

ONCOGENES AND GENETIC NETWORKS

Roumen Tsanev* and Blagovest Sendov**

Institute of Molecular Biology* and Institute of Mathematics**

Bulgarian Academy of Sciences, Sofia, Bulgaria

SUMMARY

The “oncogene concept” assumes that cellular gene exist which can transform normal cells into malignant cells when overexpressed or modified by point-mutations. The presence of such cellular oncogenes (c-onc’s) in a large variety of eukaryotic cells from east to man and the high evolutionary conservation of their coding sequences have suggested that they should normally play an important role, most probably in the control of cell proliferation and differentiation.

In spite of some experimental evidence, the role of c-onc’s in carcinogenesis has been questioned due to many contradictory facts. Thus, c-onc’s are expressed in many normal tissues (in some in a high level); the frequency of activated c-onc’s in tumors is not high; it is not clear whether point-mutations are cause of tumor initiation or result of tumor progression; no correlation has been found between a particular cancer and the amplified c-onc; some doubt was cast on the possibility of c-onc’s to transform normal cells in transfection experiments, etc. or these reasons the “oncogene concept” explaining cancer by the activation of latent cancer genes was thought to be an overinterpretation of facts and a paradox.

Another way of understanding carcinogenesis is to consider not separately individual genes only, but the whole set of interacting genes forming in the genome a functional genetic network, a concept which has been very rarely used. We have shown that such an approach can be useful in explaining the mechanisms controlling cell proliferation and differentiation, as well as the mechanisms leading to the closely related process of oncogenesis.

The model of a genetic network of our studies was used on the following principles:

1. Each gene of an eukaryotic cell can be in three different functional states – permanently repressed (blocked), inactive but available for transcription (deblocked inactive) and actively transcribing (deblocked active).
2. Interactions between genes are realized by trans-acting products of different genes acting each upon several other genes (due to the presence of operations or of controlling sequences common to several genes).

3. Three types of trans-acting products are involved: repressors, activators (acting directly or via elimination of repressors) and factors blocking gene activity.
4. All genes are classified in three categories: genes vitally important for the cellular life processes (house-keeping genes), genes carrying out the mitotic cycle (mitotic genes) and genes controlling specialized cell functions (differentiation genes).
5. Some of the differentiation genes are functionally linked to the mitotic genes by a mutual repression, so that mitotic activity and some differentiation functions are mutually exclusive.
6. Interaction between controlling elements obeys the law of mass action. Mathematical description of such a genetic network and quantitative computer studies have shown that it sufficiently well simulates the behavior of different living systems. It was also found that this system is quite stable within certain domains of the parameters space. However, extremely small changes of a parameter of the boundary of these domains disturb its stability and can lead to uncontrolled growth associated also with changes in the state of differentiation. The model shows that both mutational and epigenetic mechanisms can lead to carcinogenesis. It can explain the properties of malignant cells and also the contradictory facts concerning c-onc's. Depending on the parameters of the genetic network of different cellular types a gene can or cannot appear as a c-onc. Thus, the concept of genetic networks seems to be a useful complement to the concept of cellular oncogenes.

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Autor(en)/Author(s): Tsanev Roumen, Sendov Blagovest

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