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Interaction between the immune system and acute myeloid leukemia: A model incorporating promotion of regulatory T cell expansion by leukemic cells

Yoshiaki Nishiyama [a], Yutaka Saikawa [b], Nobuaki Nishiyama [a,c,*]

[a] Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Ishikawa, 9201192, Japan
[b] Department of Pediatrics, Kanazawa Medical University, Uchinada, Ishikawa, 9200293, Japan
[c] Institute of Liberal Arts and Science, Kanazawa University, Kakuma, Ishikawa, 9201192, Japan

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ABSTRACT

Population dynamics of regulatory T cells (Treg) are crucial for the underlying interplay between leukemic and immune cells in progression of acute myeloid leukemia (AML). The goal of this work is to elucidate the dynamics of a model that includes Treg, which can be qualitatively assessed by accumulating clinical findings on the impact of activated immune cell infusion after selective Treg depletion. We constructed an ordinary differential equation model to describe the dynamics of three components in AML: leukemic blast cells, mature regulatory T cells (Treg), and mature effective T cells (Teff), including cytotoxic T lymphocytes. The model includes promotion of Treg expansion by leukemic blast cells, leukemic stem cell and progenitor cell targeting by Teff, and Treg-mediated Teff suppression, and exhibits two coexisting, stable steady states, corresponding to high leukemic cell load at diagnosis or relapse, and to long-term complete remission. Our model is capable of explaining the clinical findings that the survival of patients with AML after allogeneic stem cell transplantation is influenced by the duration of complete remission, and that cut-off minimal residual disease thresholds associated with a 100% relapse rate are identified in AML.

1. Introduction

Cancer progression occurs through the dynamical crosstalk between cancer cells and immune cells involved in both immunosurveillance and tumor-promoting inflammation. A better understanding of their co-evolutionary dynamics and the underlying mechanism is therefore critical for improved treatment outcomes. The leukemias represent unique models to assess the impact of cancer on the host immune system as the cancer cells and immune cells originate from the same hematopoietic tissue and are in close proximity in peripheral blood and bone marrow. The initial treatment for acute myeloid leukemia (AML) is intensive induction chemotherapy, which aims to diminish leukemic cells and restore normal hematopoiesis, leading to complete remission (CR). Even though many patients achieve CR with induction and consolidation chemotherapy, the relapse rate is still high. Early or higher recovery of peripheral blood lymphocytes, neutrophils or platelets after cytotoxic chemotherapy are favorable prognostic factors for survival in patients with AML (Malkan et al., 2015; Yanada et al., 2008), suggesting the essential role of bone marrow reconstitution and recovered or enhanced anti-leukemic activity in the inherent immune system.

On the other hand, the regulatory T cell (Treg) is a contributing factor to suppression of anti-leukemic activity (Ustun et al., 2011). While Tregs play a critical physiological role in immune tolerance to suppress excessive responses in allergy or autoimmunity (Lindley et al., 2005; DiPaolo et al., 2007) and to protect hematopoietic stem cells in bone marrow during inflammation (Riether et al., 2015), the immunosuppressive function of Tregs contributes to leukemia progression (Riether et al., 2015). This has been supported by a growing body of evidence, which shows that lower frequency of Tregs at diagnosis is correlated with a higher rate of achieving CR (Shenghui et al., 2011), and that the frequency of Tregs in relapsed patients is dramatically higher (Shenghui et al., 2011), and that a high frequency of Tregs persists during CR (Szczepanski et al., 2009; Ersvaer et al., 2010; Yang and Xu, 2013).

A number of mechanistic mathematical models (Mackey et al., 2006; Wodarz et al., 2014; Michor et al., 2005; Roeder et al., 2006; MacLean et al., 2014; Stiehl et al., 2015) have been proposed to explain cell population dynamics and the effects of

* Corresponding author at: Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Ishikawa, 9201192, Japan.
E-mail address: nnishiya@staff.kanazawa-u.ac.jp (N. Nishiyama).

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chemotherapy and targeted therapy against leukemia, and have been calibrated against time evolution data for leukemia obtained from patients. Some studies of mathematical modeling have focused on the impact of immune responses on leukemia progression during chemotherapy (Kuznetsov et al., 1994; Kim et al., 2008; Roesch et al., 2014). In this work, we constructed an ordinary differential equation model to describe the dynamics of three components in AML: leukemic blast cells (L), mature regulatory T cells (Treg), and mature effective T cells (Teff), including cytotoxic T lymphocytes (CTLs). Our modeling strategy arises from the assumption of dynamic equilibrium among leukemic cells and blood cells, even in relapsed AML, leading to the system having two discrete, alternative stable steady states, one corresponding to leukemic cell dominance and the other to negligible leukemic cell load. Experimental evidence for bistability has been provided in diverse biological systems, and positive-feedback loops or mutually inhibitory, double negative-feedback loops have been proposed as the underlying mechanisms (Gardner et al., 2000; Angeli et al., 2004; Tyson et al., 2008; Ferrell, 2012; Wanga et al., 2009). With a given parameter set, our model exhibits two coexisting, stable steady states corresponding to high leukemic cell load at diagnosis or relapse, and to long-term complete remission, and the transition between two steady states during chemotherapy and immunotherapy is simulated and visualized by trajectories over time in three-dimensional (variable) space. Such viewpoints are based on a dynamical systems framework for resilience (Meyer, 2016).

In this work, we have interpreted the transient dynamics of the system spending time before returning to the state of high leukemic cell load as corresponding to transient CR before relapse. In addition, our mathematical model can explain the clinical findings that the survival of patients with AML after allogeneic stem cell transplantation is influenced by the duration of CR (Estey, 1996; Michelis et al., 2013a) and that cut-off minimal residual disease (MRD) thresholds associated with a 100% relapse rate are identified in AML (Liu Yin et al., 2012).

2. Materials and methods

2.1. The model

Our interest is in the dynamics that originate from the mechanism by which immune cells paradoxically contribute to leukemia progression. While a number of models have focused on cancer cells and cancer-specific cells such as CTLs, our motivation leads to the present model including Treg as the third player, which could be assessed by accumulating clinical findings on the impact of activated immune cell infusion with selective Treg depletion.

Mature T cells, including CTLs and Tregs, are generated as a result of terminal differentiation in the hematopoietic hierarchy, in which hematopoietic stem cells (HSCs) at the top proliferate to give rise to progenitor cell types maintaining self-renewal ability. Leukemic stem cells (LSCs) and poorly differentiated leukemic progenitor cells with highly proliferative capability produce leukemic blast cells with resistance to apoptosis, leading to blast cell accumulation in peripheral blood (Riether et al., 2015). In our model as illustrated in Fig. 1, we consider the populations of leukemic blast cells (L), mature regulatory T cells (Treg), and mature effective T cells (Teff), including CTLs. We assume that the dynamics of each cell population (L, Treg, Teff) are due to constant influx and first order decay by apoptosis, in which constant influx rates are denoted by aL, aTreg, and aTeff, and decay rate constants are denoted by dL, dTreg, and dTeff. In the model, the production of L results from the differentiation of LSCs and progenitor cells, and the production of Treg and Teff results from the differentiation of

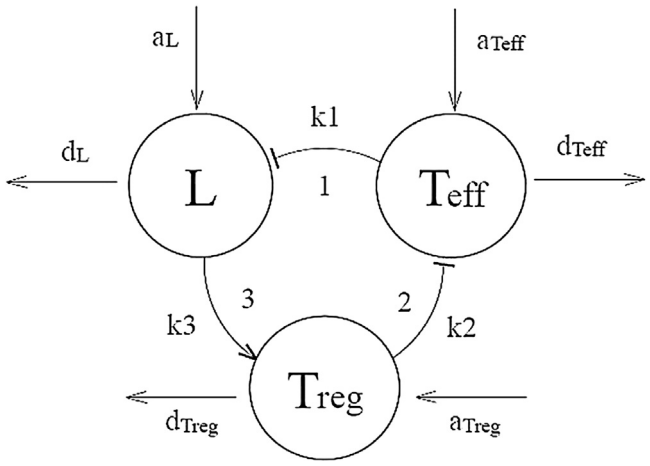

Fig. 1. Mechanistic model for crosstalk among leukemic cells and immune cells in AML. The processes of cell-cell interaction are numbered as follows: 1. Leukemic stem cells and progenitor cells targeted by effector T cells, 2. Effector T cell suppression mediated by Treg, and 3. Treg formation promoted by leukemic blast cells (L).

HSCs and progenitor cells. Together, aL, aTreg and aTeff are related to constant influxes from stem cells and progenitor cells collectively regarded as upstream cells. In addition, three intercellular interactions are identified as follows, and are modeled as Hill functions with threshold constants (k1, k2, k3) specifying the strength of intercellular interactions and the Hill coefficient p.

1) Leukemic stem cell and progenitor cell targeting by CTLs: experimental evidence has suggested CTL-mediated elimination of LSCs in a situation with low levels of IFN-γ (Schürch et al., 2013) and myeloid leukemic progenitor cell targeting by alloreactive CTLs (Norde et al., 2009), leading to aL modulation by [Teff].
2) Treg-mediated effector T cell suppression: inhibition of the proliferation and differentiation of effector T cells (Shen et al., 2005), and IL2-dependent inhibition of CTL differentiation (McNally et al., 2011) have been proposed as the mechanisms of Treg-mediated suppression of immune responses and hematopoiesis, leading to aTeff modulation by [Treg].
3) Promotion of Treg formation by leukemic blast cells: The expression of PD-L1, indoleamine 2,3-dioxygenase (IDO) and CD200, a type-1 transmembrane glycoprotein in leukemic blast cells, promotes formation of Tregs (Ustun et al., 2011; Curti et al., 2007; Francisco et al., 2009; Coles et al., 2012), leading to aTreg modulation by [L].

Since the model proposed here is to be primitively assessed by focusing on dynamics after hypothetical treatment, chemotherapy and immunotherapy were designed to shift the system from one point to another in three-variable space in a simple manner as follows. We assume that the concentrations of drugs are constant and the decay rate of each cell population (L, Treg, Teff) is proportional only to the cell population ([L], [Treg], [Teff]) during induction chemotherapy. The rate constants of decay due to apoptosis and drugs are accordingly combined together as dL, dTreg, and dTeff during chemotherapy. Hematopoietic cell transplantation (HCT) or CTL infusion and Treg targeting as immunotherapy was modeled by instantaneous increases and decreases in [Teff] and [Treg], respectively.

The above model is translated into the following ordinary differential equations.

$$\frac{d[L]}{dt} = a_L\left(\frac{k_1^p}{k_1^p + [T_{eff}]^p}\right) - d_L[L] \tag{1.1}$$