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Opinion

Abnormal Methylation Enzymes as the Bullseye of Targeted Cancer Therapies

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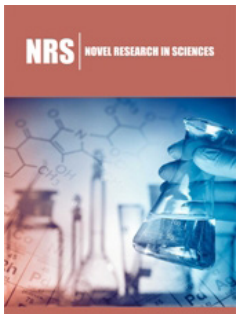

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Opinion

Targeted therapy vs non-targeted therapy

Non-targeted cell killing is the choice of cancer therapy in the past, because it is the most effective strategy to stop the perpetual proliferation of cancer cells. Non-targeted cell killing includes cytotoxic chemotherapy and radiotherapy that aims to kill cells in replication indiscriminately. Non-targeted cell killing dominates cancer therapy for as long as one can remember, but cancer mortalities remain at old time high worldwide. Obviously, non-targeted cell killing is unable to save the majority of cancer patients. We have presented reasons to explain why non-targeted cell killing was unable to save cancer patients [1-4]. The inability of non-targeted therapy to eradicate Cancer Stem Cells (CSCs) and the contribution to fatally damage the functionality of chemo-surveillance denied the success of non-targeted cell killing to put cancer away. Since non-targeted cell killing is unable to put cancer away, we have no choice but to turn to other therapies to win the war on cancer. Targeted therapy is of course a logical choice. We all know that targeted therapy is always a better therapy, because it has the selectivity which can avoid adverse effects. But we put too much emphasis on the reduction of tumor mass in the past for the evaluation of effective cancer drugs. Targeted therapy is disfavored, because targeted drugs are not as good as non-targeted drugs to cause the reduction of tumor mass. The reduction of tumor mass is a valid criterion for the evaluation of drugs based on cell killing. Since the drugs based on cell killing cannot get the job done, the reduction of tumor mass should be dropped as a valid criterion to judge the effectiveness of cancer drugs. There are a wide variety of therapeutic targets unique to cancer cells, it is difficult to set up a common criterion for the evaluation of targeted cancer drugs. We may have to develop different criteria for the evaluation of therapeutic efficacy against different cancer targets.

Cancer targets

Targets specific to cancer cells include abnormal Methylation Enzymes (MEs) which are responsible for the blockade of differentiation, oncogenes and suppressor genes which are responsible for enhanced cell replication, oncoproteins including growth factors, growth factor receptors, and signal transductions, which are also responsible for enhanced cell replication. Oncogene and suppressor gene abnormalities are a very active and fascinating cancer field. The correction of gene abnormality is a highly sophisticated technology, which is not within the scope of this article. But there are easy solutions to the difficult gene abnormalities. Oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cells are in cell cycle replicating. But if the replicating cells exit cell cycle to undergo Terminal Differentiation (TD), these genes have no roles to play. Therefore, destabilization of abnormal MEs to induce TD will automatically put to rest difficult problems of gene abnormalities. Killing cancer cells is another easy way to put out difficult problems of gene abnormalities. Growth factors, growth factor receptors, and signal transductions are related problems, all leading to enhanced cell replication. Inhibitors of growth factors, growth factor receptors, and signal transductions can be very good cancer drugs. In fact, many excellent cancer drugs have been approved for cancer therapy. Growth factors, growth factor receptors, and signal transductions are all oncogene products. Different cancers have different oncogene activations, so a drug effective against a particular oncogene is only good for the therapy of this particular cancer. Since there are multiple ways to activate oncogenes, resistance may

quickly develop, which is a major disadvantage of targeted therapy. The inhibitors of growth factors, growth factor receptors, and signal transductions end up producing factors to destabilize MEs through inhibition of S-adenosylhomosysteine hydrolase, which are excellent Differentiation Helper Inducers (DHIs) [5]. The therapeutic endpoints are either TD if the functionality of chemo-surveillance is not badly destroyed as early stage cancer, or apoptosis if the functionality of chemo-surveillance is fatally destroyed as advanced stage cancer. Like non-targeted therapy, only early stage cancer can be benefited from targeted therapy, whereas advanced stage cancer always loss to the multiplication of CSCs. Development of excellent DHIs to help perfection of differentiation therapy can achieve effective cancer therapy attributable to targeted therapy. Therefore, abnormal MEs stand out as the most important target for cancer therapy.

Abnormal MEs as the bullseye of targeted cancer therapies

MEs play a critical role on the regulation of cell replication, differentiation, and apoptosis by virtue of the fact that DNA MEs control the expression of tissue specific genes [6], and pre-rRNA MEs control the production of ribosome [7], which in turn dictates the commitment of cells to initiate replication [8]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [9]. Biological methylation is mediated by a ternary enzyme complex consisting of Methionine Adenosyl Transferase (MAT)-Methyl Transferase (MT)-S-Adenosylhomocysteine Hydrolase (SAHH) [10,11]. These enzymes must be in a ternary enzyme complex to become stable and functional. In the monomeric state, individual enzymes are quickly inactivated. SAHH is the most unstable enzyme, followed by MT, and then MAT. MTs in the monomeric state have a great tendency to be converted into nucleases to trigger apoptosis. The conversion of MTs into nucleases can be prevented by keeping MTs in the dimeric state with SAHH, or by the use of inhibitors of MTs to resist protease modification. SAHH requires a steroid factor to assume confirmation favorable for the formation of a dimeric enzyme complex with MT, which can then associate with MAT to form the ternary enzyme complex. In steroid hormone target tissues, such as prostate or breast, steroid hormones are the stabilizing factors of SAHH. Other tissues require steroid factors similar to steroid hormones to stabilize SAHH [5]. In normal cells, steroid factors are the dominant factors to modulate MEs. In cancer cells and telomerase expressing stem cells such as Embryonic Stem Cells (ESCs) and PSCs, MEs are associated with telomerase to turn MEs to become abnormal MEs [12]. The abnormal MAT-SAHH isozyme pair display K_m values 7-fold higher than the normal isozyme pair [10,12]. The higher K_m values are the reason why the abnormal MEs are exceptionally stable, because S-adenosylmethionine (AdoMet) can protect protein against protease digestion [13]. The increased pool sizes of AdoMet and S-Adenosylhomocysteine (AdoHcy) of the cancer cells are important for the promotion of malignant growth. It has been shown by Chiba et al. [14] that the pool sizes of AdoMet and AdoHcy shrunk greatly when cancer cells were induced to undergo TD. Thus, abnormal MEs are essential for the promotion of malignant growth.

Abnormal MEs are due to the association of MEs with telomerase. Many normal cells express telomerase, for example ESCs and PSCs. Then abnormal MEs should not be regarded as cancer target. During the transition from normal stem cells to cancer cells, TET-1 enzyme is silenced [15,16]. The silencing of TET-1 enzyme completely wipe out the differentiation capability of cancer cells. Therefore, abnormal MEs are a specific cancer target. Evidently, destabilization of abnormal MEs is also a critical mechanism for PSCs to carry out TD to heal the wound [1-4]. Wound healing is a major biological mission of PSCs. The functionality of chemo-surveillance is required for the perfection of wound healing [3]. Healthy people are able to produce a steady level of metabolites active as DIs and DHIs to ensure perfect wound healing. DIs are chemicals that can eliminate telomerase from abnormal MEs and DHIs are inhibitors of individual enzymes of the ternary MEs. Wound healing metabolites constitute the basis of chemo-surveillance brought up by Liau et al. [17]. If the functionality of chemo- surveillance is damaged due to pathological conditions cause by chronic wounds, then wounds cannot be healed properly to result in continuous proliferation of PSCs beyond what is needed to complete wound healing. The proliferation of PSCs always runs a risk for PSCs to evolve into CSCs simply by a single hit to silence TET-1 enzyme, which is well within the reach of PSCs equipped with abnormally active MEs. PSCs and CSCs are protected by drug resistance mechanism. Toxic chemicals cannot put these cells out. Wound healing metabolites, on the other hand, are freely accepted into these cells to carry out wound healing. Therefore, wound healing metabolites are the best hope to take out PSCs and CSCs. Inability to eradicate CSCs is the primary cause of treatment failure of cancer in the past. Development of Cell Differentiation Agent (CDA) formulations to target abnormal MEs of CSCs and cancer cells is the best hope to win the war on cancer [18]. In stark contrast to multiple abnormal genes, abnormal MEs are common to all human cancers [19]. If an effective drug is developed to target abnormal MEs, it is likely to be applicable to all cancers. The active DIs and DHIs involved must work directly on abnormal MEs. DIs of wound healing metabolites work on abnormal MEs directly [11]. Other DIs such as all-trans retinoic acid and phorbol ester, however, work through receptors to generate oligoisoadenylate to affect abnormal MEs. In such cases, the activity of DIs relies on the existence of receptors [20]. Otherwise, there is no concern on the development of drug resistance. The effective drugs to target on abnormal MEs are wide spectrum drugs effective against CSCs and cancer cells of all different cancers. One more merit of cancer drugs to target on abnormal MEs is the ability to prevent tumor progression. Aberrant DNA hypermethylation is frequently observed in the cancer cells of advanced cancer patients due to abnormal MEs. Aberrant DNA hypermethylation can knock out suppressor genes or DNA repair genes to turn cancer cells to become very vicious cells unresponsive to any treatments. Aberrant DNA hypermethylation takes place more readily when DNA synthesis is interrupted by cytotoxic drugs [21,22]. DNA hypermethylation arising naturally or due to drug-

induction can be prevented by wound healing metabolites [23]. So wound healing metabolites are a great help for cancer therapy to avoid tumor progression.

A big problem remains on the therapy to target on abnormal MEs. The endpoint for the evaluation of therapeutic efficacy is not available. The therapeutic endpoint is TD, not cell death. This endpoint is acceptable to the therapy of hematological cancers, which is based on the disappearance of cancer cells. Cancer cells and terminally differentiated cells of hematological cancers can be easily distinguished. The acceptance for the therapy of solid tumors is a problem. There is no clear cut morphological difference between cancer cells and terminally differentiated cells. The remaining tumor mass is nevertheless a fearful concern, even though it is harmless. The examination of circulating cancer cells and CSCs may be a valid therapeutic endpoint. The quantitative measurement of plasma and urinary wound healing metabolites, for example peptides as we have done previously [17] or other markers such as arachidonic acid or pregnenolone, can also be considered valid diagnostic endpoint.

Conclusion

Targeted therapy is better than non-targeted therapy, because targeted therapy has the selectivity to avoid adverse effects. Since non-targeted therapy including cytotoxic chemotherapy and radiotherapy in a very long practice cannot put away cancer, we have to seek other therapies to win the war on cancer. Therapy targeted on abnormal MEs is the most outstanding choice among targeted therapies, because abnormal MEs are universal to all cancer cells. Once abnormal MEs are destabilized by the employment of DIs and DHIs to direct cancer cells, CSCs included, to undergo TD, all other cancer abnormalities can also be put to rest. It is a perfect solution to win the war on cancer. However, there remains a problem to establish a criterion for the evaluation of therapeutic efficacy.

References

1. Liau MC, Baker LL (2021) Cancer arises as a consequence of wound not healing properly. Thus, perfection of wound healing must be the most appropriate strategy to win the war on cancer. Adv Complement Alt Med 6(2), ACAM.000637.2021.
2. Liau MC, Baker LL (2021) The proliferation and the terminal differentiation of progenitor stem cells determine the success of wound healing. Likewise, the proliferation and the terminal differentiation of cancer stem cells determine the success of cancer therapy. Nov Res Sci 6(3), NRS.000636.2021.
3. Liau MC, Baker LL (2021) The functionality of chemo-surveillance dictates the success of wound healing as well as cancer therapy. Nov Res Sci 7(2): 1-3, 1-3 to NRS.000657.2021.
4. Liau Mc, Baker LL (2021) Wound healing, evolution of cancer, and war on cancer. Intl Res J Oncol, 4(3): 13-20.
5. Liau MC, Kim JH, Fruehauf JP (2019) Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. Pharmacol Pharmaceu Pharmacovigi 3(1): 1-9 to 9-17.
6. Racanelli AC, Turner FB, Xie LY, Taylor SM, Moran RG (2008) A mouse gene that coordinates epigenetic controls and transcriptional interference to achieve tissue-specific expression. Mol Cell Biol 28(2): 836-848.
7. Liau MC, Hunt ME, Hurlbert RB (1976) Role of ribosomal RNA methylases in the regulation of ribosome production. Biochemistry 15(14): 3158-3164.
8. Bernstein KA, Bleichert F, Bean JM, Cross FR, Baserga SJ (2007) Ribosome biogenesis is sensed at the start cell cycle check point. Mol Biol Cell 18(3): 953-964.
9. Justilien V, Ali SA, Jamieson L, Yin N, Cox AD, et al. (2017) Ect_2-dependent rRNA synthesis is required for KRAS-TRP_{53}-driven lung adenocarcinoma. Cancer Cell 31(2): 256-269.
10. Liau MC, Chang CF, Saunders GF, Tsai YH (1981) S-Adenosylhomocysteine hydrolases as the primary target enzymes in androgen regulation of methylation complexes. Arch Biochem Biophys 208(1): 261-272.
11. Liau MC (2004) Abnormal methylation enzymes: A selective molecular target for differentiation therapy of cancer. Chin Pharm J 56(2): 57-67.
12. Liau MC, Zhuang P, Chiou GCY (2010) Identification of the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. Chin Oncol Cancer Res 7(2): 86-96.
13. Prudova A, Bauman Z, Braun A, Vitvitsky V, Shelly CL, et al. (2006) S-adenosylmethionine stabilizes cystathionine beta-synthase and modulates redox capacity. Proc Natl Acad Sci USA 103(17): 6489-6494.
14. Chiba P, Wallner C, Kaizer E (1988) S-Adenosylmethionine metabolism in HL-60 cells: Effect of cell cycle and differentiation. Biochim Biophys Acta 971(1): 38-45.
15. Kudo Y, Tateishi K, Yamamoto K, Yamamoto S, Asaoka Y, et al. (2012) Loss of 5-hydroxymethylcytosine is accompanied with malignant cellular transformation. Cancer Sci 103(4): 670-676.
16. Ficz GM, Giben JG (2014) Loss of 5-hydroxymethylcytosine in cancer: Cause or consequence? Genomics 104(5): 352-357.
17. Liau MC, Szopa M, Burzynski B, Burzynski SR (1987) Chemo-surveillance: A novel concept of the natural defense mechanism against cancer. Drug Exptl Clin Res 13(1): 71-76.
18. Liau MC, Fruehauf PA, Zheng ZH, Fruehauf JP (2019) Development of synthetic cell differentiation agent formulations for the prevention and therapy of cancer via targeting of cancer stem cells. J Cancer Studies Ther 4(1): 1-15.
19. Liau MC, Chang CF, Giovanella BC (1980) Demonstration of an altered S-adenosylmethionine synthetase in human malignant tumors xenografted into athymic nude mice. J Natl Cancer Inst 64(5): 1071-1075.
20. Liau MC, Kim JH, Fruehauf JP (2020) In pursuance of differentiation inducers to combat cancer via targeting of abnormal methylation enzymes. J Cancer Tumor Intl 10(2): 39-47.
21. Nyce J Liu L, Jones PA (1986) Variable effects of DNA synthesis inhibitors upon DNA methylation in mammalian cells. Nucleic Acid Res 14(10): 4353-4367.
22. Nyce J (1989) Drug-induced DNA hypermethylation and drug resistance in human tumors. Cancer Res 49(21): 5829-5836.
23. Liau MC, Luong Y, Liau CP, Burzynski SR (1992) Prevention of drug induced DNA hypermethylation by antineoplaston components. Intl J Exptl Clin Chemother 5(1): 19-27.