Clonal evolution of leukemia from G6PD studies

Tal Bacharach[1] and Liran I. Shlush[1,2]

[1]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot and [2]Molecular Hematology Clinic Maccabi Healthcare Services, Tel Aviv, Israel

E-mail: liranshlush3@gmail.com

https://doi.org/10.3324/haematol.2023.284215

TITLE	Clonal origin of chronic myelocytic leukemia in man.
AUTHORS	Fialkow PJ, Gartler SM and Yoshida A.
JOURNAL	Proceedings of the National Academy of Siences 1967;58(4):1468-1471. PMID: 5237880.

It is now well-established that acute myeloid leukemia (AML) emerges following a long evolution involving a pre-leukemic phase, in which mutations occur in normal hematopoietic stem cells, which clonally expand while maintaining differentiation. The basic evidence for this concept came from a series of studies by Philip J. Fialkow, in which simple and elegant experiments led to groundbreaking conclusions regarding the clonality, cell of origin, and evolution of AML.

These works rely on the inference of the active X chromosome in women as a clonal marker. In women, due to X-inactivation, each cell expresses either the paternal or the maternal X chromosome. Thus, a healthy adult tissue consists of a mixture of cells expressing either the paternal or the maternal X, while a clonal leukemia arises from one cell and, therefore, consists entirely of cells expressing either the paternal or the maternal X.

In 1967, Fialkow studied 3 chronic myeloid leukemia (CML) patients who were heterozygous for X-linked gene *G6PD*.[1] He measured the *G6PD* gene product as a clonal marker in patient-derived erythrocytes and granulocytes, as well as skin-derived fibroblasts. While the fibroblasts expressed both *G6PD* types, the erythrocytes and granulocytes expressed only one type, suggesting they were derived from one cell. From this he concluded that CML is a clonal disease, and suggested that it is derived from a stem/progenitor cell common to both erythrocytes and granulocytes.

The same methodology was applied to studies of AML, in which Fialkow demonstrated that AML too is a clonal disease.[2] Furthermore, he performed lineage tracing in AML patients by studying the *G6PD* gene product in various hematopoietic cell types, and established that AML can originate in two distinct cell types: either a multipotent stem cell or a progenitor of granulocytes and macrophages.[2,3] By studying the *G6PD* gene product in samples from AML remission, he showed two distinct remission types, either non-clonal (suggested to originate in normal stem cells that re-populated the bone marrow after treatment) or clonal remission.[2,4] He further linked the cell of origin with remission type in AML. He observed that one form of AML is typical of younger patients, in which the leukemia originates in a granulocyte-macrophage progenitor, and non-clonal remission is obtained from normal stem cells; the second type, typical to older patients, originates in a multipotent stem cell, in which remission is clonal.[5] The observation that in 100% of patients with clonal remission, the clone in remission shows the same marker as the clone in diagnosis, proved that clonal remission starts from a pre-leukemic stem cell.[6] This led to the conclusion that AML occurs in a multi-step fashion, starting with a preleukemic phase which involves the clonal proliferation of hematopoietic stem cells, followed by a late stage involving the acquisition of 'late' chromosomal changes which give a selective advantage of subclones to evolve to leukemia.[6]

The important concepts introduced by these experiments are the consequence of scrupulous observation, but even more so, of bold and brilliant interpretation that has revolutionized the understanding of the evolution of AML.

Disclosure

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

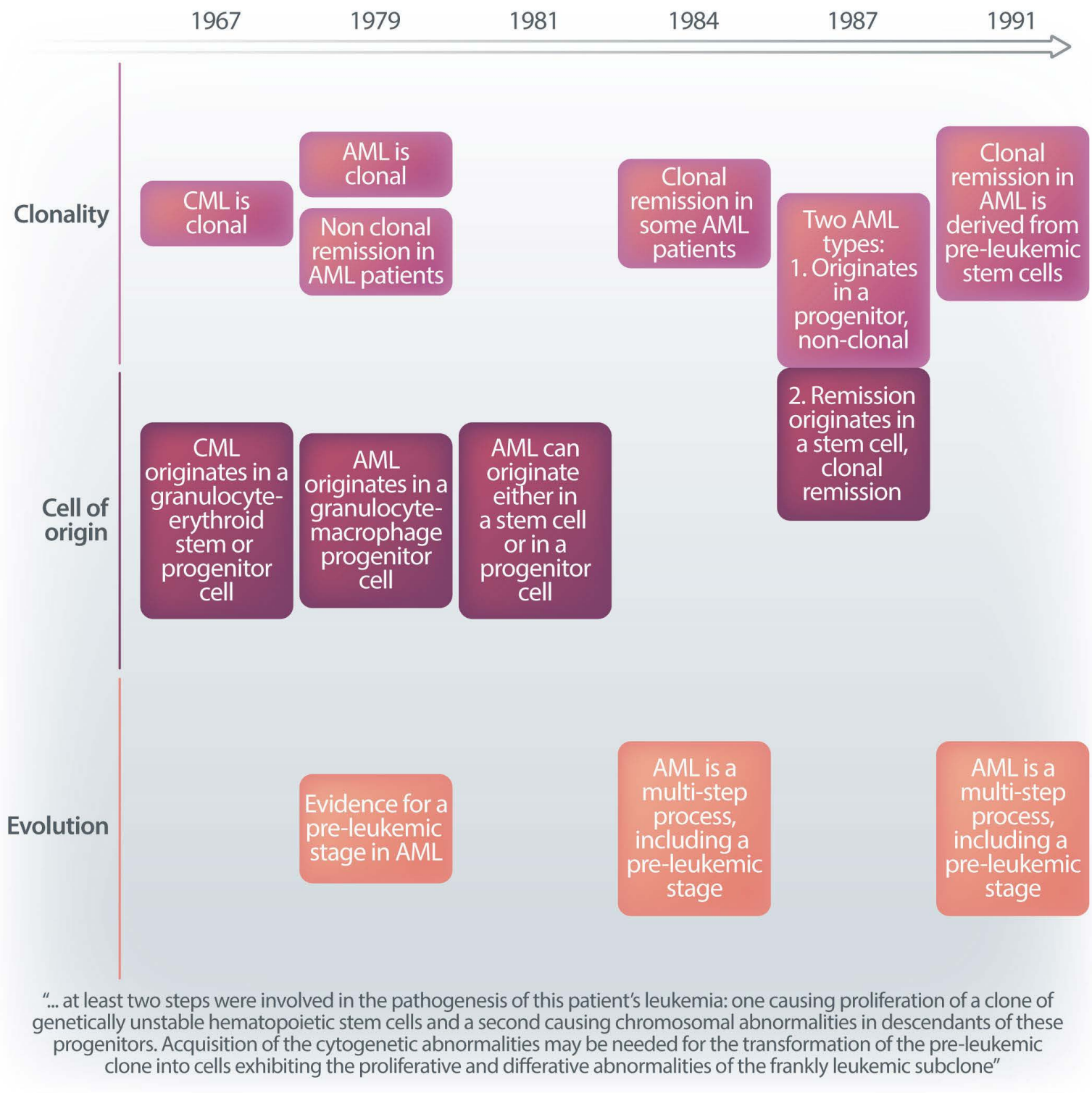

Figure 1. Main contributions of the works by Fialkow to the study of acute myeloid leukemia (AML) evolution over the years. CML: chronic myeloid leukemia.

References

1. Fialkow PJ, Gartler SM, Yoshida A. Clonal origin of chronic myelocytic leukemia in man. Proc Natl Acad Sci. 1967;58(4):1468-1471.
2. Fialkow PJ, Singer JW, Adamson JW, et al. Acute nonlymphocytic leukemia. N Engl J Med. 1979;301(1):1-5.
3. Fialkow P, Singer JW, Adamson JW, et al. Acute nonlymphocytic leukemia: heterogeneity of stem cell origin. Blood. 1981;57(6):1068-1073.
4. Jacobson RJ, Temple MJ, Singer JW, Raskind W, Powell J, Fialkow PJ. A clonal complete remission in a patient with acute nonlymphocytic leukemia originating in a multipotent stem cell. N Engl J Med. 1984;310(23):1513-1517.
5. Fialkow PJ, Singer JW, Raskind WH, et al. Clonal development, stem-cell differentiation, and clinical remissions in acute nonlymphocytic leukemia. N Engl J Med. 1987;317(8):468-473.
6. Fialkow P, Janssen J, Bartram C. Clonal remissions in acute nonlymphocytic leukemia: evidence for a multistep pathogenesis of the malignancy. Blood. 1991;77(7):1415-1417.