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Editorial

Mutator phenotype in cancer: Origin and consequences

The concept that cancers express a mutator phenotype was formulated eons ago [1]. Its origin stems from observations that within each tumor there are many different chromosomal alterations in each malignant cell and the shape and structure of these cells are strikingly heterogeneous. We surmised that many human cancers harbor large numbers of mutations and hypothesized that these multiple mutations could not be accounted for by the exceptional accuracy of DNA replication in normal cells. Instead, we postulated that many cancers accumulate mutations in DNA polymerases and in proteins functioning in DNA repair and replication and mutations in these genes render DNA synthetic processes error-prone, resulting in genetic instability. With each generation, more and more mutations occur, some of which are in other genes that are required to maintain the genetic stability of normal cells. As tumors grow, there are repetitive rounds of selection for mutants that allow the tumors to invade and metastasize, ultimately killing the host. The genetic heterogeneity within a tumor is advantageous for overcoming environmental growth impediments and constitutes a repository of different mutant cells that allows for the rapid emergence of resistance to treatment with chemotherapeutic agents.

The concept of a mutator phenotype in cancer has been expanded [2], based on recent experimental results indicating that: (1) each human cell undergoes more than 20,000 DNA damaging events per day [3], (2) there are multiple mechanisms to repair these lesions by excision and recombination [4], (3) there are specialized DNA polymerases in eukaryotic cells that efficiently copy unrepaired DNA damage and incorporate non-complementary nucleotides at a higher frequency [5], (4) there is extensive regulation of DNA synthetic processes during the cell cycle [6], and (5) there are alterations in translation, gene splicing and protein synthesis in cancer cells [7]. Perhaps, most importantly, genetic redundancy provides proteins or functions that can substitute for one another in catalyzing metabolic processes. As a result, cancer cells can tolerate extensive genetic instability without the loss of viability.

Our current concept envisions tumor progression as a stochastic process. Unrepaired DNA damage in cancer progenitor cells results in random mutations throughout the genome, some of which occur in exons and regulatory sequences that normally function to maintain genetic stability. Some of these mutant gene products are mutators. As tumors progress they need to overcome multiple barriers that restrict their growth including: the presence of surrounding tissues, inadequate blood supply and lymphatic drainage, and host immunological defenses. Cells that have acquired mutant phenotypes that overcome these barriers proliferate and form subclones within the tumor. Repetitive rounds of selection result in increasing diversity and in mutations in multiple gene products and pathways that contribute to the cancer phenotype. Random mutations, or private mutations, that arise after the last round of selection also contribute to cellular heterogeneity within a tumor. Many mutations are carried within a tumor as passengers; even though they do not provide a selective growth advantage in one environment, they may do so in a different environment. By the time a tumor is manifested clinically, it contains multiple clonal mutations (detected by current DNA sequencing methods); millions of subclonal mutations (which we predict will be found in large numbers in cancer using deep sequencing); and an even larger number of random mutations (identified by sequencing single molecules) [8]. This mutational diversity within a tumor provides a fertile assemblage for the emergence of variants resistant to any therapeutic agent. As a result, cancer therapy will be limited by the rapid selection and proliferation of pre-existing resistant cells; similarly, the inhibition of one or a few metabolic pathways is unlikely to provide adequate therapy for most tumors. Multiple and simultaneous therapeutic approaches might be the most effective. New approaches to cancer therapy, including one directed at altering mutation rates in cancer cells need to be considered.

The expression a mutator phenotype in cancer has been either controversial or ignored. In particular, it is not attractive for the pharmaceutical industry; the current drug development paradigm is to target one or a few genes. It has been argued that extensive rounds of cell proliferation in cancers would be adequate to generate multiple mutations and that it is not necessary to invoke an increase in the mutation rate to account for the mutations identified in cancer cells. In fact, the most extensively considered model for tumor progression involves successive rounds of clonal selection [9] without requiring an increase in the generation of mutations.

This issue of Seminars in Cancer Biology presents a series of manuscripts focused on the large numbers of mutations in human cancers. Preston et al. (this issue) summarize the multiple cellular mechanisms that guard our genome, and when disrupted are associated with cancer. His laboratory pioneered the creation of mice harboring mutant DNA polymerases that lack proof-reading activity and that spontaneously develop specific malignancies. Salk and Horwitz (this issue) consider the fields of premalignant cells from which cancers arise. Neutral passenger mutations in normal appearing cells can herald the presence of emerging cancers at distant sites. Arana and Kunkel (this issue) consider the contribution of eukaryotic DNA polymerases to insuring the fidelity of eukaryotic DNA replication. This laboratory established methods for measuring polymerase fidelity and in this review present the signatures and footprints for identifying the involvement of

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specific DNA polymerases in cellular DNA synthetic processes and in tumorigenesis. Recently, ten new DNA polymerases have been discovered in eukaryotic cells that can copy past sites of DNA damage and in doing so incorporate non-complementary nucleotides. Hoffmann (this issue) summarizes data on mis-regulation of these translesional DNA polymerases in human cancers and its implications. Each of our cells repairs more than 20,000 DNA damaging events per day. Nemec et al. (this issue) postulate that variant base excision enzymes catalyze aberrant DNA repair and that this could be a major contribution to a mutator phenotype in tumors. Monnat (this issue) considers the multiple functions of RecQ DNA helicases, mutations in three of genes are manifested by an increased risk of cancer. New data suggests that acquired loss of RecQ function may provide an opportunity to improve cancer therapy. Beckman (this issue) summarizes theoretical arguments that a mutator phenotype is inevitable if multiple mutations are required for clinical cancers. The notion is that all possible mechanisms of carcinogenesis are in competition, and the most efficient cancer causing mechanism will predominate and will be observed clinically. Finally, Fox and Loeb (this issue), apply the concept of lethal mutagenesis to end stage cancers. They postulate that a subset of human tumors may be effectively treated with mutagenic nucleoside analogs to elevate the mutation frequency and push tumor cells beyond the error threshold for cellular viability.

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