Different behaviour of erythropoietin responsive and antigen responsive cells in the presence of Vinblastin *

Comportamiento diferente de las células capaces de responder a eritropoyetina y a antígeno en presencia de Vinblastina.

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Evidence from transplantation studies suggests that both immune competent and erythropoietically competent cells probably derive from a pluripotential stem cell (1) the colony forming unit (CFU) of Till and McCulloch (2). What is not yet clear is whether the CFU is a cell capable of responding to both Erythropoietin and antigen or whether the Erythropoietin responsive cell (ERC) and the cell capable of responding to antigen, in a primary response, (the so called PC_1 cell (1)) are different cells both derived from CFU. It was considered of interest to determine whether ERC and PC_1 cells, are in a state of non cell cycle "G_o", as is the case of CFU (3), or whether they are in cycle. A study of the effects of Vinblastine on these cells should contribute valuable evidence since this drug has been shown useful for the study of cell cycle "in vivo" (4).

For the study of the ERC, we chose to measure the response of fasted rats to erythropoietin, a system in which one of us has considerable experience (5). To study the response of PC_1 cells, we chose to measure the hemolysin response of rats to sheep RBC in which antibody synthesis has well defined kinetics (6) quite similar to the kinetics of Hb formation, triggered off by erythropoietin in the rat (7).

Vinblastine sulfate (kindly supplied by Eli Lilly Co.) in saline 80 and 40 µg/rat was injected intravenously either, 14 hours before or simultaneously with either 10 U "Erythropoietin" contained in one ml of anemic rat plasma, or 0,5 ml of a 0,25% suspension of sheep red blood cells. 160-180 g male A x C rats were used. In the case of the Erythropoietin assay they had been fasted for two days prior to and kept fasting for two days after Erythropoietin injection; at the end of that time a ^{59}Fe distribution study was carried out (5). Non fasted rats were used for the hemolysin study and the antibody determined (8) on the fourth day after antigen injection.

The response to erythropoietin was suppressed by 40 µg of Vinblastine given either 14 hours before or simultaneously with EP. On the other hand, even a dose of 80 µg did not affect the antibody response (Table I).

On the basis of the known half life of Vinblastine in the mouse and applying an analysis of biological similarity (9) a half life of Vinblastine in rats of about 7 hrs. can be calculated. If this is the case,

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TABLE I

Effect of Vinblastine on response to antigen and Erythropoietin

	Response	No Vlb.	Vlb.80µg. —14 hrs.	Vlb.80µg 0 hr.	Vlb.40µg —14 hrs.	Vlb.40µg 0 hrs.	No Vlb. No S
a)	50% Hemolysin units/ml	212±32	200±39	195±15	213±30	222±32	20
b)	% ^{59}Fe Erythrocytes	10%±0,6	0	0	0	0	0.12±0.01

Response, mean and standard error, to sheep RBC (a) and to 10 U of Erythropoietin (b) of rats receiving Vinblastine (Vlb.) either together with or 14 hrs. before the stimulus (S), antigen or Erythropoietin (at least four rats per group).

effective levels of the drug should be maintained for at least 14 hrs. after an 80 μg dose. The results obtained by us can be interpreted, on the basis of Valeriote's model (4) of Vinblastine action, as if ERC were in cell cycle before responding to EP and continued in cycle after. This is in agreement with recent data of Morse and Stohlman (7) and of one of us (10) from which an estimate of cycle of ERC of 9-11 hrs. can be made. PC_1 cells on the other hand behave, in the face of Vinblastine, as if they were at rest, as far as cell cycle is concerned, before antigen injection and did not go through mitosis at least for 14 hrs. after antigen injection. ERC could thus be classified (3) as cells mainly in cycle, while PC_1 cells would, like CFU, be mainly at rest. That CFU and PC_1 are not the same, is suggested by the finding that while CFU are present in normal mouse marrow, PC_1 cells are not detected if the marrow is injected into lethally irradiated Thymectomized mice (11). It is possible that CFU change into PC_1 under the influence of the Thymus. What changes CFU into ERU is not known. It may well be that ERC are simply CFU cells in cycle, that is that only CFU in cycle can respond to Erythropoietin.

RESUMEN

La Vinblastina en dosis que suprimen completamente la respuesta de la médula ósea a la eritropoyetina en ratas, no afecta la respuesta inmunitaria a eritrocitos de oveja, ya sea cuando se inyecta junto con o 14 hrs. antes que el antígeno.

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