The Multipath/Multistage Model of Carcinogenesis

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1. Abstract

The multipath/multistage model of carcinogenesis fuses the concepts of the multihit and multistage theories into one cohesive model, which in turn results in a model where there are multiple pathways leading to cancer. The biological plausability of this mathematical construct and the data that support it will be described.

2. Introduction

Biologically-based mathematical models of carcinogenesis have been used for quantifying cancer risks for approximately forty years. These models are used to understand the mechanisms of carcinogenesis and to determine reasonable margins of safety for exposure to carcinogens. By capturing the biological aspects of carcinogenesis within the framework of the mathematical model, a better understanding of the carcinogenic process may be provided. In addition, it is important to have an accurate model when extrapolating to exposures (doses) observed in the human population since predictions from these models may vary dramatically. Thus, satisfactory fit (if goodness-of-fit can be assessed) and biological plausibility are key issues in determining the appropriateness of a mathematical model.

There are two basic concepts that have been used in describing the events leading to carcinogenesis: hit theory and multistage theory. The biological hypothesis behind the hit theory of carcinogenesis is that a cell must be damaged a certain number of times before it loses growth control and becomes tumorigenic. The damage to the cell is thought to be caused by particles of the carcinogen hitting the nucleus of the cell. The damage incurred is dependent on the number of hits the cell receives and the dose of the carcinogenic agent. A majority of the literature on hit theory modelling comes from the area of biophysics where interest has centered on the interaction between radiation particles and target cells with respect to survival. Hit theory directly related to modelling the process of carcinogenesis has a limited history (Iverson and Arley, 1950[1];Rai and Van Ryzin, 1981)[2].

The multistage theory of carcinogenesis also assumes several events leading to cellular damage, however these events must occur in a particular sequence. This theory was initially conceptualized by Muller (1951)[3] and Nordling (1953)[4] from the observation that for some carcinomas the cancer incidence rate rapidly increased with increasing age. Multistage theory continues to be a popular concept since current biological evidence suggests that genetic changes usually occur in a specific order (Barrett and Wiseman, 1987)[5].

The history of carcinogenic modelling can be described as a hierarchy of models within a respective framework, i.e. hits or stages. Generally, each newly developed model encompasses the previously developed models. Thus, mathematical models attempt to include the evolution of biological evidence in cancer biology.

The multipath/multistage model incorporates the concepts of hits and stages into a single

framework. This model encompasses most carcinogenic models developed thus far and allows for the investigation of more complicated models. In essence, the multipath/multistage model is a generalized model of carcinogenesis which should allow us to compare multihit and multistage models by restricting the parameter space (Sherman, 1994)[6].

3. The Two-Path/Two-Stage Model of Carcinogenesis

In fusing the hit theory and multistage theory of carcinogenesis, it is important to understand the notions of stages and hits in the context of multipath/multistage model. Stages will be defined as necessary events for carcinogenesis that must occur in a specific order. Conversely, hits are defined as events that have no specific ordering and no direct bearing on carcinogenesis, however they may augment the rate at which a stage occurs. Consequently, by definition, hits yield alternative pathways to cancer.

Figure 1 displays a two-path/two-stage model of carcinogenesis. There are two possible paths for a normal cell to be transformed into a malignant cell:

(1) A normal cell may undergo two mutational events: transformation from the normal state to stage-one without mutation A (rate $\mu_1(t)$) and then transformation from stage-one without mutation A to the malignant state (rate $\mu_2(t)$). This is the most direct path to carcinogenesis where two stages are traversed.

(2) A normal cell may undergo three mutational events: transformation from the normal cells to hit A cells (rate $\mu_A(t)$), transformation to stage-one with mutation A (rate $\mu_{A1}(t)$), and then transformation to the malignant state (rate $\mu_{2A}(t)$).

For the model shown in Figure 1 (and all classes of semi-stochastic multipath/multistage models), the growth of normal cells is assumed to be deterministic. In the context of the model, it is assumed that the number of normal cells at any time t is constant. Stage-one cells without mutation A, hit A cells, and stage-one cells with mutation A are assumed to undergo growth kinetics via a linear birth-death process. A linear birth-death process implies that the rate of cell growth is proportional to the number of cells in the tissue. Further modelling assumptions are that the birth-death processes and mutation processes are stochastic and independent of one another. In addition, each cell acts independently of other cells. These assumptions imply that this mathematical model portrays the process of carcinogenesis as a Markov process. A Markov process describes the fate of any cell at time t as depending only on the present state of the cell at time t and not on the past history of that cell. More precisely, this model may be described as a continuous-time multiple branching process since stage cells and hit cells implement growth kinetics that spawn birth-death processes from which the progeny form branching processes.

In a modelling context, Figure 1 is a three-stage model added to a two-stage model since hits and stages are mathematically indistinguishable. However, biologically, this is not simply a three-stage model added to a two-stage model , but a construct based on some observations regarding certain carcinogenic mechanisms. Because the hit A cells still lead to stage-one cells, this state does not really constitute a stage by the definition given above. The hit A cell state reflects the definition of a hit since passage through this state in moving to the stage-one cell state is not required, but does alter the overall mutation rate.

To relate the model in Figure 1 with current biological theories, consider the roles of oncogenes and suppressor genes in tumorigenesis. Harris and Hollstein (1993)[7] suggest that the critical event in carcinogenesis is the deactivation of a tumor suppressor gene. In the figure, this deactivation would constitute stage-one. One possible role of an activated oncogene (hit A) would be to increase the chances of deactivating a suppressor gene by destabilizing the cell (either directly or through increased mitogenesis). Thus, there would be two pathways to carcinogenesis: the rare pathway of direct deactivation of a suppressor gene (stage-one) followed by a second mutation to the malignant state; and the preferred pathway of going through oncogene activation (hit A cell state), then traversing stage-one into the malignant state. In this scenario, oncogene activation is not necessary to the actual carcinogenic

mechanism, however it's importance lies in promoting the deactivation of a tumor suppressor gene.

4. Data Supporting the Multipath/Multistage Model

Initially, mathematical models of carcinogenesis were developed to describe the incidence of certain cancers in various populations (Armitage and Doll, 1954[8], 1957[9]; Neyman and Scott, 1967[10]; Moolgavkar and Venzon, 1979[11]). These models were further developed to incorporate the evolution in knowledge of the cancer process and have been implemented to describe the incidence of tumors observed in long-term animal carcinogenicity studies (Gart et al., 1986[12]; Kodell and Nelson, 1980[13]). Current experimental research in cancer has moved beyond solely collecting tumor incidence data. Experimenters are able to obtain more sophisticated data that describe the mechanisms of carcinogenesis through a variety of experimental designs, i.e. initiation-promotion, start-stop dosing regimens, etc. The data collected from these experiments may include multiple stained enzyme altered premalignant and malignant focal lesions, labelling index, and other biomarkers. Schwarz et al. (1989)[14] have observed the heterogeneity between single phenotype lesions and multiple phenotype lesions (multiple stained lesions) in experiments where enzyme-altered foci were obtained from rat liver. A single-path process (multistage model) is not adequate to describe their observations, and a multipath model is more appropriate. Further experimental evidence in support of the multipath/multistage model is found in the work of Bannasch (1988)[15].Observations in human colon carcinogenesis (Fearon and Vogelstein, 1990)[16] also point to multiple pathways for the process of cancer.

To improve the mathematical modelling of carcinogenesis we need to expand the use of additional experimental information beyond tumor incidence data alone. Additional data will allow for larger and more sophisticated models that more closely parallel current cancer hypotheses. In turn, these models may increase our understanding of the process of cancer.

5. References

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