

In this review, Dr. Thomas has discussed in brief the development of acute leukemia, with a novel eyesight, the complex adaptive system theory. The complex adaptive system works as a mean other than the hematopoietic microenvironment does, the individuals in the system (including hematopoietic stem cells themselves) react with each other and are attributed to the pre-leukemic evolution, the expansion of leukemic HSCs, the suppression of normal HSCs, and as a result, the dominance of leukemic hematopoiesis. The review paper has been well organized and the viewpoints are very interesting. This reviewer suggests that the author should correct some spelling errors that are occasionally found in the paper, like sytems (systems).

This manuscript discuss leukemia in a macro-view by taking hematopoiesis as an adaptive system. It is interesting but more evidences should be presented before drawing any conclusion. Meanwhile, the manuscript was not organized in a well order, and the key point was not highlighted enough. The author listed 4 common traits of an adaptive system. Is this an original proposal of the author or adopted from other subjects? Several aspects may involve in the mentioned adaptive system, such as leukemia stem cells and their offspring, niche and factors in the hematopoietic environment, T and B cells in adaptive immune. The author should dissect each part of the system, weigh their contributions and outline the mechanisms. Stem cells is a key point in this paper in terms of cell division model, gene mutation, immune privilege, senescence, and other behavior as well. The advantage of leukemic cell proliferation over normal cells should be depict in detail based on recent understanding. Many types of leukemia have been confirmed to be related with gene mutation, and most of them showed better response to therapies targeting the known mutation and/or mutation-induced deficiencies. Mutation does not mean adaption and it could cause a uncontrolled cell proliferation while no extra condition is needed.

This is a "point of view" article from a single author, internationally recognised in the field of leukemia, who makes an interesting scientific summary of the current knowledge of human leukemia development and its interaction with the healthy hematopoietic system and the microenvironment. The paper is written with concise and clear language, is supported by well chosen references and contributes to a broad and dynamic view of leukemogenesis. A minor comment is that there is no indication along the text on the differences of childhood versus adult leukemias. The implications that these differences may imply in the context the author's manuscript deserve a comment, that would improve the paper.

Although the author has tried to review "Leukemic Hematopoiesis" as a complex adaptive system as the title indicates, it will be quite difficult for wide-range of readers to understand what "a complex adaptive system" stands for. For me, this review seems to be an essay rather than a review. The reviewer asks the author to revise the text so that readers outside of the leukemia biology could grasp the concept of "a complex adaptive system" to follow the content. To facilitate this, the author is highly encouraged to add more figures.