Lineage interactions during prolonged combined administration of EPO and G-CSF explained by a comprehensive model of murine erythro- and granulopoiesis

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Objective

To develop a comprehensive mathematical model of murine hematopoiesis to describe and explain qualitative and quantitative hematopoietic effects of a combined administration of EPO and G-CSF

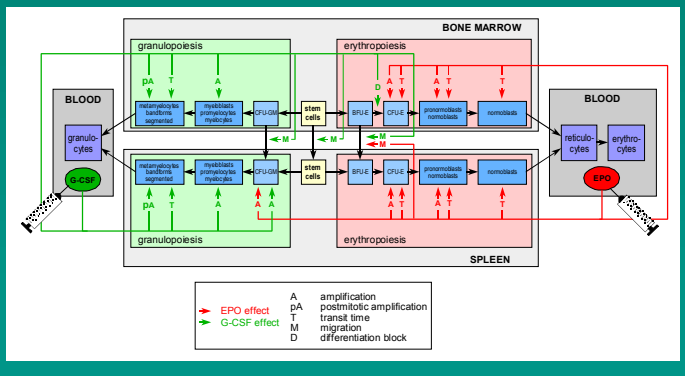
Background

Data of two experiments were available in which EPO and/or G-CSF were given subcutaneously for 7 days in a full factorial study design . The data showed some unexpected interactions of G-CSF effects on erythropoiesis and EPO on granulopoiesis.

Model structure and assumptions

- Hematopoietic cell stages are described by compartments connected by cell fluxes
- Erythropoiesis and granulopoiesis originate from a common stem cell compartment
- Bone marrow and spleen hematopoiesis are described as independent pipelines connected by migration of early progenitors
- EPO and G-CSF act dose-dependently on cell kinetic parameters, i.e. amplification, migration, transit time and differentiation capability.
- Effects of EPO and G-CSF are not only restricted to erythropoiesis and granulopoiesis, respectively. Both growth factors also act on early cell stages of the counter lineage

Model results



Material and methods

Experimental data:

Experiment 1:

Normal C57Bl/6 mice were treated with EPO and G-CSF for 7 days using subcutaneously implanted osmotic minipumps. The following dose levels were administered in a 3 x 3 factorial design:

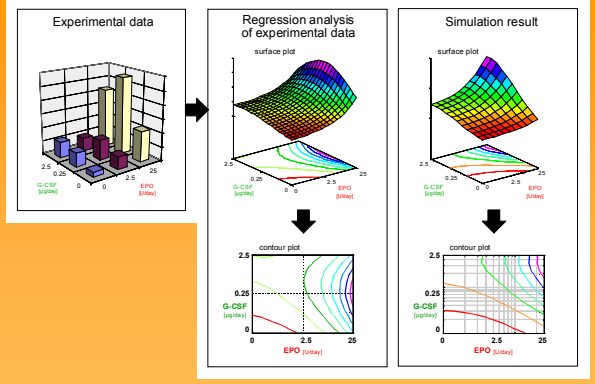
EPO: 0 / 2.5 / 25 U/mouse/day
G-CSF: 0 / 0.25 / 2.5 µg/mouse/day

Experiment 2:

Splenectomized C57Bl/6 mice were treated with EPO and G-CSF for 7 days using subcutaneously implanted osmotic minipumps. The following dose levels were administered in a 4 x 4 factorial design:

EPO: 0 / 0.5 / 5 / 50 U/mouse/day
G-CSF: 0 / 0.25 / 0.625 / 2.5 µg/mouse/day

Cell stages were determined after 7 days of treatment



Statistical data analysis:

To obtain a continous quantitative description of the experimental results a non-linear quadratic regression model was used to analyse single mouse data

Each cell stage (Z) is described by the following regression equation:

$$Z = a + b*[EPO] + c*[EPO]^2 + d*[G\text{-}CSF] + e*[G\text{-}CSF]^2 + f*[EPO]*[G\text{-}CSF]$$

The regression equations are plotted as contour diagrams consisting of 'equi-response' curves.

Except for hematocrit and reticulocytes cell numbers are given relative to the control value (fraction of normal).

Model simulation:

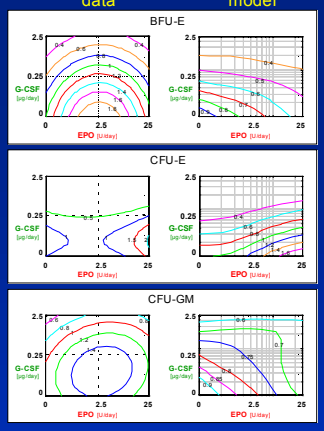
Model simulations for all grid of GCSF x EPO concentration levels were performed within the experimental dose ranges of both cytokines.

Model results of day 7 are visualized as equi-response diagrams and are compared to the contour plots derived from the experimental data.

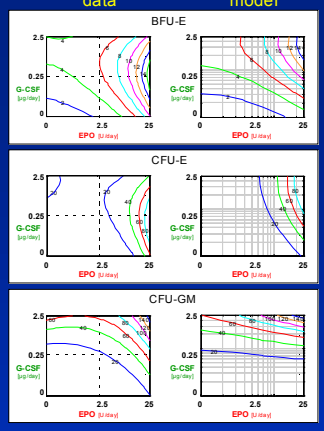
Model simulations compared to experimental data

normal mouse

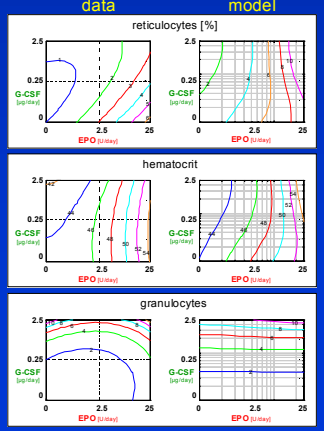
bone marrow

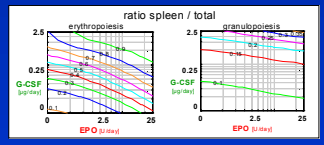


spleen



blood





synergistic effects:

Both EPO and G-CSF stimulate erythroid and granuloid progenitors in the spleen, resulting in an increased splenic cell production for both lineages:

- Induction of migration of BFU-E from bone marrow to spleen
- Increase in amplification of CFU-GM in the spleen

antagonistic effects:

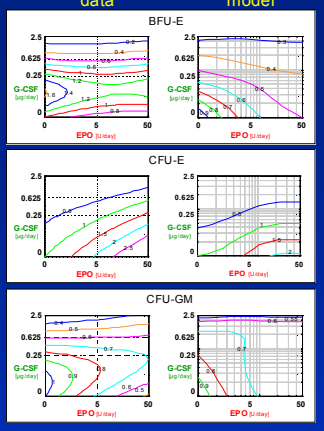
Marrow erythropoiesis is suppressed by G-CSF. EPO is able to compensate for low doses of G-CSF:

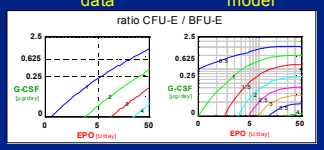
- Differentiation block of bone marrow BFU-E by G-CSF
- Increase of CFU-E amplification by EPO

Bone marrow suppression of erythropoiesis by G-CSF is quantitatively compensated by an increased splenic production: no anemia can be observed (hematocrit).

splenectomized mouse

bone marrow





In the splenectomized model bone marrow parameters were assumed to be identical to those of the normal model.

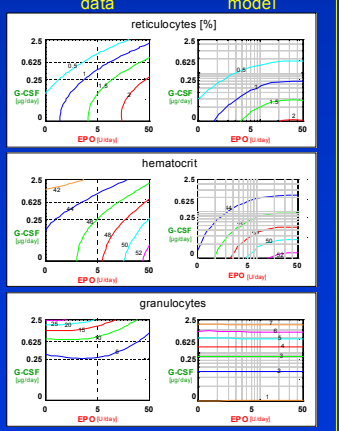
G-CSF suppresses EPO dependent marrow erythropoiesis, illustrated by the ratio CFU-E / BFU-E.

In splenectomized mice hematocrit depends on EPO and G-CSF in an antagonistic fashion.

In normal mice hematocrit depends mainly on EPO due to splenic compensation.

Missing spleen has no negative effect on granuloid cell production. However, experimental data show a more pronounced G-CSF dependent increase of granulocytes in splenectomized than in normal mice. The mechanisms leading to this phenomenon remain unclear and can not be explained by this model.

blood



Conclusions

The proposed model gives a basic insight into the quantitative effects of combined growth factor treatment in murine hematopoiesis.

Other cytokines of potential clinical relevance should also be considered to describe multiple cytokine treatment.

To improve modelling of the hematopoietic system more detailed experimental data is needed:

- Time course data on various cell stages during combined growth factor treatment
- Systematic investigations on dose-response behaviour for other cytokine combinations

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