

Review

Modeling embryogenesis and cancer: an approach based on an equilibrium between the autostabilization of stochastic gene expression and the interdependence of cells for proliferation

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Abstract

A large amount of data demonstrating the stochastic nature of gene expression and cell differentiation has accumulated during the last 40 years. These data suggest that a gene in a cell always has a certain probability of being activated at any time and that instead of leading to on and off switches in an all-or-nothing fashion, the concentration of transcriptional regulators increases or decreases this probability. In order to integrate these data in an appropriate theoretical frame, we have tested the relevance of the selective model of cell differentiation by computer simulation experiments. This model is based on stochastic gene expression controlled by cellular interactions. Our results show that it is readily able to produce tissue organization. A model involving only two cells generated a bi-layer cellular structure of finite growth. Cell death was not a drawback but an advantage because it improved the viability of this bi-layer structure. However, our results also show that cellular interactions cannot be simply based on raw selection between cells. Instead, tissue coordination includes at least two basic components: phenotypic autostabilization (differentiated cells stabilize their own phenotype) and interdependence for proliferation (differentiated cells stimulate the proliferation of alien phenotypes). In this modified autostabilization-selection model, cellular organization and growth arrest result from a quantitative equilibrium between the parameters controlling these two processes. An imbalance leads to tissue disorganization and invasive cancer-like growth. These findings suggest that cancer does not result solely from mutations in the

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cancerous cell but from the progressive addition of several small alterations of the equilibrium between autostabilization and interdependence for proliferation. In this frame, it is not solely the cancerous cell that is abnormal. The whole organism is involved. Tumor growth is a local effect of an imbalance between all the factors involved in tissue organization.

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