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Mathematical modeling of bone marrow – peripheral blood dynamics in the disease state based on current emerging paradigms, part I

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ABSTRACT

Stemming from current emerging paradigms related to the cancer stem cell hypothesis, an existing mathematical model is expanded and used to study cell interaction dynamics in the bone marrow and peripheral blood. The proposed mathematical model is described by a system of nonlinear differential equations with delay, to quantify the dynamics in abnormal hematopoiesis. The steady states of the model are analytically and numerically obtained. Some conditions for the local asymptotic stability of such states are investigated. Model analyses suggest that malignancy may be irreversible once it evolves from a nonmalignant state into a malignant one and no intervention takes place. This leads to the proposition that a great deal of emphasis be placed on cancer prevention. Nevertheless, should malignancy arise, treatment programs for its containment or curtailment may have to include a maximum and extensive level of effort to protect normal cells from eventual destruction. Further model analyses and simulations predict that in the untreated disease state, there is an evolution towards a situation in which malignant cells dominate the entire bone marrow - peripheral blood system. Arguments are then advanced regarding requirements for quantitatively understanding cancer stem cell behavior. Among the suggested requirements are, mathematical frameworks for describing the dynamics of cancer initiation and progression, the response to treatment, the evolution of resistance, and malignancy prevention dynamics within the bone marrow – peripheral blood architecture.

1. Introduction

In a recent article [1], we discussed the hematologic disorders such as the anemias, the leukemias, and the myelodysplastic syndromes (MDS) and proposed a simple delay differential equation model for quantifying the normal hematopoietic state. This was a prelude to effectively modeling and understanding the cancerous disorders that arise due to breaches of the massive physiological activity of hematopoiesis. Our modeling activities in [1] were based on considerations of cell systems in the bone marrow (BM) and peripheral blood (PB) since a number of studies, as in [2–6], deal with or generate data that are based on these cell systems. These studies provide us with the motivational impetus to proceed with modeling the disease state within the context of current emerging paradigms about cancer development by dwelling on cell behaviors in the BM and PB.

In earlier studies [7–11], we only considered single cell populations lumped together as normal and abnormal cells, respectively. Lumping together of the cell populations served as a simple first approximation to modeling and seeking insight into cell behavior but this had its limitations since it tended to hide other intricate properties such as cell cycle mechanisms but that approach served the purpose of uncovering and shedding light on the mechanisms of phenomena such as the evolution of contact inhibition. We note that new understanding of the fundamental mechanisms of tumor initiation and propagation have led to ideas such as the cancer stem cell hypothesis of which, some elucidations can be found in works such as [12–20], that may hold keys to shifts in current thinking regarding cancer treatment paradigms [21,22]. The growing evidence supporting this hypothesis is becoming extensive in scope as highlighted in a number of studies for which we herein cite a few, [18–37], a list that is in no way exhaustive but serves as a representation of active work going on in this field of endeavor. This makes it important and imperative for us to seek

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improvements to our earlier models by investigating various modeling scenarios with the view to bringing our models in line with current thinking and also with the aim of shining further spotlight on the plausibility and veracity of this hypothesis from a mathematical modeling perspective.

As the cancer stem cell hypothesis gains importance, it is becoming clear that understanding basic stem cell biology, facets of which could be discerned from [38–44], including knowledge about the replicative repertoire of different stem cells, would be crucial to the development of new approaches to cancer treatment in the future. Cancer stem cells (CSCs) are defined as a rare cell population in cancer, which acts like normal hematopoietic stem cells (HSCs) and this cell population (CSCs) is responsible for tumor growth and metastasis [12,13]. Marx points out in [45] that the CSC idea has been bounced around for about 50 years but it more or less fizzled out in the mid-1970s because researchers were not able to assess the carcinogenic potential of such cells in living animals [32]. The idea was revived in 1983 when Mackillop and others [14] hypothesized that every tumor contains a rare population of functionally distinct CSCs. This led to its rebirth along with it gaining unassailable traction in the early 1990s when Dick and his coworker [32] successfully used a mouse model to study the development of human HSCs that give rise to various types of blood cells. The notion of CSCs stems from the observation that not all cells within a tumor can maintain tumor growth; instead, most cancers consist of heterogeneous cell populations similar to the hierarchical tree of stem cell lineages and clinical observations have supported the CSC idea as findings in [15] show that CSCs remain viable even though standard chemotherapy kills most cells in a tumor. Indeed, despite the relatively small number of CSCs, they have been considered, due to their "stemness," to be the cause of tumor recurrence, sometimes many years after the "successful" treatment of a primary tumor [16].

CSCs have been said to arise either from normal stem cells or from normal progenitor cells [34,37] and experiments by Shiras and coworkers [47] show that they can be generated from normal stem cells. They are also adjudged to be similar to normal somatic stem cells that are pluripotent stem cells found in a number of organs and are responsible for tissue regeneration and repair. Somatic stem cells are said to possess three common properties: self-renewal, multilineage differentiation, and longevity (the stem cell may be immortal) [28]. Somatic stem cells and CSCs share almost all of the same factors for the regulation of their self-renewal, differentiation, and proliferation pathways [19]. The best-investigated and most comparable somatic and cancer stem cells are HSCs and leukemic stem cells (LSCs) [20,31,32] and studies of tumors such as leukemia and lymphoma, for example, suggest that the CSCs can be derived from either HSCs, or from progenitor cells that have gained the ability to self-renew [34]. HSCs are responsible for the generation of all cell types in the blood [17,30]. As in the normal system of hemopoiesis, the leukemic system is organized as a hierarchy, in which only a rare population, the LSCs, retain clonogenic capabilities upon transplantation [20]. Thus, it is notable that acute myeloid leukemia (AML) was one of the first diseases in which the existence of CSCs, using xenogeneic transplantation models, was proven [48]. As a consequence, human leukemia stem cells (LSCs) represent the most well characterized cancer stem cell population [48] and as such occupy an important space in our studies.

Despite the progress in isolating CSCs, a number of questions are still without definitive answers and one noteworthy debate has concerned the origin of CSCs and therefore of the tumor [37]. In addition to what we mentioned earlier, we note that findings from several studies in hematologic malignancies support the concept that CSCs may originate from self-renewing somatic stem cells that are transformed by dysregulation of the self-renewal pathway, resulting in expansion of tumorigenic cancer cells [15,46]. Other studies have hypothesized that CSCs could arise from committed progenitors that acquire the capacity for self-renewal as for example, a mutation that enhances nuclear b-catenin in granulocyte-macrophage progenitor cells causes blast crisis in some patients with chronic myeloid leukemia [35] when the mutated progenitor cells acquire the capacity for self-renewal and undergo unlimited growth as cancer cells [34,36]. Essentially, irrespective of how the CSCs arise, the main thrust of the CSC concept is that of functional heterogeneity within tumors with the presence of a distinct rare population of cells, no matter how small, that drives tumorigenesis. This distinct population that has the properties of quiescence, self-renewal, and proliferation may be responsible for supporting resistance to different forms of therapy and also for causing relapses. Gaining deeper insights into the development of stem cells in general and CSCs in particular with the aim of interfering with the emerging CSC population for the purpose of bringing about its eradication poses challenges to biomedical research and engenders approaches from various viewpoints including mathematical modeling. It is within this framework that this article assumes significance.

Until the CSC hypothesis started gaining traction, the existing classical view of malignant development as propounded by Clarkson [49] and upon which some representative mathematical models have been based [7–9,50,51] and have already been subjected to reviews, as in [52], held that in cancers such as those of the disseminated type like leukemia, normal and abnormal cells exist side-by-side but with the abnormal cells interfering with normal cell function and ultimately assuming dominance in the absence of treatment. In this discourse, we propose an expanded version of our earlier models in the spirit of the classical view. In the process of doing this, we employ relevant information that partially utilizes the current CSC paradigm that we discussed earlier to enhance our proposed model so as to shed light on the ensuing dynamics in the disease state that show situations in which malignant dominance may occur. In doing this, we identify the main model parameters that influence the propagation of malignancy and also discuss the difficulties in estimating model parameters. We will study and investigate more aspects of the CSC hypothesis through mathematical modeling in a sequel immediately following this article. We believe this approach would enable us to completely profile the evolution of ideas about malignant development and growth starting from the classical view of such a development and going through to the current CSC paradigm. Accordingly, it is important for us to point out at this juncture that the spotlight in this article is not on cancer treatment and the evolution of phenomena such as resistance, we plan to address these in later studies. We believe that to correctly and quantitatively predict treatment outcomes through modeling, it is essential to adopt the systems approach of first using models to accurately describe the qualitative dynamics that encompass the time evolution properties for cell production and decay, behaviors at steady state, and possible oscillatory or non-oscillatory characteristics before superimposing treatment protocols on such models. As such, what we present in this article is an expanded model that, at a relatively definitive level, captures certain essential features of behaviors in the disease state and which we will use to address wider modeling challenges in the very near future.

As we proceed, we deem it important to mention that mathematical modeling of cancer has been steadily progressing over the past few years. To underscore the significance of this progress, we find it appropriate to point to some of the contextually related works of interest that have appeared in the literature and that are discussed more exhaustively in the sequel (part 2) to this article: [53–65]. Notably in any case, most of the studies in [53–65] utilize ideas about the hierarchical structure observed in CSC development [27] to come up with multi-compartmental models that