Cyclic neutropenia in mammals

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Cyclic neutropenia (CN) has been well documented in humans and the gray collie. A recent model of the architecture and dynamics of hematopoiesis has been used to provide insights into the mechanism of cycling of this disorder. It provides a link between the cycling period and the cells where the mutated *ELA2* is expressed. Assuming that the biologic defect in CN is the same in dogs, and the observation that the structure of hematopoiesis is invariant across mammals, we use allometric scaling techniques to correctly predict the period of cycling in the gray collie and extend it to other mammals from mice to elephants. This work provides additional support for the relevance of animal models to understand disease but cautions that disease dynamics in model animals are different and this has to be taken into consideration when planning experiments. Am. J. Hematol. 83:920–921, 2008. © 2008 Wiley-Liss, Inc.

Introduction

Cyclic neutropenia (CN) is a rare congenital disorder where the neutrophil count oscillates between near normal and low levels, usually out of phase with the monocyte count and other circulating blood cells [1]. Cytokines such as G- and GM-CSF cycle out of phase with the neutrophils [2]. Therapy with these agents normally leads to a reduction in the neutrophil nadir although cycling persists [3]. Many patients with CN have mutations in the neutrophil elastase gene (*ELA2*) [4,5] that may render cells less responsive to G-CSF and perhaps also leads to an unfolded protein response with premature cell death [6]. Interestingly, CN is also observed in gray collies that have served as an excellent model to understand the disease biology [7]. In the following, we adopt an allometric scaling approach to understand cyclic hematopoiesis across mammals. Our model assumes that the underlying biology of the disease is the same across species. The fact that it correctly accounts simultaneously for the cycling periods in dogs and humans supports this hypothesis, enabling us to provide estimates for cycling that may be observed in other mammals. Our results also emphasize the importance of understanding disease dynamics when planning experimental observations in animal models.

Results and Discussion

Making use of the architectural model of hematopoiesis, we have recently investigated how cycling originates in human CN. The expression of mutant *ELA2* cells in neutrophil precursors reduces the self-renewal capability of the cells, leading to a reduction in marrow output. Therapy with G-CSF restores self-renewal [8,9] and enables enhanced marrow output. This model naturally leads to a mathematical expression relating the period of CN oscillations with the compartment where the mutant gene is initially expressed. In most patients, the period of the oscillations is 19–21 days and remains stable, which in our model allows us to fix the compartment number (see Fig. 1) [10]. Here we combine (i) the insight from Ref. 18 regarding the conserved architecture of hematopoiesis with (ii) the allometric scaling of the active hematopoietic stem cell (HSC) in mammals, and (iii) the respective marrow output across mammalian species, to understand how CN manifests itself across mammals. To this end, we shall assume that the mechanism behind CN is the same across mammals and investigate the consequences of such a hypothesis. We will show that this hypothesis naturally accommodates simultaneously what is known for CN in the humans and the gray collie, and allows us to predict the period of neutrophil oscillations in mammals from mice to elephants [11].

Our hypothesis has a very simple implication: the mutated *ELA2* gene is expressed initially in the same compartment across species (see Fig. 1). Since the period T of oscillations is inversely proportional to the replication rate ($T \sim 1/R$) [10], it scales with the mass of the adult mammal as $T = T_0 M^{1/4}$. The constant T_0 can be obtained by calibrating the formula for humans ($M \approx 70$ kg and $T \approx 21$ days): $T_0 \approx 7.25$. Using the mass of 13 kg for adult gray collies, this expression correctly leads to a period of ~ 14 days for these animals. The table in the lower panel of Fig. 1 summarizes the relevant allometric characteristics of some of the most studied mammals, from mice to man, and the predicted period of the oscillations that should be observed. Naturally, the period of the oscillations decreases with animal size (and mass). Indeed, although murine CN should manifest itself with a periodicity of only 3 days, in elephants that periodicity extends up to 60 days. In a nutshell, this implies that it is intrinsically more difficult to detect oscillations in a mouse that in humans or even larger mammals.

The common architecture of hematopoiesis across mammals translates into the same (yet scaled) dynamics for diseases with a similar etiology. CN constitutes a good example of that and confirms the relevance of animal models. Nonetheless, one should not overlook the fact that different species have different metabolic rates, and dynamics proceed with characteristic species' time scales that follow allometric principles [12]. Therefore, and in keeping with this discussion, the conclusion that mutations in *ELA2* alone cannot explain CN in a mouse model must be interpreted with caution [13]. Measuring the neutrophil count ev-

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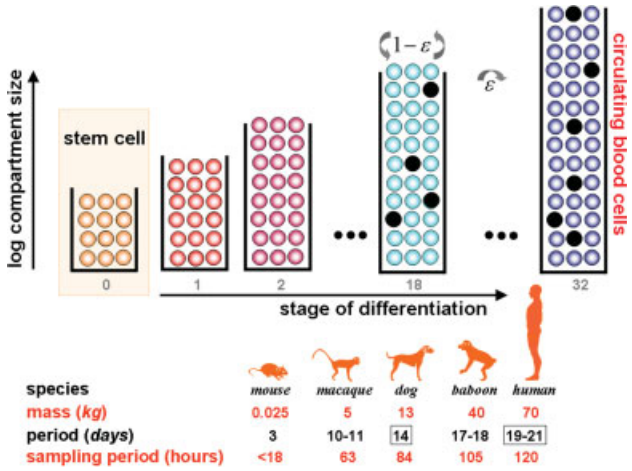

Figure 1. Multicompartmental dynamics of hematopoiesis. Upper panel: Each compartment represents a different stage of cellular differentiation where cells can either self renew with probability $1 - \varepsilon$ or differentiate with probability ε. In CN, each compartment has cells that may or may not express *ELA2* depending on their lineage and differentiation stage. *ELA2* is initially expressed (black cells) in the early neutrophil/monocyte lineage cells (compartment 18) and remains expressed in subsequent compartments. Lower panel: The table provides the mass and cycling period for CN across mammals from mice to humans (known—boxed numbers—and estimated). Also provided are guides to the minimum interval between neutrophil measurements to reliably determine potential cycling behavior.

ery week in mice proves unfortunate, as such a sampling period turns out to be a multiple of the CN cycling period. To appropriately detect the cycling behavior which is a fingerprint of CN, at least five (equally distributed in time) neutrophil counts should be obtained during one full cycle, leading to the numbers listed in the last line of the table in Fig. 1.

Our model correctly and independently predicts the period of the oscillations in the gray collie. Moreover, our hypothesis enables us to predict that such oscillatory behavior should occur in other species of mammals and the period of these oscillations will be determined by the mass of the species. Indeed, based on our study there is no reason why a baboon or macaque should not exhibit CN as should mice or elephants. The fact that the disease may be rare is irrelevant: however, experimental protocols should be carefully planned; monitoring the neutrophil count weekly and for extended periods in a large mammal is an excellent strategy but will not work for the smallest mammals. Our model further implies that if progenitor cells from patients with CN are transplanted into immunodeficient mice, the human neutrophils will oscillate with a period of 3 days instead of 21 days. Finally, the overall independence of the metabolic rate of a species on age also allows us to predict that CN cycling periods will not change during ontogeny [14] across mammals.

Methods

Normal hematopoiesis can be described in terms of a sequential multicompartment process where cells undergo replication and differentiation under the influence of the marrow microenvironment, with each compartment representing a different stage of blood cell differentiation [15]. Normal hematopoiesis corresponds to the dynamical equilibrium illustrated in Fig. 1, in which replicating cells from each compartment differentiate with probability ε, remaining in the same compartment with probability $1 - \varepsilon$. This leads to an exponential growth of compartment size with differentiation stage. Recent data on nonhuman primates [16], combined with other existing data on mammals and allometric scaling of hematopoiesis [17] has been used to predict that the hierarchical architecture is probably conserved across mammals [18]. In particular, it was shown that the number of cell divisions linking the HSC with the circulating blood is conserved in mammals [18]. What appears to be different is the number of HSC that are actively contributing to hematopoiesis (N_{SC}) [18], reflecting the very different demands across mammalian species. This number scales with the mass of the adult mammal as $N_{SC} \sim M^{3/4}$, while the rate of replication (R) of cells in each compartment scales with mass [12,17] as $R \sim M^{-1/4}$. Among the many implications of such allometric scaling relations, it is worth noting that cells replicate faster in smaller mammals [17] as documented experimentally [12,16,19]; moreover, smaller mammals are more robust against development of acquired stem cell disorders [20].

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