Estimation of Mutation, Drift and Selection in Single-Driver Hematologic Malignancy

Marek Kimmel[1]

[1] *Rice University, 3331 Main Street, Houston, TX, 77005, USA*
kimmel@rice.edu

Severe congenital neutropenia (SCN) manifests itself through an inability to produce enough granulocytes to prevent infections. SCN commonly results from a germline ELANE mutation. Large doses of the blood growth factor granulocyte colony-stimulating factor (G-CSF) rescues granulocyte production. However, SCN frequently transforms to a myeloid malignancy, commonly associated with a somatic mutation in CSF3R, the gene encoding the G-CSF Receptor. We built a mathematical model of evolution for CSF3R mutation starting with bone marrow expansion at the fetal development stage and continuing with postnatal competition between normal and malignant bone marrow cells. We employ tools of probability theory such as multitype branching process and Moran models modified to account for expansion of hematopoiesis during human development. We estimate coefficients, to obtain agreement with the age range at which malignancy arises in patients. Our model predicts the existence of a pool of cells with mutated CSF3R before G-CSF treatment begins. Estimated CSF3R mutation rates appear to be within or not far from the range typical for human somatic cells. Input from Roberto Bertolusso, Rosemary Braun, Seth Corey, Tally Glaubach, Marta Iwanaszko, Hrishikesh Mehta, and Tomasz Wojdyla, is acknowledged.

⋆Mini-Symposium: Evolutionary Theory of Disease