Dynamics of haemopoiesis across mammals

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Haemopoiesis is a fundamental physiologic process found in many animals. Among mammals, the diversity in size and function required suitable adaptations of this process. In this work, we use allometric principles to determine whether this required a change in the basic architecture of haemopoiesis. We show that it is possible to express both the number and rate with which haemopoietic stem cells replicate as well as total marrow output across all mammals as a function of adult mass. This unified view, which is compatible with the existing data, suggests that there was no need for major adaptations in the architecture of haemopoiesis across mammals.

**Keywords:** haemopoiesis; allometry; scaling; stem cells

1. INTRODUCTION

The emergence of large multicellular organisms required the development of systems for mass transport of oxygen and nutrients to cells far removed from exchange surfaces. The problem was solved by the evolution of the circulatory system and haemopoiesis. At the root of haemopoiesis, one finds haemopoietic stem cells (HSC), from which a hierarchy of cell types unfolds through several branches leading to progressively more committed cell lineages (Weissman et al. 2001; McCulloch & Till 2005; Dingli et al. 2007). Many biological observables related to the circulation (generally designated by $Y$) scale with the mass $M$ of the organism (perhaps the simplest surrogate of an organism’s complexity) as $Y = Y_0M^3$, where $Y_0$ is a constant and the exponent $a$ consistently being a multiple of 1/4 (Banavar et al. 1999). Recently, it has been found (Dingli & Pacheco 2006) that at least in mammals, the number of HSC ($N_{SC}$) that actively contribute to haemopoiesis scales allometrically with mass ($M$) with the same universal exponent (3/4) as the basal metabolic rate (BMR) of the organism (West et al. 1997; Banavar et al. 1999), i.e. $N_{SC} = N_0M^{3/4}$. The 3/4 exponent has been interpreted as resulting from either hierarchical networks organized in a fractal-like manner so as to minimize energy loss (West et al. 1997) or directed networks organized to minimize flow (Banavar et al. 1999). More recently, it has been proposed that there may be an evolutionary drive towards the emergence of self-similar, fractal-like complex networks (Song et al. 2006).

The validity of the assumptions underlying the allometric scaling relationship obtained ultimately relies on the availability of experimental data. In this context, the recent data on baboons (Papio sp.) and macaques (Macaca mulatta), published by Shepherd et al. (2007), provide important additional information regarding the principles that regulate haemopoiesis across mammals. In the following, we provide a unifying framework that captures the essential features of haemopoiesis from HSC to circulating blood across all mammals.

2. MATERIAL AND METHODS

For the purpose of this analysis, mammalian species are characterized by their average adult mass $M$. The size of their active stem cell pool, $N_{SC}$ is assumed constant in time and given by $N_{SC}(M) = N_0M^{3/4}$ ($N_0 = 15.9 \text{ kg}^{-3/4}$; Dingli & Pacheco 2006). We note that during ontogenetic growth, $N_{SC}(M)$ also scales allometrically (Dingli & Pacheco 2007). In each species, HSC replicate at a rate $R(M)$ given by $R(M) = R_0M^{-1/4}$ ($R_0 = 2.9 \text{ kg}^{1/4} \text{ yr}^{-1}$; Rufer et al. 1999; Dingli & Pacheco 2006).

Data for mammalian lifespan for a large number of species (http://www.centralspots.com/pages/mammals/other_exotics.html) were fitted to the empirical function $L(M) = L_0M^{1/4}$ (figure 1b) to obtain $L_0 = 8.6 \text{ kg}^{-1/4} \text{ yr}$ (Lopes et al. 2007). We assume that the fundamental architecture of haemopoiesis remains unchanged across mammalian species and consider that haemopoiesis is composed of a total of $K = 32$ different stages of cell replication/differentiation in mammals. These stages or ‘compartments’ should not be considered as discrete in space but more as a convenient way to account for the number of cell divisions that link HSC with the circulating blood. Thus, a cell may divide and move from compartment $k$ to $k+1$ and functionally still be the same (e.g. myeloblast). The size of each compartment $k$ ($k = 1, \ldots, K = 32$) grows as $N(k) = N_{SC}(M)g^\gamma$ ($\gamma = 1.93$; Dingli et al. 2007) while the rate of replication in each compartment scales as $r(k) = R(M)g^\varepsilon$ ($r = 1.26$; Dingli et al. 2007), such that the average time between cell divisions in each compartment is $\tau(k) = r^{-1}$. In our model, short-term repopulating cells (STRC) are represented by cells in compartments $k = 1–5$ ($N_{STRC} = 1.2 \times 10^4$ cells for humans). With probability $\varepsilon = 0.85$, cell division leads to differentiation into the next compartment. In each of the $k$ compartments, the average number of cell divisions is then given by $\sum_{j=0}^{\infty} e^{1-\varepsilon}(1-\varepsilon)\varepsilon^j = 1/\varepsilon$. Hence, the average time a cell remains in compartment $k$ is $\tau(k)/\varepsilon$ and the average time $\tau(M)$ that an STRC contributes...
It appears that the BMR dictates the rate of replication of cells in vivo since the rate of HSC replication across various mammals scales in the same way with their adult mass (Dingli & Pacheco 2006). In vitro, the cells isolated from different mammalian species replicate at an approximately constant rate (figure 1a), providing compelling evidence that it is the organism that regulates the cell's mitotic clock (West et al. 2002). The inverse relationship between rate and time suggests that animal lifespan \(L(M)\) also follows qualitatively a 1/4 scaling relationship (Lopes et al. 2007), as shown in figure 1b. On the other hand, the 3/4 scaling of the size of the active HSC pool follows from the assumptions that (i) each HSC is equally represented in the blood such that the scaling exponent of the active HSC pool should be identical to that of the reticulocyte count across adult mammalian species and (ii) the haemopoietic tree (Dingli et al. 2007) remains invariant across mammals.

Taken together, these scaling relationships suggest that HSC replicate faster in a mouse than in a cat or a human. Given the mass of non-human primates such as baboons \((m \approx 20 \text{ kg})\) and macaques \((m \approx 6.5 \text{ kg})\), allometric scaling predicts that their HSC replicate at rates intermediate between that of humans and smaller animals such as mice \((m \approx 25 \text{ g})\) and cats \((m \approx 4 \text{ kg})\): we obtain that HSC replicate, on average, once in every 29 weeks in macaques and once in every 36 weeks in baboons, in excellent agreement with the data reported by Shepherd et al. (2007; see also table 1).

From these allometric relationships, the total number of divisions \(T\) a typical HSC undergoes during the lifetime of the mammal in which it resides scales as \(T \sim M^{-1/4} \cdot M^{1/4} \sim M^0\). Hence \(T\) becomes independent of mass, and the average number of replications of each HSC should remain approximately constant for all mammals and compatible with the Hayflick hypothesis of a limited number of divisions for a given cell (Hayflick & Moorhead 1961). This result has been recently proposed by Shepherd et al. (2007) based on their experimental data. Our scaling analysis provides a natural explanation for this finding.

More generally, this behaviour derives from the principle that it is the organism (and its self-regulatory complexity) that regulates the rate of cell replication and not vice versa; otherwise it would be impossible to rescue a lethally irradiated mouse with human HSC: the inherent rate of replication of the human HSC would be too slow to allow haemopoietic reconstitution in the time frame necessary for the recovery of the mouse. Rather, the human HSC transplanted in the mouse will replicate at a rate dictated by the murine BMR. Allometric scaling also allows us to predict that the length of time that HSC contribute to haemopoiesis varies across species, following a 1/4 scaling relationship with mammalian mass. Indeed, since each cell roughly replicates the same number of times during the lifetime of the organism, the length of time will scale with the same power as the average lifespan, e.g. \(M^{1/4}\).

We further investigated the robustness of the allometric predictions by combining them with our recently developed multi-compartment model of haemopoiesis in humans. In this model, cell division is associated with either differentiation or self-renewal (Dingli et al. 2007), along a cascade of progressive stages of cell commitment. Using this model in combination with the allometric scaling of \(N_{SC}\) (see §2), we determined the average daily...

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3. RESULTS AND DISCUSSION

A paradigmatic example of allometric scaling is the mass-specific BMR, which scales with mass as \(B(M) = B_0 M^{-1/4}\) across 27 orders of magnitude (West et al. 2002; figure 1a).
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Table 1. Some haemopoiesis-related properties of mammalian species derived from the allometric scaling relationships studied in this work. (M, average mass of mammalian species; N_{SC}, size of the active stem cell pool; N_{SC}^0, size of the active stem cell pool contributing to haemopoiesis after bone marrow transplantation; R(M), rate of replication of HSC; r_{\infty}(M), average time STRC contribute to haemopoiesis; \Omega, daily bone marrow output.)

<table>
<thead>
<tr>
<th>property</th>
<th>Mus</th>
<th>Rattus</th>
<th>Felis</th>
<th>Macaca</th>
<th>Canis</th>
<th>Papio</th>
<th>Homo</th>
<th>Gorilla</th>
<th>Elephas</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (kg)</td>
<td>0.025</td>
<td>0.250</td>
<td>4.0</td>
<td>6.5</td>
<td>12.5</td>
<td>18.0</td>
<td>70.0</td>
<td>135.0</td>
<td>4500.0</td>
</tr>
<tr>
<td>N_{SC}</td>
<td>1</td>
<td>6</td>
<td>45</td>
<td>65</td>
<td>105</td>
<td>139</td>
<td>385</td>
<td>630</td>
<td>8736</td>
</tr>
<tr>
<td>N_{SC}^0</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>20</td>
<td>32</td>
<td>42</td>
<td>116</td>
<td>190</td>
<td>2634</td>
</tr>
<tr>
<td>R(M)^{-1} (in weeks)</td>
<td>7^a</td>
<td>13</td>
<td>25</td>
<td>29</td>
<td>34</td>
<td>37</td>
<td>52</td>
<td>61</td>
<td>147</td>
</tr>
<tr>
<td>r_{\infty}(M) (in weeks)</td>
<td>3.3</td>
<td>5.9</td>
<td>11.9</td>
<td>13.4</td>
<td>15.8</td>
<td>17.3</td>
<td>24.3</td>
<td>28.7</td>
<td>68.8</td>
</tr>
<tr>
<td>\Omega (cells)</td>
<td>10^8.91</td>
<td>10^8.66</td>
<td>10^10.6</td>
<td>10^{10.72}</td>
<td>10^{10.93}</td>
<td>10^{11.05}</td>
<td>10^{11.49}</td>
<td>10^{11.71}</td>
<td>10^{12.85}</td>
</tr>
</tbody>
</table>

^aData for mice, for which the active stem cell pool made up of a single HSC is the one that deviates most from available estimates (Spangrude et al. 1991). This is not surprising, given the average nature of the allometric scaling relationship, although it conforms with the notion that haemopoiesis in the mouse may not reflect that characteristic of larger mammals (Abkowitz et al. 1995).

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