Effects of tissue size regulation on somatic evolutionary processes in hierarchical tissues

Daniel Grajzel, Imre Derény and Gergely J. Szöllősi

ELTE, Department of Biological Physics, Budapest, Hungary

MTA-ELTE „Lendulet” Evolutionary Genomics Research Group
Motivation

Cancer Arises From DNA Mutations in Cells

- Normal cell
- DNA mutations
- Uncontrolled proliferation

Last DNA mutation from:
- heredity
- radiation or chemicals
- spontaneous errors during DNA duplication

Artwork by Jeanne Kelly © 2010.
Hierarchical tissue model

a) differentiation hierarchy

- terminally differentiated cells
- transiently differentiated cells
- differentiation rates
- stem cell

b) possible events implementing hierarchy

- $p_k$: symmetric division with differentiation
- $1 - p_k$: symmetric division without differentiation
- $q_k$: differentiation from below
- $1 - q_k$: cell replenishment

Event type:
- symmetric division with differentiation
- asymmetric division
- symmetric division

Rate:
- $r_k^{\uparrow\uparrow} = \frac{1}{2} \frac{\delta_k}{N_k} p_k$
- $r_k^{\uparrow\circ} = \frac{1}{2} \frac{\delta_k}{N_k} p_k q_k = \frac{\delta_k}{N_k} (1 - q_k)$
- $r_k^{\circ\circ} = \frac{1}{2} \frac{\delta_k}{N_k} p_k (1 - q_k) < r_k^{\uparrow\uparrow}$

Source: Derenyi and Szollosi: Hierarchical tissue organization as a general mechanism to limit the accumulation of somatic mutations, Nature Communications, 2017
Hierarchical tissue model

a) differentiation hierarchy

- terminally differentiated cells
- transiently differentiated cells
- differentiation rates
- stem cell

b) possible events implementing hierarchy

\[
S = 1 - \frac{r_k^{\uparrow\uparrow}}{r_k^{\bigcirc\bigcirc}} = \frac{\alpha}{1 + \alpha}
\]

source: Derenyi and Szollosi: Hierarchical tissue organization as a general mechanism to limit the accumulation of somatic mutations, Nature Communications, 2017
Tissue size regulation

Confining potential: \[ \frac{1}{2} \beta (N_k (t) - N_k^0)^2 \]

\[ +N_k: \quad e^{-\frac{\beta}{2} \left( \frac{N_k (t) - N_k^0}{N_k^0} \right)} \]
\[ -N_k: \quad e^{-\frac{\beta}{2} \left( \frac{N_k (t) - N_k^0}{N_k^0} \right)} \]

Number of cells

\[ N_k^0 \]

\[ N_k (eq) = N_k^{wt} (eq) + N_k^{mt} (eq) \]

\[ N_k^{wt} (eq) = N_k^0 (1 - S) \]

\[ N_k^{mt} (eq) = N_k^0 \left( S + \frac{\ln \left( \frac{1}{1-S} \right)}{\beta} \right) \]
Results

- Regulation leads to threshold in proliferation rate of mutant cells

\[ S = 1 - \frac{r_k^{↑↑}}{r_k^{∞∞}} = \frac{α}{1 + α} \]

\[ \tilde{r}_k^{∞∞} = (1 + α) r_k^{↑↑} \]
Results

\[ S = 1 - \frac{r_k^{\uparrow\uparrow}}{r_k^{\infty\infty}} = \frac{\alpha}{1 + \alpha} \]

\[ \tilde{r}_k^{\infty\infty} = (1 + \alpha) r_k^{\uparrow\uparrow} \]
Results

- Smaller compartment size shifts this threshold to higher S values

\[ S = 1 - \frac{r_k^{\uparrow\uparrow}}{r_k^{\infty}} = \frac{\alpha}{1 + \alpha} \]

\[ \tilde{r}_k^{\infty} = (1 + \alpha) r_k^{\uparrow\uparrow} \]
Summary

• Regulation leads to a threshold in proliferation rate
• The transition point depends on the strength of regulation, compartment size
• There is a stationary number of mutant and wild type cells which depends on the strength of regulation, compartment size and proliferative advantage
• Biological example: Colonic crypts are hierarchically organized, they have a relative small number of cells in a compartment
• In order to minimize the risk of cancer it is preferable to have smaller compartment size and a hierarchical organization
Thank you for the attention!

#ReBiCon2018