Chapter 15
Systems Modeling of Proliferation Mechanisms in Childhood Acute Lymphoblastic Leukemia

George I. Lambrou
University of Athens, Greece

Apostolos Zaravinos
University of Athens, Greece

Maria Adamaki
University of Athens, Greece

Spiros Vlahopoulos
University of Athens, Greece

ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is the most common neoplasm in children, but the mechanisms underlying leukemogenesis are poorly understood, despite the existence of several theories regarding the mechanics of leukemic cell proliferation. However, with the advent of new biological principles, it appears that a systems approach could be used in an effective search of global patterns in biological systems, so as to be able to model the phenomenon of proliferation and gain a better understanding of how cells may progress from a healthy to a diseased state. This chapter reviews the current knowledge on proliferation dynamics, along with a discussion of the several existing theories on leukemogenesis and their comparison with the theories governing general oncogenesis. Furthermore, the authors present some "in-house" experimental data that support the view that it is possible to model leukemic cell proliferation and explain how this has been performed in in vitro experiments.

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INTRODUCTION

Acute Lymphoblastic Leukemia-Disease Description and Preliminaries

Acute leukemia mainly appears during childhood but it can also occur in adolescence manifesting a poor prognosis regardless of age. Progress in childhood leukemia has been immense the last decades with an overall survival rate exceeding 75% (Carroll, et al., 2003). Still though there is an approximate 20% that relapses, which in many cases can prove fatal. Acute lymphoblastic leukemia, as most cases of childhood neoplasms, is characterized by chromosomal aberrations (Gagos & Irminger-Finger, 2005). In the majority of cases leukemia appears to have a greater incidence of chromosomal abnormalities compared to solid tumors (Saha, Young, & Freemont, 1998). Also, gene expression is aberrantly regulated and in certain cases fusion genes form, that are similarly aberrantly expressed. It has been reported that those genes, involved in leukemia progression, are very potent regulators of cell proliferation, differentiation, cell cycle progression and anti-apoptosis (Saha, et al., 1998). In addition, it has been observed that certain types of leukemia are resistant to chemotherapeutics while others are more sensitive. In other words, depending on the type of leukemia, different chemotherapy intensities might be required. Therefore, it is imperative to mention that classifying patients into risk categories may improve the therapeutic outcome. Hence, recurrence of the disease requires usually more intense chemotherapeutic protocols and in several cases bone marrow transplantation. The prognostic factors have also been well characterized in childhood leukemia; including white blood cell count at presentation (diagnosis), age and gender, immunophenotype, as well as the presence of CNS blast presentation or certain chromosomal aberrations (Carroll, et al., 2003). Treatment of childhood leukemia is successful for the majority of patients, mainly due to the use of classical chemotherapeutics. Recently, individualized treatments have also been applied, as in the case of *BCR/ABL* positive (also known as Philadelphia positive (Ph^+)) leukemia, using imatinib mesylate, a new agent specific for the particular gene fusion.

Yet, the question that might rise is why leukemia and especially childhood leukemia? Acute lymphoblastic leukemia (ALL) is the most frequent occurring malignancy among childhood cancers (Severson & Ross, 1999). It originates from the undifferentiated lymphoblast, which abnormally ceases to develop into the mature lymphoid cell giving rise to a tumour. Hence, one of the most interesting characteristics of leukemia is its trait of clonal expansion. That is, the almost uniform phenotype of cells giving rise to the tumour. But, what does this has to do with leukemogenesis? Necessarily, leukemia as a disease has a starting point and a diagnosis point. Between those two there is an immense lack of knowledge. This does not apply only to leukemia but to any neoplasm in general or even inflammation. For example, as mentioned, absolute lymphocyte count is a prognostic factor in childhood leukemia (De Angulo, Yuen, Palla, Anderson, & Zweidler-McKay, 2008). In that sense, cell counts thus proliferation, is tightly connected to disease prognosis. The next question that would arise is: what is the connection between the first steps of disease emergence and the presentation stage. That is the most difficult part to answer since we simply do not, and cannot, have the slightest clue about what happens between that time and the present. A necessary approach to this phenomenon would be the modeling approach. That is the understanding and prediction of the phenomenon on a physical and systems basis. In order for such an approach to succeed it must entail a range of "crafts" ranging from mechanics, systems theory and thermodynamics to mathematical analysis and chaos dynamics.