriptions to put away cancer.

2. COMMENTARIES AND DISCUSSION

2.1 Allosteric Regulation of MEs

Methylation enzymes are a ternary enzyme complex consisting of MAT-MT-SAHH [11]. MEs maintain enzyme complex on gel filtration and sucrose density sedimentation, but dissociated into individual enzymes upon DEAE-agarose chromatography. Individual enzymes display sedimentation values as 4S for SAHH, 5.5S for MT and 6S for MAT. SAHH is a steroid hormone receptor, which is the most unstable enzyme requiring steroid hormone or related allosteric regulators to become stable configuration to form dimeric complex with MT. MT-SAHH dimer displays a sedimentation value of 6S similar to that of MAT. A ternary enzyme complex is formed between MAT and MT-SAHH dimer. Thus, MEs are under the allosteric regulation to form stable and active ternary enzyme complex and become inactive as dissociated individual enzymes in the absence of allosteric regulators. MTs in the individual enzyme state have the tendency to be modified to become nucleases which can trigger apoptosis to cause organ involution.

MEs play a critical role on the regulation of cell replication and differentiation by virtue of the fact that DNA methylation controls the expression of tissue specific genes [16], and pre-rRNA methylation controls the production of ribosome [17], which in turn dictates the commitment of cell to initiate cell replication [18]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [19]. Because of such important biological role, MEs are subject to delicate allosteric regulation to maintain biological optimum. Usually, only enzymes involved in important regulatory roles are subject to allosteric regulation. The allosteric regulation of MEs is not limited to individual enzymes. Another allosteric regulation is imposed on the ternary enzyme complex. In telomerase expressing cells, MEs are associated with telomerase [12]. The association with telomerase changes kinetic properties of MAT-SAHH isozyme pair and the regulation in favor of cell replication. K_m values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the normal isozyme pair. The increased K_m values suggest that telomerase expressing cells have much larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are important for the build up of cells with abnormal MEs. It has been shown by Prudova et al. [20] that the association with AdoMet could protect protein against protease digestion. Chiba et al. [21] found that the pool sizes of AdoMet and AdoHcy shrunk greatly when HL-60 cells were induced to undergo terminal differentiation. A larger pool size of AdoMet and AdoHcy is really important for the build up of cells with abnormal MEs. Evidently, the build up of normal stem cells with abnormal MEs is necessary for the development of fetus in the case of embryonic stem cells and for the healing of wound in the case of PSCs. Differentiation of normal stem cells with abnormal MEs is blocked because differentiation requires DNA hypomethylation to activate differentiation related genes, the expression of which are blocked by DNA methylation at the promoter of these genes [22]. The nature creates chemo-surveillance as an allosteric regulation that can destabilize abnormal MEs for the differentiation to proceed [13]. Thus, the stabilization of MEs by association with telomerase and destabilization of abnormal MEs by chemo-surveillance is an important allosteric regulation on cells with abnormal MEs. Normal stem cells with abnormal MEs have another mechanism to carry out lineage transitions through TET-1 enzyme [23,24] that can bypass the blockade of differentiation due to abnormal MEs. It can be stated that because of the exceptionally important role of MEs on the regulation of cell replication and differentiation, these enzymes are subject to exceptional double allosteric regulations. The

smooth operation of allosteric regulations is utterly important for the maintenance of health. If the operation of allosteric regulations is breaking down, the build up of cells with abnormal MEs may become problematic to display clinical symptoms such as tissue fibrosis, dementia, organ failure and cancer [13,25-27].

"Wound healing and cancer are closely related to involve PSCs as the critical common elements. Wound healing requires the proliferation and the terminal differentiation of PSCs" [9]. PSCs are pluripotent stem cells capable of differentiation into all constituent cells of the organ or tissue to repair the wound. "Wound triggers biological and immunological responses" [28]. Biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs), which are good for wound healing to function as the differentiation inducers (DIs). PGs are unstable metabolites. The function of PGs is believed to cause edema for the extravasation of inhibitors for PSCs to proliferate. The promotion of terminal differentiation of PSCs is accomplished by metabolites active as DIs, which are chemicals capable of eliminating telomerase from abnormal MEs, and differentiation helper inducers (DHIs), which are inhibitors of MEs capable of potentiating the activity of DIs. Cell differentiation agents (CDAs) were terms we created to designate preparations containing DIs and DHIs as the active ingredients [29]. Abnormal MEs by favoring cell replication enable the build up of PSCs to repair the wound. The completion of the terminal differentiation is the critical event of wound healing. This is the essence of allosteric regulation. Abnormal MEs to build up cell mass for repair and CDAs to destabilize abnormal MEs to carry out repairing function. Both abnormal MEs and destabilization of abnormal MEs are important for wound healing. Therefore, the execution of allosteric regulation is so important to maintain health. Breakdown of allosteric regulation often results in the creation of clinical symptoms. Healthy people could maintain a steady high level of CDA to prevent the built up of cells with abnormal MEs, whereas only 2% of cancer patients could have this high level [13]. CDA levels decline as the disease progresses. Treatment with cytotoxic agents accelerate the decline of CDA levels. The progression of the disease and the administration of cytotoxic agents are to blame for the destruction of allogenic regulation important to maintain health. "The breakdown of allosteric regulation by the progression of cancer and the administration of cytotoxic agents is attributable to tumor necrosis factor (TNF) which is produced in response to wound and immunological responses. TNF is also named cachectin after its effect to cause cachexia symptoms. A manifestation of cachemia symptoms is the excessive urinary excretion of low molecular weight metabolites. DIs and DHIs are among such metabolites lost" [13]. The effect of TNF to cause the breakdown of chemo-surveillance could be effectively antagonized by phenylacetylglutamine [13]. By protecting the function of allosteric regulation, phenylacetyl-glutamine was found effective to prevent carcinogenesis induced by potent carcinogens [30,31]. Our previous hepatocarcinogenesis studies revealed that the host liver was involved in active repair of wounds caused by hepatocarcinogens manifested as numerous small preneoplastic hyperplastic nodules, which displayed abnormal MEs obviously representing the replication of PSCs in the process of healing wounds created by hepatocarcinogens [32]. Most of these small hyperplastic nodules disappeared, suggesting the completion of wound healing. Only a few large sized carcinomas appeared later, resulting from unhealed hyperplastic nodules. Our carcinogenesis studies were indicative that carcinogenesis process and wound healing process were very similar. Carcinogenesis prevailed only when healing process failed. The functionality of chemo-surveillance as an allosteric regulation plays a decisive role on abnormal MEs to dictate the success of wound healing to avoid cancer [13,25,26].

2.2 Wound Unhealing Can Be Disastrous

Wound healing comes naturally without having to put up any effort. Take treatment of surgical wound for example, suture and antibiotic treatments are basically subsidiary to speed up the healing process and to prevent infection. Since wound healing comes so easy, nobody cares how wound is healed. Actually, wound healing is a very important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing. Pulmonary fibrosis is the most fatal symptom of COVID-19 infection, which is caused by the build up of PSCs unable to undergo terminal differentiation because of the collapse of chemo-surveillance [27]. Dementia is initiated by amyloid-beta peptide analogous to TNF to trigger a cascade of events resulting in wound unhealing, so are most cases of organ failure. Myelodysplastic syndrome

(MDS) is a classic case of disease to show cancer evolution due to wound unhealing. MDS often starts with a display of an immunological disorder [33] to trigger the production of TNF to cause the collapse of chemo-surveillance [34]. TNF causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patients to produce hematopoietic cells such las erythrocytes, platelets and neutrophils. "TNF is responsible for the collapse of chemo-surveillance to result in the build up of PSCs unable to undergo terminal differentiation. Pressure is then building up to force more proliferation of PSCs. Contact inhibition limits the capacity of PSCs to replicate, which are then evolved into CSCs to escape contact inhibition. It takes only a single hit to silence TET-1 enzyme to convert PSCs to become CSCs, which is an easy task for PSCs to achieve since these cells are equipped with abnormally active MEs" [12]. CSCs are cancer cells which do not obey contact inhibition to keep on replicating. MDS is at the stage of propagation of CSCs [35]. Without TET-1 enzyme to carry out lineage transitions, and without wound healing metabolites to promote terminal differentiation, pressure will increase to force chromosomal abnormalities such as translocations or deletions to activate oncogenes or inactivate suppressor genes to speed up replication, eventually pushing slow growing CSCs to progress to faster growing acute myeloid leukemia. MDS are a classic case of cancer evolution due to wound unhealing.

"The concept of cancer as wound unhealing was first introduced by the great German scientist Virchow in the 19th century" [36]. It was again brought up by Dvorak in 1986 [37]. "The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin" [38]. We provided the most important details on this subject that included abnormal MEs to block differentiation [10,12,29,39,40]; chemo-surveillance as the nature's creation of allosteric regulation to ensure perfection of wound healing to avoid cancer [5,13,25,26,29]; DIs and DHIs as wound healing metabolites and also as active players of chemo-surveillance [5,13,25,26,29]; hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal differentiation of cells with abnormal MEs [22]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [9,41,42]; and the evolution of CSCs from PSCs due to wound unhealing [43-45]. These studies clearly established that cancer arose as a consequence of wound unhealing. Our carcinogenesis studies also confirmed the validity of these findings [26,27]. Cancer is obviously caused due to wound unhealing. Then the most appropriate therapy of cancer should be the process of wound healing [5, 29, 43, 46-48].

2.3 MDS as a Litmus Test to Screen for Right Cancer Drugs

MDS is a classic disease to demonstrate the evolution of cancer due to wound unhealing. Wound triggers the production of a toxic peptide TNF to induce a cascade of events resulting in the display of cachexia symptoms responsible for the collapse of chemo-surveillance. Chemo-surveillance is the creation of the nature as an important allosteric regulation to keep the proliferation of cells with abnormal MEs under control. The loss of this control mechanism can force PSCs, the cells involved in wound healing, to evolve into CSCs in order to escape the restriction of contact inhibition. The evolution of CSCs from PSCs requires a single hit to silence TET-1 enzyme [43-45], which is a task easily accomplished by PSCs equipped with abnormally active MEs. The propagation of CSCs is an effort of the patient to repair unhealed wound in order to eliminate the symptom created by the wound. MDS is at the stage of propagation of CSCs [35]. The only solution of MDS is to follow the critical process wound healing by the destabilization of abnormal MEs to convert pathological CSCs to become functional cells such as erythrocytes, platelets or neutrophils. CDA-2, Vidaza and Decitabine are three drugs approved for the therapy of MDS by the Chinese FDA, and Vidaza and Decitabine are the two drugs approved by the US FDA. CDA-2 was a cancer drug of our creation [29]. The effectiveness of these drugs on MDS therapy is based on the elimination of abnormal MEs, CDA-2 by targeting telomerase to convert abnormal MEs into normal MEs [10, 12, 29, 43, 46-48], and Vidaza and Decitabine by promoting covalent bond formation between methyltransferase and 5-aza- cytosine base incorporated into DNA [49]. Director Jun Ma of the Harbin Institute of "Hematology and Oncology was instrumental in conducting clinical trials of these three drugs for successful approval in China. Based on two cycles of treatment protocol each 14 days, he found CDA-2 had a slightly better therapeutic efficacy based on cytological evaluation and a marked better therapeutical efficacy based on hematological improvement evaluation, meaning patients were no longer dependent on blood transfusion to stay

healthy. Evidently, CDA-2 is a better drug for the therapy of MDS, which has demonstrated a better therapeutic effect without adverse effects, whereas Vidaza and Decitabine were proven carcinogens" [50,51], and very toxic to DNA [52-54].

Obviously, inactivation of abnormal MEs is the critical mechanism to achieve MDS therapy. It is also the critical mechanism to achieve wound healing. MDS can serve as a Litmus test for the screen of right cancer drugs. A right cancer drug must be able to cure MDS. Drugs inactivating abnormal MEs can pass this test. None of other cancer drugs based on killing of CCs can pass this test. Killing of CSCs cannot cure MDS. Besides, killing of CSCs cannot be easily done, which are protected by drug resistant and anti-apoptosis mechanisms. Destabilization of abnormal MEs is the right approach of cancer therapy. Once abnormal MEs are eliminated, cells with abnormal MEs are induced to become functional cells to eliminated symptoms created by the wound. Terminal differentiation of CSCs and CCs can also put to rest other factors important for the maintenance of malignant growth such as oncogenes and suppressor genes. Oncogenes and suppressor genes are, after all, cell cycle regulatory genes which play important functions when cells are in cell cycle replicating. But if the replicating cells exit cell cycle to undergo terminal differentiation, these genes have no roles to play. That is the advantage of targeting abnormal MEs to accomplish cancer therapy [5, 29, 43, 46, 55- 57].

3. CONCLUSIONS

Enzymes playing important regulatory roles are often subject to allosteric regulations to maintain biological optimum that can avoid hazardous extreme to display clinical symptoms. MEs play an important role on the regulation of cell replication and differentiation. This regulatory role is so important to require double allosteric regulations, one on the individual enzymes and the other on the enzyme complex. On the individual enzymes, SAHH is the receptor of steroid hormones or related allosteric regulators to maintain the optimum growth and differentiation. On the enzyme complex, the association with telomerase change the kinetic properties of MAT-SAHH isozyme pair and the regulation to tilt the regulation in favor of growth, which is important for the function of normal stem cells to carry out the development of fetus or the repair of wound. The nature creates contact inhibition, TET-1 enzyme and chemo-surveillance as allosteric regulations to keep cells with abnormal MEs from getting out of control. If such safety mechanisms become dysfunctional, hazardous consequences may ensue. Cancer is the worst case of the failure of allosteric regulation. Thus, abnormal MEs are the most critical issue of cancer. Consequently, CDA formulations to destabilize abnormal MEs are the right solution of cancer.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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