CHAPTER 7

Intercellular Communication: A Paradigm for the Interpretation of the Initiation/Promotion/Progression Model of Carcinogenesis

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... during the critical periods, the cancer cells are susceptible to the influence of the host and are restrained by the normal cells. The basis for this is the fact that the normal sequel to an injury is growth which reaches a certain level and then stops when the injury has been repaired. ... This growth must stop by some self-regulatory process which is possessed by normal cells but is not possessed by tumor cells.

V. R. Potter (1)

I. INTRODUCTION: CANCER AS A PROBLEM OF HOMEOSTATIC DYSFUNCTION

The insight provided by this quotation of Potter seems to have been lost or overshadowed by recent spectacular advances in the molecular biology of cancer. This is illustrated by the statement, “Understanding the cellular basis of cancer means being able to describe the biochemistry of the regulated pathways between cell surface and nucleus that control cell growth” (2). In spite of the success in elaborating the identity and structure of many oncogenes and their cellular products, as well as elucidating the details of several transmembrane signaling mechanisms, Varmus (3) has recently stated: “The hopes ... must be balanced against pessimism borne of two long-standing frustrations in oncogenetics: (a) the failure to identify the relevant targets for the neoplastic action of oncogenes, even when the oncoproteins have provocative biochemical properties, such as protein kinase or guanine nucleotide binding activity ... ”.

Fundamentally, one might ask “why, with so much success on the molecular level, do we not have an understanding of how oncogenes function?” The answer seems to be
because the bulk of the cancer research effort has been guided by a reductionist rather than an interactive or holistic approach. Cancer seemed to be a problem within a cell, rather than a “problem of cell interaction, not only within tissues, but with distant cells in other tissues” (4).

In reaction to the current pressure to approach the solution to the understanding of the “mechanism” of carcinogenesis only by means of molecular biology, Levitt (5) stated, “As a matter of fact, a number of areas crucial to our understanding of cellular homeostasis—the key to unraveling the biology of cancer—are not ready to make the transition to the molecular phase of investigation”.

To begin to view the cancer problem from another perspective, one must recognize that multicellular organisms, including rats and humans, are the result of a hierarchical organization of levels (e.g., cells, tissues, organs, systems) held together by various homeostatic or cybernetic mechanisms. Claude Bernard and W. B. Cannon were the first to introduce the cybernetic or homeostatic control concept of living organisms on the physiological level (6,7).

The objective of this Chapter is to examine several paradigms associated with the understanding of the cancer problem at some level and to integrate these paradigms into one which reflects cancer as a problem of homeostatic dysfunction. Toward this aim the initiation/promotion/progression theory of carcinogenesis (8), the oncogene concept (9), the paradigm of “carcinogenesis as mutagenesis” (10), “cancer as a disease of differentiation” (11) or “oncogeny as partially blocked or blocked ontogeny” (12), cancer as a stem cell disease (13), and the concept of intercellular communication (14) will be examined.

II. THE NATURAL HISTORY OF CARCINOGENESIS

The objective of the scientific method is to explain observations in order to make useful and testable predictions. In order to formulate a theory of carcinogenesis, a tremendous number of observations must be examined in order to generate a meaningful theory.

From experimental studies in animals, epidemiological examination of human cancers, and recent oncogene research, it has been concluded that the conversion of a normal cell to a metastasizing, invasive cancer cell is not the result of a single step (15). The multistep carcinogenic process seems to involve the evolution of phenotypes, including the inability to terminally differentiate (11,16), the loss of growth control (17) or contact inhibition (18), the inability to perform normal gap-junctional intercellular communication (19), and to migrate to distal tissues and to invade these tissues (20).

The tumor, once formed, appears to be clonally derived from the single errant stem cell (21). However, the clonal expansion during the multistep carcinogenic process involves acquisition of many phenotypes within the tumor, possibly due to additional genetic and/or epigenetic changes (22).

The operational concepts of initiation, promotion, and progression were derived from observations on experimental animals (23) (Figure 1). The multistage nature of carcinogenesis in studies on mouse skin carcinogenesis and, more recently, in liver and bladder (24) indicated very discrete and distinctive characteristics associated with the different phases of carcinogenesis. Although the operational concepts of initiation/promotion/progression do not imply any particular mechanism of action, it is clear that the mechanisms underlying these three stages are different (25).

Assuming the initiation event takes place in a single stem or progenitor cell, the experimental observations suggest strongly that the event is ostensibly irreversible. True