A mathematical model of murine granulo- and erythropoiesis during continuous rhG-CSF stimulation

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Background

G-CSF has multiple effects on hematopoietic cell numbers during long-term administration

Stem cells and progenitors (CFU-S, CFU-GM, BFU-E):

- Bone marrow: ↓
- Peripheral blood ↑↑
- Spleen: ↑↑

Granulopoiesis:

- Blood neutrophils: ↑↑
- Small increase of marrow granuloid precursors
- Splenic granuloid precursors: ↑

Erythropoiesis:

- Bone marrow: ↓
- Spleen: ↑
- Red blood cells: no major changes

Objective

Explanation of the experimental findings by

- Identification of G-CSF dependent cell kinetic mechanisms and their individual dose response characteristic in vivo
- Characterization of the interaction of G-CSF dependent parameters within the dynamic hematopoietic system

Problem

In vivo most G-CSF dependent cell kinetic parameters (e.g. amplification or migration rates) cannot be characterized quantitatively by experimental studies in a direct way. This problem is approached by a mathematical model of hematopoiesis.

Features of the model

Dynamic description of the cell numbers of the various hematopoietic cell stages (concatenated compartments) by cell flux rates and cell kinetic parameters (e.g. amplification rates, transit times), which are goverened by feedback loops.

This model can be used to

- test various hypotheses about the possible G-CSF sensitive parameters by comparing dynamic model simulations with experimental data
- derivate and estimate experimentally inaccessible cell kinetic parameters or system properties (e.g. regulation loops)
- make predictions on yet unknown experimental situations

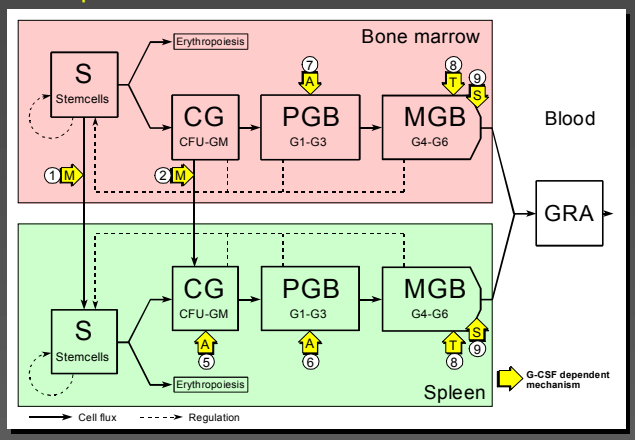
Basic model properties and assumptions

- Description of Granulopoiesis, Erythropoiesis and their common stem cell compartment
- Separate but structurally identical description of bone marrow and spleen hemopoiesis (ratios between bone marrow and spleen compartment sizes are adjusted for correct estimation of each site's contribution to total blood cell production)
- Endogenous production of G-CSF is neglected during exogenous administration of pharmacological doses
- Erythropoiesis is regulated by endogenous EPO, according to our previous model results

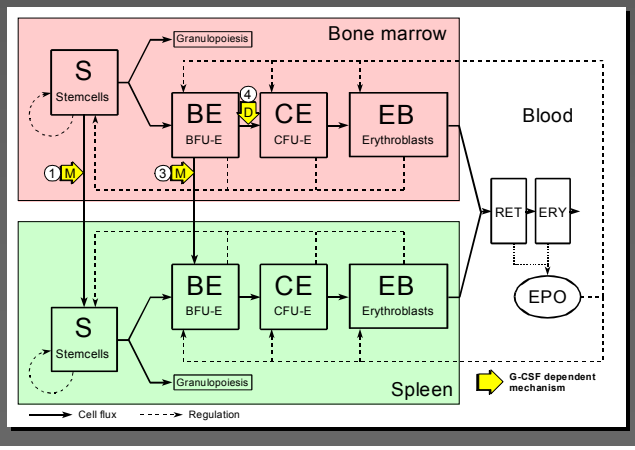
Results

Model structure and identified G-CSF sensitive cell stages and mechanisms ① - ⑨

Granulopoiesis

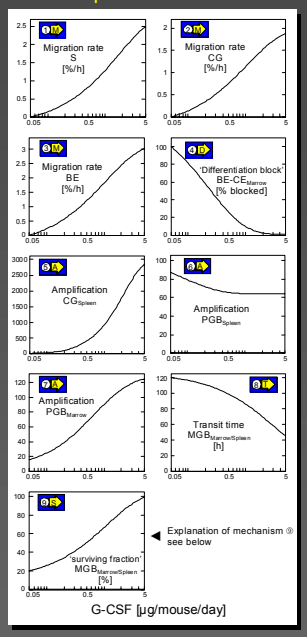


Erythropoiesis



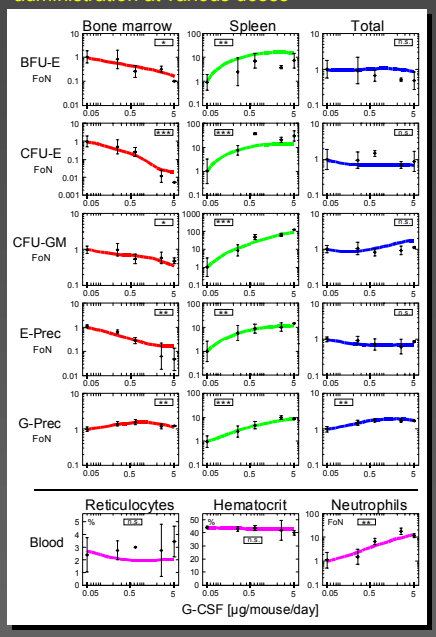
Quantification of G-CSF effects

Dose response curves



Model simulations compared to own experimental data

Hematopoietic state after 7 days of G-CSF administration at various doses



Nearly all experimental data are quantitatively well explained by the mechanisms ① - ⑨ and their interaction within the dynamic system.

- **Migration is a quantitatively relevant mechanism:** The difference of CFU-S, CFU-GM and BFU-E between bone marrow and spleen can be explained by cell fluxes (migration) from marrow to spleen.
- **Amplification is different between marrow and spleen:** The strong increase of spleen CFU-GM cannot be explained by immigration of CFU-S and CFU-GM from marrow only. Additional increase of CFU-GM amplification in the spleen has to be assumed.
- **Migration of CFU-S and BFU-E explains splenic increase of erythropoiesis, but not marrow decrease:** An additional G-CSF dependent 'block' between marrow BFU-E and CFU-E has to be assumed.
- **The spleen fully compensates for the inhibition of erythropoiesis in the marrow:** Constant red blood cell counts can be maintained during G-CSF stimulation.

A new hypothesis for the quantitative explanation of G-CSF induced neutrophilia (Mechanism ⑨)

Problem:

During G-CSF stimulation a strong increase of blood neutrophils can be observed, but only a comparably low increase of total granuloid precursors (marrow plus spleen).

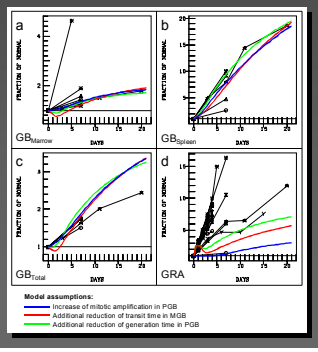
Increased mitotic amplification in PGB in combination with maximum reasonable transit time shortening fails to explain this phenomenon.

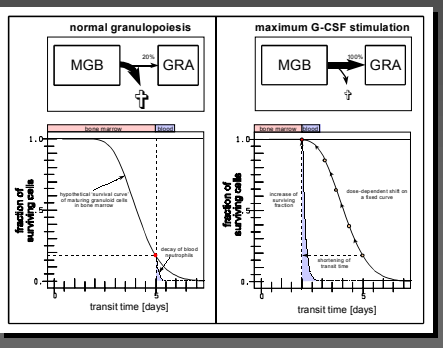
Hypothesis:

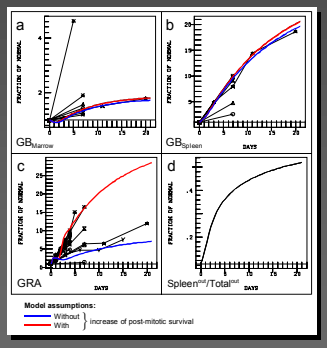
During normal conditions, a large fraction of produced neutrophils die in marrow/spleen, only a small fraction enters circulation ('surviving fraction'). The fraction of surviving cells is assumed to be dependent from post-mitotic transit time ('survival curve'). During G-CSF stimulation, the fraction of surviving cells increases with the reduced transit time.

Result of model simulation:

The additional assumption of this G-CSF dependent survival of post-mitotic cells is able to explain both the strong increase of blood neutrophils (c) and the moderate increase of total precursors (a+b). The spleen's contribution to total neutrophil production is calculated to increase from normally 10% to 50% during stimulation.







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