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Review

Many different tumor types have polyclonal tumor origin: Evidence and implications

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ABSTRACT

Few ideas have gained such strong acceptance in the scientific community as the monoclonal origin of tumors; the idea that tumors start with a single mutated cell (or a single clone of cells) that go on to accumulate additional mutations as a tumor develops. The certainty with which this concept is held by the scientific community reflects the length of time it has been unchallenged and the experimental difficulty in obtaining direct evidence to the contrary. Yet, recent findings regarding X chromosome inactivation patch size indicate that the X-linked marker data previously interpreted as evidence of monoclonal tumor origin is actually more consistent with polyclonal tumor origin, a situation where two or more cells or clones of cells interact to initiate a tumor. Although most tumors show homotypy for X-linked markers (as expected given the bias conferred by X chromosome inactivation patch size), the literature contains numerous examples of tumors with X-linked marker heterotypy, examples of which encompass 24 different tumor types. Chimeric models have yielded direct unequivocal demonstrations of polyclonality in rodent and human tumors. Also, mutational data are consistent with polyclonal tumor origin. Methods that analyze levels of tumor-associated oncogene and tumor suppressor gene mutations demonstrate that initiated cells are much more common in normal tissues than previously realized. Also, while tumors have higher levels of mutation than normal tissues, oncogenic mutations frequently are present as subpopulations within tumors, rather than as the pure mutant populations expected to develop from a single initiated cell. Understanding the mutational basis of tumor etiology has important practical significance for assessing cancer risk, as well as in modeling and treating cancer. Therefore, the scientific community needs to re-examine this issue and consider the implications of polyclonal origin for, perhaps, a majority of tumors, encompassing many different tumor types.

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Contents

1. Introduction . . . 233
2. Current mutation theory of carcinogenesis . . . 234
3. Strength and basis of the scientific acceptance of tumor monoclonality . . . 234
4. Failure to detect marker heterogeneity is not evidence of monoclonal tumor origin . . . 235
5. Re-interpreting data on heterotypy of X-linked markers . . . 236
6. Other evidence of monoclonal tumor origin . . . 238
7. Direct evidence of polyclonal tumors . . . 240
8. Frequency of tumor-associated mutation in tissues and tumors is consistent with polyclonal tumor origin . . . 241
9. Conclusions . . . 242
10. Implications of polyclonal tumor origin . . . 243
Acknowledgements . . . 244
References . . . 244

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Abbreviations: ACB-PCR, allele-specific competitive blocker polymerase chain reaction; ACF, aberrant crypt foci; APC, *adenomatous polyposis coli*; CML, chronic myelocytic leukemia; DGGE, denaturing gradient gel electrophoresis; FAP, Familial Adenomatous Polyposis; G-6-PD, glucose-6-phosphate dehydrogenase; HPRT, *hypoxanthine-guanine phosophoribosyltransferase*; *HUMARA*, human androgen receptor gene; Ig, immunoglobulin; MF, mutant fraction; RFLP, restriction fragment length polymorphism.

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1. Introduction

Monoclonal tumor origin refers to the idea that all cells within a tumor can be traced back to a single progenitor cell (Fig. 1A). The monoclonal origin of cancer is commonly accepted as fact. This tenet of cancer biology has become so entrenched within the scientific community that the data upon which this conclusion is based is no longer presented in the textbooks used in medical and graduate education. Many scientists are unaware that the data that led to the acceptance of the monoclonal origin of tumors have been re-interpreted in a manner that nullifies the original conclusions. Furthermore, positive evidence of tumor polyclonality has been accumulating. Polyclonal tumor origin refers to the idea that two or more different progenitor cells or clones of cells cooperate in the genesis of a tumor (Fig. 1B). While the acceptance of polyclonal tumor origin has been expressed in at least two editorials and one review on bladder cancer [1–3], the data supporting this mechanism have not been systematically collected and scrutinized for the purpose of refuting the generalized acceptance of monoclonal tumor origin. Thus, the main focus of this review is to re-evaluate the data from which the nature of the very earliest stage of tumor development (tumor origin) can be inferred. While it is understood that not all tumors have to be either monoclonal or polyclonal, both types of tumor origin may exist, any single tumor has to have been derived from either a single cell lineage (one cell or a clone derived from one cell) or from two or more cell lineages (two or more cells or two or more clones of cells). Distinguishing whether tumors arise from a single mutated cell or single clone of cells (monoclonal) or from two or more cells or clones of cells (polyclonal) is at the core of this review. Furthermore, this review is intended to argue that the monoclonal origin of tumors is an idea held with a certainty not supported by the literature, to point out how the categorical acceptance of this idea may be impeding progress in cancer research, and to stimulate investigation into the earliest events in tumor development, including the potential interaction between multiple mutant clones. This review does not deal with the large literature characterizing the relationship between multiple synchronous tumors, where genetic markers are investigated in order to distinguish the spread of tumor cells through a tissue from the development of multiple independent tumors from a field of cells with underlying genetic lesions (field cancerization).

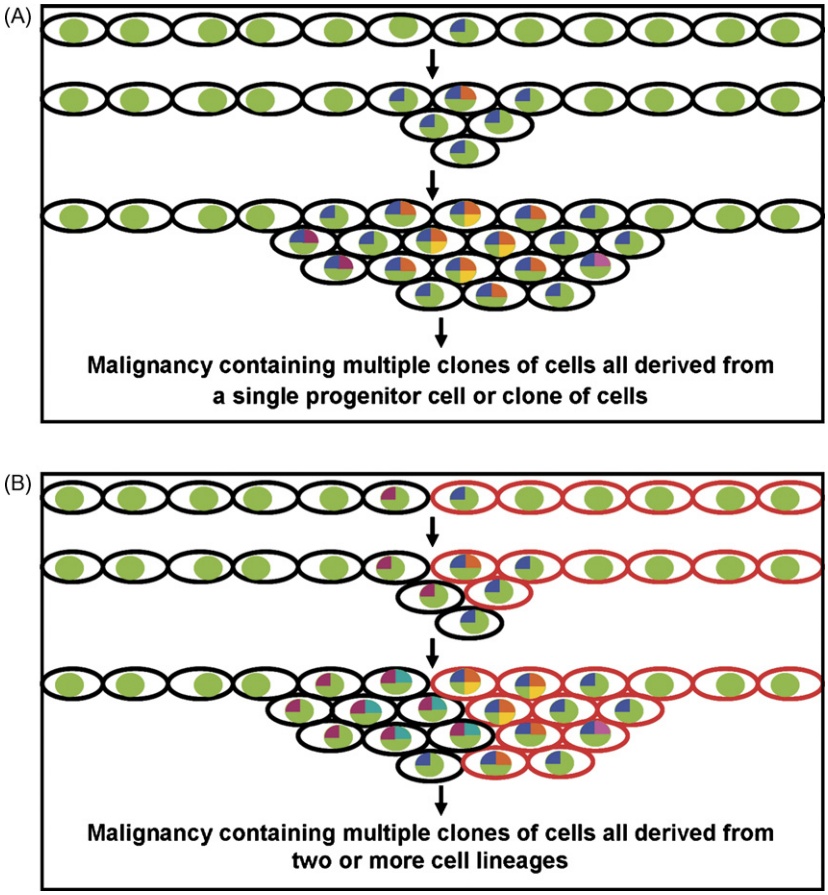

Fig. 1. Schematic representation of the initial events in carcinogenesis. Monoclonal (A) and polyclonal (B) tumor origins are depicted. The outline of the "cells" is colored (red or black) to represent a cell lineage marker independent of the carcinogenic process, like X-linked glucose-6-phosphate dehydrogenase activity or methylation at an X-linked locus. Nuclei are depicted as green circles. Genetic lesions are denoted by the different colored inserts in the nuclei. Theoretically, genetic lesions could include epigenetic changes, as well as different types of mutations (point mutations, insertions, deletions, translocations, etc.). According to monoclonal tumor origin (A), all the cells of the nascent tumor are derived from a single cell carrying the initial genetic lesions (indicated by the blue sector). Accumulation of additional mutations in this cell (or the daughters of this cell) follows, producing a clone of cells with multiple mutations whose propagation is favored (cells with blue, orange, and yellow sectors). Such multiply mutated cells are thought to develop into a malignancy, but tumors are heterogeneous because clones of cells containing different subsets of these genetic lesions, as well as additional genetic lesions (*e.g.*, pink sector), may also be present. According to polyclonal tumor origin (B), genetic lesions in two or more cells or clones of cells (indicated by blue and maroon sectors) interact to begin tumor development. Aside from this critical difference in the number of cells lineages involved in tumor initiation, concepts regarding the types of the genetic lesions, the need for the accumulation of additional mutations, and subsequent clonal selection are equally applicable to both schemes (monoclonal and polyclonal tumor origin).