B cell development in aging mice: Lessons from mathematical modeling

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Introduction

The immune system's function deteriorates with age. Previous studies have not completely clarified the precise defect(s) that characterize B cells development in aged animals. The question of which developmental mechanism is actually damaged in aging remains controversial.

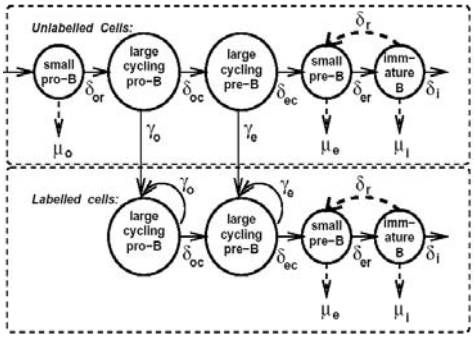
The goal of this study was to elucidate the effects of aging on bone marrow B cell population dynamics. We used mathematical modeling to predict the outcome of the different possible effects, and then compared these predictions to experimental data, to find the most plausible effects.

Our model shows that the main three differences between young and old mice are in the rate of transition from cycling pre B cells to resting pre B cells, the carrying capacity of the bone marrow for pre-B cells, and the fractions of static (non-developing) cells included in the immature B cell subset.

Aim: To discover which parameter(s) of the developmental process change with age.

Methodology: Fit the mathematical model of B cell population dynamics to data from P. Witte's group (Johnson *et al*., Int. Immunol. 14:1313-23, 2002.)

Model with labeling of dividing cells:



Equations (labeling not shown):

$$dB_{or}/dt = s - (\mu_o+\delta_o)B_{or}$$

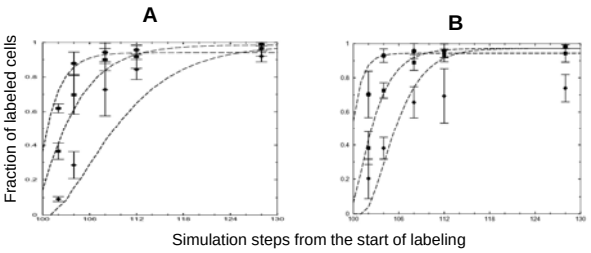
$$dB_{oc}/dt = \delta_{or}B_{or} + \gamma_o[1-(B_{or}+B_{oc})/K_o]\,B_{oc} - \delta_{oc}B_{oc}$$

$$dB_{ec}/dt = \delta_{oc}B_{oc} + \gamma_e[1-(B_{er}+B_{ec})/K_e]\,B_{ec} - \delta_{ec}B_{ec}$$

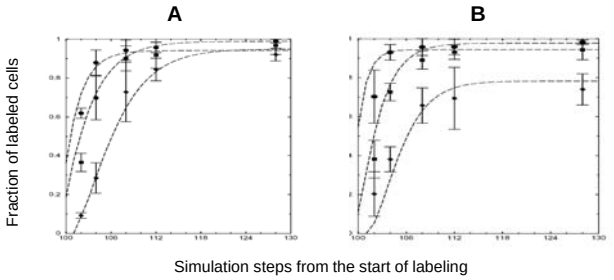
$$dB_{er}/dt = \delta_{ec}B_{ec} - (\mu_e+\delta_{er})B_{er} + \delta_{re}B_i$$

$$dB_i/dt = \delta_{er}B_{er} - (\mu_i+\delta_i)B_i - \delta_{re}B_i$$

Results (1): with the model as is.
A - young mice; B - old mice.
● - pro-B cells; ■ - pre-B cells; ♦ - immature B cells.



Results (2): A Simulation of the best fit model, with a certain number of static cells in the immature B cell compartment.
A - young mice; B - old mice.
● - pro-B cells; ■ - pre-B cells; ♦ - immature B cells.



Parameters:

sebset:		Pro-B		Pre-B	Immaure B
	Resting	cycling	Resting	cycling	
Young mice					
Entry rate(10^{*4})	1-10				
Proliferation rate		0.3-1.4	0.9-1.3		
Carring capacity(10*6)		2-3	5.3-5.5		
Death rate	0-1		0.1-1		0.05-0.2
Output rate	0.1-1	0.1-0.3	0.2-0.25	0.5-1.2	0.01-0.1
Regression rate					0-0.19
static cells(10*6)					1
Old mice					
Entry rate(10^{*4})	1-10				
Proliferation rate		0.1-1.4	0.5-1.2		
Carring capacity(10*6)		2.4-3	3.5-4		
Death rate	0-1		0.1-1		0.05-0.2
Output rate	0.1-1	0.1-0.3	0.3-0.4	0.5-1.2	0.05-0.2
Regression rate					0-0.19
static cells(10*6)					5

Conclusions and discussion:

The main three differences between young and old mice are:

The rate of transition from cycling pre-B cells to resting pre-B cells is higher in old mice than in young mice. As the animal gets older, there probability that any given cell will stop proliferating may increase, due to accumulation of genetic defects. This assumption is in line with conclusions of previous studies on T cells (Mehr et al).

The carrying capacity of the pre-B cells subpopulation is lower in old mice than in young mice. This suggests that the space and resources, such as contact with the bone marrow stroma, the availability of growth factors and nutrients, are lower in old animals.

The fraction of static cells included in the immature-B cells subset is higher in old mice than in young mice. Immature B Cell longevity may increase in age because those cells have some signaling defect in the apoptotic signaling pathways. This age-related defect would lead to fewer immature-B Cell that are sensitive to selection against self-antigen, which would increase the production of both auto-reactive and functionally defective B cells.