Modelling and simulation of erythropoiesis disruption by multiple myeloma

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Erythropoiesis is a physiologicall process by which erythrocytes are produced and released in blood. The erythroblastic island (EBI) is the primary unit of erythropoiesis in mammalians. Multiple myeloma (MM) is a malignancy characterized by the infiltration of cancerous myeloma cells to the bone marrow. These cells proliferate and expand to the detriment of EBIs resulting in severe anemia. Furthermore, malignant myeloma cells also secrete CFU-E cells apoptosis-inducing cytokines such as FasL and TRAIL. Another important effect of MM on erythropoiesis is the reduction of the levels of erythropoietin (EPO)[1], a kidney hormone that regulates erythrocytes production. Many treatments of MM exist. Among them, exogenous EPO is a hypoxia treatment that increases the resistance of CFU-Es. Other more effective treatments include chemotherapy regimens. Such treatments are effective because not only they make CFU-Es more resistants, but they also induce the apoptosis of malignant myeloma cells. However, since many chemotherapeutical protocols exist and can be conceived, the choice of which one of them to apply to which patients remains difficult.

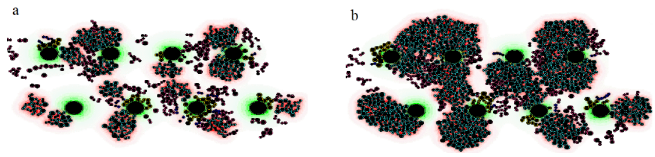

Figure 1: Two stages of the development of MM infiltration in a part of the bone marrow. Malignant myeloma cells (in cyan) form tumors that expand and destroy EBIs mechanically and biochemically: a) EBIs continue to be functional after the infiltration of MM cells to the bone marrow b) The tumors formed by MM cells expand and destroy all islands.

We use a hybrid discrete-continuous multi-scale model that was developed in a previous work [2]. In this approachl, cells are represented by soft spheres that can move, auto-renew, differentiate or die by apoptosis. The fate of each CFU-E cells is determined by the concentrations of an intracellular proteins network. These concentrations depend on the levels of extracellular proteins such as KL/SCF and FasL. Using this model, we study erythropoiesis under normal conditions in a part of the bone marrow. We simulate the disruption of erythropoiesis in a part of the bone marrow by MM infiltration. We then describe the effect of EPO on erythrocytes production and model the treatment by exogenous EPO. The last part of this work is dedicated to modelling different chemotherapy protocols from biological data. We propose a novel method to predict the efficiency of different MM treatment protocols using mathematical modelling and simulation.

Références

[1] Koury MJ, *Erythropoietin: the story of hypoxia and a finely regulated hematopoietic hormone*, Exp Hematol. 2005.

[2] Eymard N, Bessonov N, Gandrillon O, Koury MJ, Volpert V., *The role of spatial organization of cells in erythropoiesis.*, J Math Biol. 2014 Feb 5.

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