Chapter 15
Proliferation and Nonlinear Dynamics of Childhood Acute Lymphoblastic Leukemia Revisited

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ABSTRACT

Acute Lymphoblastic Leukaemia (ALL) is the most common neoplasm in children but the mechanisms underlying leukemogenesis along with the dynamics of leukemic cell proliferation are poorly understood. The importance in understanding the proliferation dynamics of leukaemia lies in the fact that our knowledge from the point of first appearance to the moment of clinical presentation, we know almost nothing. Further on, describing cell proliferation dynamics in a more mature, probably mathematical, way it could lead us to the understanding of disease ontogenesis and thus its action. This chapter reviews the current knowledge on proliferation dynamics and proliferation non-linear dynamics of the leukemic cell. Furthermore, we 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.

INTRODUCTION

Acute Lymphoblastic Leukaemia-Disease Description and Preliminaries

Acute leukaemia mainly appears during childhood but it can also occur in adolescence manifesting a poor prognosis regardless of age. Progress in childhood leukaemia has been immense with an overall survival rate exceeding 75% the last decades (Carroll et al., 2003). Still there is an approximate 20% that relapses, which in many cases can prove fatal. 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

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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).

Yet, the question that might rise is why leukaemia and especially childhood leukaemia? Acute lymphoblastic leukaemia (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 leukaemia 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.

THE MERGING OF BIOLOGICAL SCIENCES WITH THE “EXACT” SCIENCES

As we have mentioned numerous times before, until recently, one of the main approaches in scientific research was the study of molecules in a sequential order. That is, we were able to discover the function and roles of genes or protein in pairs or maximal three at the same time. The last decade, this has changed. With the advent of high-throughput methodologies, the study of thousands of factors (and even millions meanwhile) has been plausible. Microarrays and deep-sequencing are two examples of such methodologies. Yet, we must admit that this revolution was facilitated with the development of the personal computer. From the time point that computational power became publicly available has revolutionized the way science has preceded with its steps. On the other hand, biology was a science that was based, and to a great extent still is, on observation. This of course was true for all natural sciences, yet other disciplines such as the physical or chemical sciences were more mature since they were able to describe their phenomena through a common mathematical language. For example, it is of great certainty that a falling weight will go down towards the gravitational force of the earth and as a matter of fact we are in position, knowing the initial height of the falling body, to calculate the exact velocity just before it crashes to the ground. Also, given the time interval we are able to calculate, again with great certainty, the exact position of the falling body from its initial point. The amazing thing is that if we took consecutive measurements on the falling weight we would find very similar results and we would obtain for our results a very high confidence interval. On the other hand, if we take cultured cells (cell lines) and need to know their number at a given time point, it is impossible to do so, if we know, with great certainty, the initial cell number. As in the case of the falling body, if we could perform
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