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On the Mechanism of Wound Healing and the Impact of Wound on Cancer Evolution and Cancer Therapy

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Authors' contributions

This work was carried out in collaboration between both authors. Author MCL designed the study, wrote the protocol and wrote the first draft of the manuscript. Author CLC managed the analyses of the study. Both authors read and approved the final manuscript.

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Opinion Article

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ABSTRACT

This opinion article highlights the mechanism of wound healing and the impact of wound on cancer evolution and cancer therapy. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs). PSCs are pluripotent stem cells capable of undergoing differentiation to become various cells needed for the repair of the wound. Wound healing is deeply influenced by metabolites involved in chemo-surveillance and cachexia. Wound triggers the production of prostaglandins (PGs) which play an essential role to promote the proliferation of PSCs at the initial stage of the wound. At the final stage of wound healing, chemo-surveillance comes into play to induce TD of PSCs. The functionality of chemo-surveillance dictates the success of wound healing. The functionality of chemo-surveillance is usually intact in healthy people, so wounds typically heal nicely without having to put up any efforts. Wound also triggers production of tumor necrosis factor (TNF) which is responsible for the display of cachexia symptoms leading to the collapse of chemo-surveillance. TD of PSCs will be impaired, allowing PSCs to evolve into cancer stem cells (CSCs). It takes only a single hit to silence TET-1 enzyme to convert PSCs to become CSCs, which is well within the reach of PSCs because MEs of PSCs are abnormally active like cancer cells (CCs) due to association with telomerase. Wound healing and evolution of cancer are so closely related to involve PSCs as the critical common elements. Cancer can arise if a wound is not healed properly. The most appropriate strategy for cancer therapy is to follow successful

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process of wound healing. The appropriate strategy must be able to eliminate cachexia symptoms, to restore the functionality of chemo-surveillance, to eradicate CSCs, to eliminate differentiation blockade, and to put away oncogenes and cancer suppressor genes. Wound healing metabolites are the best candidates to fulfill such requirements.

Keywords: Stem cells; wound healing; cancer therapy.

1. INTRODUCTION

Wounds in healthy people are usually healed without having to put up any effort. Wound healing is a natural human response; nobody cares how a wound is healed. However, if wound is not healed properly, serious consequences, such as the evolution of cancer may ensue. We have better to pay attention on how the wound is healed so that bad consequence of cancer can be avoided. The lesson of wound healing can also shed light on how to pursue appropriate therapy of cancer.

2. OPINIONS AND DISCUSSION

2.1 On the Mechanism of Wound Healing

Wound healing requires the proliferation and the TD of PSCs [1]. PSCs are the most primitive stem cells of the adult body which are pluripotent stem cells capable of differentiation into various cells such as parenchyma and epithelial cells, connective tissues, and blood vessels needed for the repair of the wound. These cells are protected by a drug resistance mechanism to exclude toxic chemicals, and express chemokine receptors to respond swiftly to signals for expansion or repair. Methylation enzymes (MEs) of these cells are abnormal like most cancer cells (CCs) due to association with telomerase [2]. The association of MEs with telomerase locks MEs in an exceptionally stable and active state to block TD [3,4]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [5]. Destabilization of abnormal MEs by metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) are an effective mechanism to induce TD of cells with abnormal MEs [3, 4]. DIs are chemicals capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of ternary MEs which can greatly potentiate the activity of DIs. Destabilization of abnormal MEs through DIs and DHIs was the basic mechanism of chemo-surveillance we brought up as a natural defense against cancer [6]. The hypothesis of chemo-surveillance was based on the observation that healthy people were able to maintain a steady level of metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites due to excessive urinary excretion attributable to cachexia symptoms. It turns out DIs and DHIs are wound healing metabolites. Thus, the primary objective of chemo-surveillance is to ensure perfection of wound healing to avoid cancer evolution.

Wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane-bound phosphatidylinositol through phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [7,8]. Although AA and PGs are active DIs [9], the induction of TD of PSCs at the initial stage of the wound is not the primary objective of PGs. Rather the localized inflammation caused by PGs [10] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound resulting in edema response which is the primary objective of PGs to orchestrate the healing process. Chemo-surveillance mediated through DIs and DHIs normally functions as a brake to prevent the buildup of PSCs. This brake must be released in order for PSCs to produce enough cells for the repair of the wound. PGs are metabolically unstable [7]. Their biological effects are most likely brief and confined to the wound area. Thus, the promotion of the proliferation of PSCs is the primary objective of PGs on wound healing, whereas the induction of TD of PSCs at the final stage of wound healing is accomplished by wound healing metabolites involved in chemo-surveillance. The stable end products of PGs may also participate in the final stage of wound healing. The stable end products of PGs are also active as DIs, although not as active as PGs [9]. The relatively inactive DIs of the endproducts of PGs can always be remedied by DHIs to boost their activity. Pregnenolone is a particularly good DHI to potentiate the DI activity of AA and related metabolites [9]. In short, the mechanism of wound healing requires the production of PGs to promote the proliferation of PSCs, and then the

involvement of chemo-surveillance to induce TD of PSCs to complete wound healing process.

3. THE IMPACT OF WOUND ON CANCER EVOLUTION

The immunological response prompts the production inflammatory cytokines which are bad for wound healing, particularly tumor necrosis factor (TNF) which is also named cachectin, a name to characterize its effect on cachexia symptoms. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of leaky blood vessels caused by TNF [11,12]. The loss of low molecular weight metabolites results in the collapse of chemo-surveillance and the incompletion of wound healing. Acute wound affects chemo-surveillance only temporarily, which is quickly recovered to the normal state. The good effect of biological response to wound usually prevails in this case. It is the chronic wound that produces a persistent damage to the functionality of chemo-surveillance to impair the ability to heal wound, resulting are cancer evolution. If wound is not healed properly, the continuous proliferation of PSCs runs a risk to evolve into cancer stem cells (CSCs). A single hit to silence TET-1 enzyme can convert PSCs to become CSCs [13], which is a task well within the reach of PSCs equipped with abnormally active MEs. Therefore, the functionality of chemo-surveillance is so important to ensure the perfection of wound healing to avoid cancer evolution [14].

Myelodysplastic syndrome (MDS) is a classic example of cancer evolution due to wound not healing properly. MDS often starts with a display of an immunological disorder [15]. This disorder prompts the production of inflammatory cytokines. Among cytokines produced, TNF is the critical factor related to the development of MDS [16]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF is responsible for the cachexia symptoms which is commonly shared by cancer and inflammatory patients. Cachexia symptoms causes the collapse of chemo-surveillance as above described. As a consequence, chemo-surveillance normally operating in healthy people to keep PSCs in check becomes dysfunctional, allowing PSCs to buildup in order to replenish unipotent stem cells wiped out by TNF. The high level of telomerase in the peripheral and bone marrow leukocytes is an indication of the widespread multiplication of PSCs [17,18]. During MDS progression, mutations affecting enzymes were frequently observed [19-21], which might play significant roles in the evolution of PSCs to become CSCs [22]. As anemia in MDS patients becomes worse, chromosomal abnormalities such as translocations and deletions characteristic of cancer cells arise to accelerate replication, eventually pushing MDS patients to progress to acute myeloid leukemia (AML) [23-26].

The evolution of cancer due to wound not healing properly is not unique to AML. It is rather a common occurrence. We have previously observed that the protection of the integrity of chemo-surveillance by Antineoplaston A10, namely phenylacetylglutamine, could effectively prevent chemical carcinogenesis [27,28], and achieve effective therapy of early stage cancer [6]. We have also noticed that abnormal MEs were detectable in preneoplastic hyperplastic nodules before the appearance of carcinomas during chemical hepatocarcinogenesis [29]. Carcinomas were derived from cells expressing abnormal MEs in the preneoplastic state, which were very likely PSCs. So the occurrence of human cancer and experimental animal cancer all point to PSCs as the origin of cancer, and imperfection of wound healing is the culprit.

4. THE IMPACT OF WOUND ON CANCER THERAPY

We were not alone to notice that cancer arose as a consequence of wound not healing properly [1]. MacCarthy-Morrough and Martin made a similar observation that the hallmarks of cancer were also the hallmarks of wound healing [30]. Perfection of wound healing is the most appropriate strategy for cancer therapy [1,31,32]. It is clear that cachexia symptom is responsible for the collapse of chemo-surveillance, and the collapse of chemo-surveillance allow PSCs to evolve into CSCs which can progress to faster growing CCs. Elimination of cachexia symptoms and restoration of the functionality of chemo-surveillance become an important matter for the success of cancer therapy [33]. In this regard, phenylacetylglutamine may have an important role to play, which we have found effective to prevent excessive urinary excretion of low molecular weight metabolites to restore the functionality of chemo-surveillance [6,27,28].

CSCs are originated from PSCs. Naturally, CSCs display cell features and biological missions very

similar to PSCs. Both PSCs and CSCs express ATP binding drug pumps that can effectively exclude toxic chemicals, and have upregulated anti-apoptosis programs that negate the pro-apoptotic signals activated by DNA damaging therapies [34-37]. Thus, these cells are resistant to cytotoxic drugs and radiation. These cells normally reside in acidic and hypoxic microenvironments hard to reach by the bloodstream. They remain dormant unless situations such as wounds arise that stimulate their recruitment. Although CSCs constitute only a small side population, they are the primary cause of treatment failure in the past based on destruction strategy [38-40]. Primary causes of treatment failure such as metastasis, drug resistance, angiogenesis, and recurrence can all attribute to CSCs. It is apparent that CSCs stand in the way to deny the success of destruction therapies to put cancer away in the past [1,31,41]. Therefore, the ability of the drug to eradicate and CSCs becomes an important consideration for the evaluation of cancer drugs [42]. Since CSCs reside in microenvironments hard to reach by the bloodsteam, small molecules easily diffusible such as wound healing metabolites are a better choice. In fact such molecules are routinely employed by PSCs on wound healing. Afterall, wound healing metabolites are the partners of the biological missions of PSCs and CSCs, they are easily tolerated by these cells equipped with drug resistance mechanism. CDA-2 was a preparation of wound healing metabolites purified from freshly collected human urine [43]. CDA-2 is obviously a drug of choice for the therapy of MDS since it has better therapeutic efficacies than Vidaza and Decitabine, the two US approved drugs, both on cytological evaluation and hematological improvement evaluation [44,45]. Better yet, CDA-2 is devoid of serious adverse effects, whereas Vidaza and Decitabine are proven carcinogens and very toxic to DNA [46-49]. MDS is a disease attributable entirely to CSCs [22]. Thus, wound healing metabolites are proven drugs to display clinical efficacy against CSCs.

Destabilization of abnormal MEs by means of DIs and DHIs is the critical mechanism of wound healing. It is also the most appropriate strategy for cancer therapy. Abnormal MEs are also detectable in primitive stem cells such as embryonic stem cells and PSCs, so that they cannot be considered a specific cancer target. But the silencing of TET-1 enzyme in CSCs and CCs qualifies abnormal MEs as a specific cancer target. Targeted therapies are always better therapies to avoid adverse effects. Unfortunately in cancer therapy, destructive agents are privileged, because cancer establishments set up disappearance of tumor as the most important criterion for the evaluation of therapeutic efficacy. Targeted therapies which do not cause cell death are excluded from consideration as cancer drugs. Destructive agents such as cytotoxic drugs and radiation are apparently contraindication for cancer therapy. They create more wounds to aggravate the already bad situation. Their inability to eradicate CSCs and their contribution to further damage chemo-surveillance lay the ground for inevitable recurrence and fatality. So even the fortunate few who have achieved complete remission through destructive therapies are eventually succumbed to recurrence. That is why cancer mortalities remain at old time high worldwide. May be a very few early stage cancer patients whose functionality of chemo-surveillance is not fatally damaged in the process can recover to subdue surviving CSCs. Disappearance of tumor definitely is a questionable therapeutic endpoint for the evaluation of cancer therapy. Other criteria must be established such as disappearance of circulating CCs and CSCs, disappearance of cancer markers, restoration of the functionality of chemo-surveillance, etc. Gene therapy is of course the most fascinating and attractive field. To correct abnormal gene is a very difficult task. Even one gene abnormality is successfully corrected, there may soon pop up another gene abnormality. It is an endless struggle to correct difficult gene abnormalities. Oncogenes and suppressor genes are, after all, cell cycle regulatory genes. They have important roles to play when cells are in cell cycle replicating. But if cells exit cell cycle to undergo TD, they have no roles to play. So a stroke to destabilize abnormal MEs can also put to rest abnormal gene problems. Abnormal MEs can be considered as the bullseye of targeted cancer therapies [50].

5. CONCLUSION

Wound healing and the evolution of cancer are closely related to involve PSCs as the critical common elements. The study of the mechanism of wound healing and the impact of wound on cancer evolution and cancer therapy can shed light on more appropriate strategy for cancer therapy. The mechanism of wound healing is mediated by PGs to promote the proliferation of PSCs and by DIs and DHIs to direct TD of PSCs. Cancer arises as a consequence of the wound not healing properly, allowing PSCs to evolve

into CSCs, and then to progress to faster growing CCs. Destabilization of abnormal MEs, exactly the same strategy of successful wound healing, is the most appropriate strategy for cancer therapy. There remains a big problem. This strategy cannot make tumors to disappear.

DISCLAIMER

The products used for this research are commonly and predominantly used products of our area of research. There is no conflict of interest between the authors and the producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also the research was not funded by producing company, rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Liau MC, Baker LL. Wound healing, evolution of cancer and war on cancer. Intl Res J Oncol 2021; 4(3): 13-20.
2. Liau MC, Zhuang P, Chiou GCY. Identification of the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. Chin Oncol Cancer Res 2010; 7(2): 86-96.
3. Liau MC, Lee SS, Burzynski SR. Hypomethylation of nucleic acids: A key to the induction of terminal methylation. Intl J Exptl Clin Chemother 1989; 2: 187-199.
4. Liau MC, Lee SS, Burzynski SR. Modulation of cancer methylation complex isozymes as a decisine factor in the induction of terminal differentiation mediated by Antineoplaston A5. Intl J Tiss React 1990; 12(Suppl.): 27-36.
5. Liau MC, Chang CF, Saunders GS, Tsai YH. S-Adenosylhomocysteine hydrolases as the primary target enzymes in androgen regulation of methylation complexes. Arch Biochem Biophys 1981;208(1): 261-272.
6. Liau MC, Szopa M, Burzynski B, Burzynski SR. Chemo-surveillance: A novel concept of the natural mechanism against cancer. Drug Exptl Clin Res 1987; 13(Supptl. 1): 77-82.
7. Hwa J, Martin K. Chapter 18: The eicosanoids: prostaglandins, thromboxanes, and related compounds. In: Katzung BG (ed.) Basic and Clinical Pharmacology (14th ed) New York, NY: McGraw-Hill Education, 2017.
8. Ho ATV, Palla AR, Blake MR, Yual ND, et al. Prostaglandin E2 is essential for efficacious skeletal muscle stem cell function, augmenting regeneration and strength. Proc Natl Acad Sci USA 2017; 114(26): 6675-6684.
9. Liau MC, Kim JH, Fruehauf JP. Arachidonic acid and its metabolites as surveillance differentiation inducers to protect healthy people from becoming cancer patients. Clin Pharmacol Toxicol Res 2021;4(1):7-10.
10. Riciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011; 31(5): 986-1000.
11. Itkin T, Rafii S. Leukemia cells ”gas up” leaky bone marrow blood vessels. Cancer Cell 2017;32(3): 276-278.
12. Passaro D, Di Tullo A, Abarrategi A, Rouault-Pierre K, et al. Increased vascular permeability in the bone marrow microenvironment contributes to disease progression and drug response in acute myeloid leukemia. Cancer Cell 2017;32(3): 324-341.
13. Liau MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes: Nature’s way to eradicate cancer stem cells. Online J Complement Alt Med 2019; DOI: 10.33552/OJCAM.2019.02.000546.
14. Liau MC, Baker LL. The functionality of chemo-surveillance dictates the success of wound healing as well as cancer therapy. Nov Res Sci 2021;7(2):NRS.000657.2021.
15. Willamson PJ, Kruger AR, Reynolds PJ, Hambin TJ, et al. Establishing the incidence of myelodysplastic syndromes. Br J Haemato 1994;87(4):743-745.
16. Boula A, Vougarelis SM, Grennouli S, Kotrinakis G, et al. Effect of cA2 antitumor necrosis factor-a antibody therapy on hematopoiesis of patients with

myelodysplastic syndromes. Clin Cancer Res 2008; 12(10): 3099-3108.
17. Counter CM, Gupta J, Harley CB, Leber B, et al. Telomerase activity in normal leukocytes and hematological malignancies. Blood 1995; 85(9): 2315-2320.
18. Fu C, Chen Z. Telomerase activity in myelodysplastic syndrome. Chin Med J (Eng) 2002; 115(10): 1075-1078.
19. Larson CA, Cote G, Quintas-Cardama A. The changing mutational landscape of acute myeloid leukemia and myelodysplastic syndrome. Mol Cancer Res 2013; 11(8): 815-827.
20. Papaemmanuil E, Gerstung M, Malconvati L, Tauro SM et al. Clinical and biological implication of driver mutations in myelodysplastic syndromes. Blood 2013; 124(17): 2705-2712.
21. Kennedy JA, Ebert BI. Clinical implication of genetic mutations in myelodysplastic syndrome. J Clin Oncol 2017; 35(9): 967-974.
22. Woll PS, Kjallquist U, Chowdhury O, Doolittle H, et al. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo. Cancer Cell 2014; 25(6): 794-808.
23. Maeck L, Hasse D, Schoch D, Hiddemann W, et al. Genetic instability in myelodysplastic syndrome: Detection of microsatellite instability and loss of heterozygosity in bone marrow sample with karyotype alteration. Br J Haemato 2000; 109(4): 842-846.
24. Xie D, Hefmann KW, Mori N, Miller CW. Allotype analysis of the myelodysplastic syndrome. Leukemia 2001; 14: 805-810.
25. Kuramoto K, Ban S, Oda K, Tanaka H, et al. Chromosomal instability and radiosensitivity in myelodysplastic syndrome. Leukemia 2002; 16(10): 2253-2258.
26. Takada A, Goosby C, Yaseen NR. NUP98-HOXA 9 induces long term proliferation and blocks differentiation of primary human CD34+ hematopoietic cells. Cancer Res 2006; 66(13): 6628-6637.
27. Kampalath BN, Liau MC, Burzynski B, Burzynski SR. Chemoprevention by Antineoplaston A10 of benzo(a)pyrene induced pulmonary neoplasia. Drug Exptl Clin Res 1987; 13(Suppl. 1): 51-56.
28. Kampalath BN, Liau MC, Burzynski B, Burzynski SR. Protective effect of Antineoplaston A10 in hepatocasrcinogenesis induced by aflatoxin B1. Intl J Tissue React 1990; 12(Suppl.): 43-50.
29. Liau MC, Chang CF, Becker FF. Alteration of S-adenosylmethionine synthetases during chemical hepatocarcinogenesis and in resulting carcinomas. Cancer Res 1979; 39: 2113-2119.
30. MacCarthy-Morrough L, Martin P. The hallmarks of cancer are also the hallmarks of wound healing. Science Signaling 2020; 13: 648.
31. Liau MC, Baker LL. Destruction promotes the proliferation of progenitor stem cells and cancer stem cells. Therefore, non-destruction is a better strategy for cancer therapy: A commentary. J Pharmacol Pharmaceu Pharmacovig 2020; 4: 029. DOI: 10.24966/PPP-5649/100029.
32. Liau MC, Baker LL. Eradication of cancer stem cells to win the war on cancer. Nov Res Sci 2021; 6(5): NRS.000647.2021.
33. Liau MC, Fruehauf JP. Restoration of the chemo-surveillance capability is essential for the success of chemotherapy and radiotherapy to put cancer away. Adv Complement Alt Med 2019; 5(4): ACAM.000617.2019..
34. Zhou S, Schuetz JD, Bunting KD, Colapietro AM, et al. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side population phenotype. Nat Med 2001; 7: 1028-1034.
35. Montra K, Lou H, Dean M. Multidrug efflux pumps and cancer stem cell in sights into multidrug resistance and therapeutic development. Clin Pharmacol Ther 2011; 89: 491-502.
36. Frome FM, Maitland NJ. Cancer stem cell, model of study and implication of therapy resistant mechanism. Adv Exp Med Biol 2011; 720: 105-118.
37. Zhang M, Atkinson RI, Rosen M. Selective targeting of radiation resistant tumor initiating cells. Proc Natl Acad Sci USA 2010; 107: 3522-3527.
38. Jordan CT, Guzman ML, Noble M. Cancer stem cells. N Eng J Med 2006; 355(12): 1253-1261.
39. Zabierowski SE, Herlyn M. Melanoma stem cells: The dark seed of melanoma. J Clin Oncol 2008; 26(17): 2890-2894.
40. Hemmings C. The elaboration of a critical framework for understanding cancer: The cancer stem cell hypothesis. Pathology 1020; 42(2): 105-112.

41. Liau MC, Fruehauf JP. It has been half a century since President Nixon declared war on cancer: Destabilization of abnormal methylation enzymes has the blessing of the nature to win the war on cancer. Adv Complement Alt Med 2020; 6(1): ACAM>000630.2020.
42. Liau MC, Fruehauf JP. The winner of the contest to eradicate cancer stem cells wins the contest of cancer therapies: The winner is cell differentiation agent formulations. Adv Complement Alt Med 2020; 5(4): ACAM.000620.2020.
43. Liau MC. Pharmaceutical composition inducing cancer cell differentiation and the use for the treatment and prevention of cancer thereof. US Patent 7232578 B2, 2007.
44. Ma J. Differentiation therapy of malignant tumor and leukemia. CSCO Treaties on the Education of Clinical Oncology 2007; 480-486.
45. Liau MC, Fruehauf JP. Destabilization of abnormal methylation enzymes as a critical mechanism for CDA-2 to reverse MDS progression. The First International Forum of Myelodysplastic Syndrome in Tai Zhou, Jiangsu, China 2015; 31-35.
46. Prassana P, Shack S, Wilson VL, Samid D. Phenylacetate in chemoprevention of 5-aza-2'-deoxycytidine-induced carcinogenesis. Clin Cancer Res 1995; 1(18): 865-871.
47. Palii SS, van Emburgh BO, Sankpal UT, Brown KD, et al. DNA methylation inhibitor 5-aza-2'-deoxycytidine induces reversible DNA damage that is distinctly influenced by DNA methyltransferase 1 and 3B. Mol Cell Biol 2008; 28(2): 752-771.
48. Kizietepe T, Hideshima T, Catley L, Raje N. 5-Azacytidine, a DNA methyltransferase inhibitor, induces ATR-mediated DNA-double strand break responses, apoptosis, and synergistic cytotoxicity with doxorubicin and bortezomib against multiple myeloma cells. Mol Cancer Ther 2007; 8(6): 1718-1727.
49. Yang Q, Wu F, Wang F, Cai K, et al. Impact of DNA methyltransferase inhibitor 5-aza-cytidine on cardiac development of zebrafish in vivo and cardiomyocyte proliferation, apoptosis, and the homeostasis of gene expression in vitro. J Cell Biochem 2019; 120(10): 17459-17471.
50. Liau MC, Baker LL. Abnormal methylation enzymes as the bullseye of targeted cancer therapies. Nov Res Sci 2021; 7(4): NRS.000677.2021.

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