Cell Death and the Efficiency of the Erythropoietic System

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The efficiency of the erythropoietic system is studied with the aid of mathematical modeling under conditions of a high fraction of cell death. A criterion limiting the magnitude of cell death is proposed for possible forms of chronic pathology.

Key Words: *erythropoiesis; cell death; efficiency*

When health gives way to the majority of chronic forms of pathology, the death of erythroid cells from the bone marrow is significantly increased, and therefore the efficiency of the cellular erythropoietic system falls off. It is of interest to ascertain the laws of behavior of the parameters which are responsible for the increase in cell death and are the most informative with respect to the efficiency of operation of the cellular erythropoietic system. Mathematical modeling was used to solve this problem [1].

MATERIALS AND METHODS

The study was performed for the stage of cell differentiation in which cells first divide and then mature forming a maturation pool. A pool of morphologically identifiable cells is an example of such a stage. It is assumed that this stage is a steady-state stage. Using a mathematical model [1], the following expression may be obtained:

$$g=(aT)=\sum_{i=1}^{m} g_i(aT);\ g^{out}(aT)=\sum_{i=1}^{m} g_i^{out}(aT);$$

$$N^P(aT)=\sum_{i=1}^{m} N_i^P(aT);$$

$$g_i(aT)=P\gamma_i \sum_{l=1}^{k_i+1} 2^{l-1}\exp\left\{-\sum_{j=1}^{l-1}\lambda_{j,i}B_{j,i}aT\right\}\times$$

$$\times[1-\exp\{-\lambda_{l,i}B_{l,i}aT\}];$$

$$g_i^{out}(aT)=P\gamma_i 2^{k_i+1}\exp\left\{-\sum_{l=1}^{k_i}\lambda_{l,i}B_{l,i}aT\right\};$$

$$N_i^P(aT)=PT\gamma_i \sum_{l=1}^{k_i+1} 2^{l-1}\exp\left\{-\sum_{j=1}^{l-1}\lambda_{j,i}B_{j,i}aT\right\}\times$$

$$\times(1-\exp\{-\lambda_{l,i}B_{l,i}aT\})/\lambda_{l,i}aT,$$

where $g(aT)$ is the number of cells which leave the proliferative pool and the pool of maturing cells at the stage of differentiation examined per unit time due to death; $g^{out}(aT)$ is the number of cells which leave the given stage of differentiation per unit time after the completion of differentiation; $N^P(aT)$ is the number of cells in the pool of proliferating and maturing cells; γ_i defines the fraction of cells from the flow at input P which go through k_i divisions in the proliferative pool of the stage; for $j<k_i$ the $B_{j,i}T$ values are the generation times, while if $j=k_i$ they are the times of cell maturation; $\lambda_{j,i}a$ define the magnitude of the fraction of cell death in the generation with number j of flow $P\gamma_i$, $\lambda_{j,i}$ and $B_{j,i}$ are dimensionless quantities; m is the number of flows.

RESULTS

As the fraction of death a increases ratio $g(aT)/P$ rises, reaching a maximum at $aT=(aT)_{cr}$, and then falls. Critical point $(aT)_{cr}$ can be found using the extremum condition. The parameters for $\lambda_{j,i}=B_{j,i}=1$ which characterize the efficiency of the differentiation stage being exam-

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TABLE 1. Characteristics of Cell Kinetics at the Critical Point

k_i+1	$(aT)^i_{cr}$	$\frac{g^{out}_i[(aT)^i_{cr}]}{g_i[(aT)^i_{cr}]}$	$\frac{g^{out}_i(0)}{g^{out}_i[(aT)^i_{cr}]}$	$\frac{\tilde{N}^P_i[(aT)^i_{cr}]}{N^P_i(0)}$
2	1.390	0.11	16.13	3.26
3	0.693	0.33	8.00	2.16
4	0.440	0.64	5.82	1.79
6	0.241	1.43	4.22	1.45
8	0.162	2.83	3.65	1.29
14	0.081	5.39	3.12	1.14
20	0.054	8.42	2.96	1.09

ined, and found for $aT=(aT)_{cr}$, are listed in Table 1. The values of $g^{out}_i[(aT)^i_{cr}]$, $g_i[(aT)^i_{cr}]$, and $g^{out}_i[0]$ are found for the same flow at input Pg_i, while $\tilde{N}^P_i[(aT)^i_{cr}$ is the number of cells in the proliferating and maturing pool found for the flow at input $\tilde{P}\gamma_i=P\gamma_i g^{out}_i(0)/g^{out}_i[(aT)^i_{cr}]$, which fully compensates for the cell losses in the flow at the output from the stage of differentiation, and $g^{out}_i(0)$ is the outflow of cells from the stage examined in the absence of cell death.

From Table 1 it follows that for a pool of morphologically identifiable cells (in which $2 \le k_i+1 \le 8$), for each cell which leaves it after completing differentiation there are from 3 to 15 cells which are lost due to death. The flow at input $P\gamma_i$, at which cell losses due to death are fully compensated, increases 3.7-16 times as compared with the situation without cell death. The number of proliferating and maturing cells rises 1.27-3.26 times in comparison with the case where cell death is absent. The flow of cells leaving the poll of morphologically identifiable cells as a result of differentiation is of the same order of magnitude as the flow of cells leaving it due to death. The findings attest to very inefficient operation of the stage of morphologically identifiable cells in states where $aT=(aT)_{cr}$ (at the critical point). For $\lambda_{ji} \neq 1$ the inefficiency of the differentiation stage further increases because death is confined to a smaller number of generations. It can be shown that these results are valid for a stage of differentiation which does not contain a pool of maturing cells.

Thus, when cell death is localized in a pool of morphologically identifiable cells, it may be surmised that for actually occurring forms of chronic pathology the fraction of cell death should not exceed the critical value and therefore should satisfy criterion $aT<(aT)_{cr}$.

REFERENCES

1. V. V. Svishchenko and E. D. Gol'dberg, *Mathematical Modeling of Erythropoiesis Kinetics* [in Russian], Tomsk (1995).