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REVIEW ARTICLE

Leukemic stem cells: clone wars

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Abstract

Leukemic stem cells arise as the effect of mutations of normal hematopoietic cells and overgrow normal hematopoietic tissue. They may also infiltrate other organs. While they begin their life from mutations, they continue to mutate, creating daughter leukemic stem cells that harbor two, three, or more mutations, and these mutations can be different in different daughter stem cells of the same parental line in the same individual. These daughter stem cells then compete between themselves as to which one will overgrow the host tissues with its progeny, and finally will contribute to the host's death. This process can be shaped by therapy, which may preferentially eliminate some subclones and simultaneously favor others. To eliminate such stem cells, therapy is needed that will preferentially attack their self-renewal.

Key words: stem cells, self-renewal, oncogenic mutations

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Introduction

Understanding that leukemias are genetic diseases, and subsequently that they are clonal diseases i.e. they originate from a single mutated cell, has paved the way to the elaboration of a more detailed scenario of the development and course of this group of disorders.

The main question facing researchers was: what properties must a cell acquire to become the initiating cell of leukemia? Firstly, it has to have unlimited self-renewal potential, because otherwise its progeny will sooner or later become exhausted and self-eliminate, which does not occur. As the second necessary property, it has to have either a proliferation or a survival advantage over normal hematopoietic stem cells. In other words, it has to be able to successfully compete with normal cells for the limited space in the host body during subsequent generations. Otherwise, it might survive somewhere hidden but would be overgrown by normal cells, and the visible disease would not develop. As the third property, it has to acquire the capacity to omit, escape, resist or disregard host mechanisms that can put restrictions on its expansion.

Pathway of discoveries

The original paradigm of leukemia development was based on the example of chronic myelocytic leukemia where a single genetic change: translocation 9;22 was identified [1]. Attention was focused on the role of abnormally activated *ABL* gene transferred from chromosome 9 to 22, and fused to *BCR* gene [2]. *ABL* gene was earlier identified as associated with leukemia development in mice after infection with the Abelson Leukemia virus carrying this gene [3]. While viruses do not play a significant role in initiating human leukemia, their role in leukemia development in birds and other mammals was instrumental in allowing discoveries of the first oncogenes. Of note, the first mammalian oncoviruses were discovered in the 1950s by Ludwik Gross [4], a Polish-Jewish virologist who escaped to the United States in 1940. However, it soon became clear after elaborating on chronic myelocytic leukemia that such a single genetic change is insufficient to produce a more aggressive malignancy such as acute leukemia.

Then the 'two-hit' theory was proposed by Alfred G. Knudson [5] who originally (based on studies of retinoblastoma) suggested that inactivation of two antioncogenes

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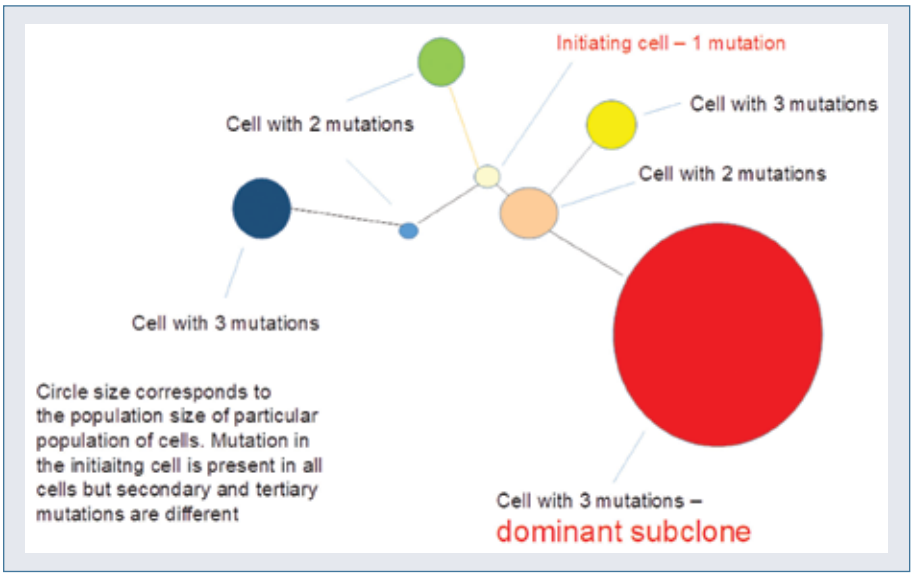

Figure 1. Hypothetical relative clonal composition of leukemic stem cell subclones. In this model, seven subclones compete but only one subclone with three mutations dominates and is clinically evident

on both chromosomes is necessary to allow neoplastic cell behavior. This theory was later modified to allow the co-occurrence of two events: activation of a protooncogene to produce an oncogene, and inactivation of an antioncogene [6].

Therefore, based on this theory, a leukemia-initiating cell should first undergo one mutation, expand, and then one of its progeny cells has to undergo a second mutation to cause further expansion of a subclone with two mutations to produce clinically visible disease. According to this theory, the original clone with one mutation that was outgrowing normal cells had to be finally overgrown by its subclone with two mutations.

This prompted vigorous research worldwide that has led to the identification of many genes mutated in various forms of leukemia. If we focus on acute myeloid leukemia, at least nine groups of genes have been identified that play a role in various forms of this group of disorders [7]. They are not all mutated in a single cell, but various compositions of mutations of these genes may produce clinically similar disorders. Furthermore, some of the genes whose mutations were initially identified in leukemias are mutated also in cells exhibiting normal behavior in subjects with completely normal blood counts.

This condition has been termed clonal hematopoiesis of indeterminate potential (CHIP) [8]. It is present in c.10% of healthy 70-year-old people, and has 1–2% yearly potential to develop into overt disease, either myelodysplastic syndrome or acute leukemia. Interestingly, genes whose mutations are responsible for CHIP which could correspond to the original 'first hit' are neither oncogenes nor antioncogenes, but usually are responsible for DNA methylation [9]. Altogether, this has expanded the 'two-hit' theory to become 'three-hit'.

The introduction of next-generation sequencing allowed the sequence of entire genomes of many subclones of the same leukemia in individual patients to be obtained. Firstly, this has led to our understanding that mutations occur much more frequently than originally anticipated, probably during each cell division. But most of them affect non-coding portions of the genome, or affect cellular functions that are irrelevant for hematopoietic cells [10]. However, they can modify the background on which leukemia-relevant mutations may occur. Consequently, the same leukemia-relevant mutations in cells with different background mutations can produce slightly different effects. It is, for instance, known that the same mutation in different strains of mice (different background) would produce different phenotypes [11].

Clone wars

Then, it was found that in fact in the same patient with leukemia not just two but more subclones of the original leukemic clone coexist, but the only visible one is the one with the best survival advantage (Figure 1). There is constant competition between various subclones. A subclone that once was dominating can be replaced by a new subclone that has acquired another mutation providing either a survival or a proliferation advantage [12–15]. This is additionally influenced by therapy. Depending on the mechanisms of action of a particular drug, different subclones may be eliminated or inhibited, and others may get a survival advantage.

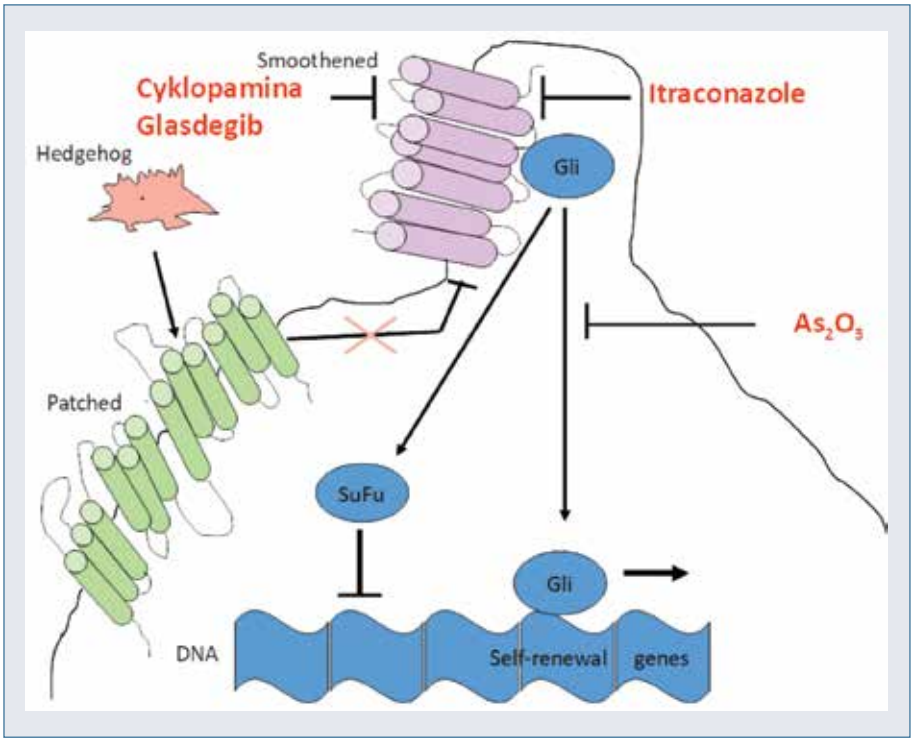

Figure 2. Some known possibilities of interference with self-renewal pathways in leukemic stem cells; Gli, and SuFu — positive and negative regulators of genes controlling self-renewal of stem cells, respectively; AS_2O_3 — arsenic trioxide

In order to operationally cure leukemia, the complete elimination of leukemic clones may not be necessary. Returning to the CHIP level could be sufficient in many cases to allow a patient to survive to his or her normal life expectancy.

Moreover, currently available therapies focus on mechanisms active relatively late in molecular machinery that allow leukemic stem cell expansion. Coming back to the first necessary property of leukemic stem cell that is self-renewal, new therapies should act on this level. Several self-renewal pathways have already been identified including Hedgehog, WNT, NOTCH, and BMP. There is evidence for the role of each of them in leukemic stem cells, but it is usually activation through indirect mechanisms and not by direct mutation. Nevertheless, some of the inhibitors of these pathways are in advanced stages of clinical trials in acute myeloid leukemia [16–19] and some are compounds already used in the clinic for other indications (Figure 2) [20].

Conclusion

Leukemia is a clonal disease in which various subclones of the original clone first outgrow normal hematopoietic cells and their progeny, and later compete between themselves until one of them wins the war and becomes resistant to therapy that will kill the host, thus committing suicide.

Author's contributions

WWJ — sole author.

Conflict of interest

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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