Cyclic neutropenia in animals

Jorge M. Pacheco[1], Arne Traulsen[2], Tibor Antal[3], David Dingli[4],

[1] *ATP-Group, CFTC & Departamento de Física da Faculdade de Ciências, P-1649-003 Lisboa Codex, Portugal*

[2] *Max Planck Institute for Evolutionary Biology, 24306 Plön, Germany*

[3] *Program for Evolutionary Dynamics, Harvard University, Cambridge, MA 02138, USA*

[4] *Division of Hematology, College of Medicine, Mayo Clinic, Rochester, MN 55905, USA*

Correspondence:	David Dingli, MD, PhD
	Mayo Clinic
	200 First Street SW
	Rochester, MN 55905
Telephone:	507 284 3417
Fax:	507 266 4972
Email:	dingli.david@mayo.edu

To the editor:

We thank Dr Newburger for his comments regarding our paper on cyclic neutropenia (CN) in mammals. It is clear that the same phenotypic effect can be the consequence of a number of genetic mutations. For example, almost half of the patients with CN do *not* have a mutation in neutrophil elastase (*ELA2*) (1), yet they have cycling of their neutrophils, implying that other defects have to lead to the same phenotype. Similarly, many patients with SCN have mutations in *ELA2* without neutrophil oscillations (2). Patients with the rare type 2 Hermansky Pudlak syndrome (HPS2) have neutropenia (SCN) (2) as part of the phenotype. We are not aware that neutrophil kinetics has been studied in detail in the few patients with HPS2 described to date. In the only report where details of the neutrophil counts are provided, these were normal on a couple of occasions and then profoundly low at other times, although it was reported that 'cycling was not observed'(3). The central issue remains that neutrophil elastase is either mutated or abnormally trafficked in several disorders that lead to cyclic hematopoiesis in humans and dogs, implying that its abnormal biodistribution within the myeloid series is central for cycling (phenotype). This is what we mean by the 'biological defect in CN'. Our mathematical analysis is independent of the intricate molecular details that can be diverse yet lead to similar phenotypes. Based on our model, the fundamental problem in CN is a consequence of (i) expression of *ELA2* in the early myeloblast compartment (regardless of whether the mutation is in the *ELA2* gene itself or another gene such as *AP3*) and (ii) feedback based on G-CSF that enhances survival and self-renewal of progenitor and precursor cells (4).This feedback mechanism, when appropriately scaled for the specific mammal, leads to the species-specific cycling frequency.

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