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Instability in Oncogenesis Directly Implicates Mutator Phenotype Progression through Genetic Lesion Heterogeneity

Lawrence M Agius*

Department of Pathology, Mater Dei Hospital, Tal-Qroqq, University of Malta Medical School, Msida, Malta, Europe

***Corresponding author:** Lawrence M Agius, Department of Pathology, Mater Dei Hospital, Tal-Qroqq, University of Malta Medical School, Msida, Malta, Europe, Tel: 356-21451752; E-mail: lawrence.agius@um.edu.mt

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Abstract

Theoretical uncertainties regarding the dimensions of mutator mutations are reflected particularly in the parameter uncertainties of the oncogenic pathways that are heterogeneous in individual tumor cells. The key attribute of marked heterogeneity in genomic lesions attests for the essential evolution of the mutator phenotype per se, and allows for the emergence of oncogenesis beyond initial or middle course events in malignant transformation. Although initial or early mutator mutations may prove rare events in oncogenesis, the emergence also of passenger mutations reflect an essential establishment of a mutator phenotype as essential genomic instability and mutability.

Keywords: Mutations; Phenotype; Oncogenesis tumor cells

Introduction

Mutator mutations are generally considered cooperative pathways associated with the high degrees of heterogeneity of tumors. Mutations in polymerase delta in mice and humans promote genomic instability, mutator phenotype and tumorigenesis [1]. Driver oncogenic mutations presumably progress with expansion of clonally selected subpopulations of tumor cells in a manner that calls into operative modes the development of genetic instability. A reduced accuracy in DNA replication during tumor progression leads to marked heterogeneity of malignant cells and therapeutic resistance [2]. In such terms, the emergence of genome-wide selectivity to mutation may underlie a pseudo-Darwinian series of theoretical models for tumorogenesis and subsequent tumor progression. Low-fidelity compensatory back-up alternative DNA repair pathways may drive multistep neoplastic development [3].

Mutator Phenotype

Predilection for mutator phenotype dynamics has been invoked through the setting for selective genomic instability in a manner that underlies the whole integral progression of oncogenic mutation. Colorectal cancer arises from chromosomal instability, CpG island methylator phenotype and microsatellite instability [4]. In terms that increasingly recruit dynamics of increased cell proliferation there also evolves insensitivity to apoptosis of the tumor cells or of premalignant cells. A multi-step model of skin carcinogensis involves a cellular mutator phenotype even more prone to mutation acquisition [5].

It is with strict reference to increments of a coupling of increased tumor cell proliferation and anti-apoptosis that there emerge systems of genomic instability. Accurate repair of double stranded breaks is essential for cell survival and involves kinases, nucleases, helicases or core recombinational proteins [6]. The powerful pro-carcinogenesis effects of genomic instability invoke the dimensions of an expanded tumor cell niche that inclusively involves both bulk tumor cell sub-populations and also stem cells. Cell fusion is a powerful inducer of aneuploidy, genomic instability and like mutations and aneuploidy might induce a mutator phenotype [7].

Initiator mutator mutations are regarded as rare events, and hence evolving genomic instability emerges as a generally later form of predisposition to ongoing oncogenesis. The DNA glycosylase gene MBD4 safeguards genomic stability at CpG sites and may contribute to carcinogenesis by acting as modifier of MMR-deficient cancer phenotype [8]. It is further to the dimensions of susceptibility ratios when contrasted with normal surrounding tissues that the tumorigenesis phenomenon both envelopes and further incorporates the varied heterogeneity of tumor cell sub-populations within a given neoplastic lesion. Chromosomal changes of chromosomal instability correlate with specific alterations such as APC, K-RAS, DCC and p53 and genomic instability in the mutator pathway focused on KRAS and BRAF mutations in colorectal carcinogenesis [9].

Tumorigenesis

A sharp dynamic contrast develops between increased sensitivities to growth-factor stimulation on the one hand and decreased sensitivities to growth factor inhibitory effects. The varied incorporation of operator mutations in oncogenesis are essential pathogenesis to the emergence of mutator mutations in a manner that often target and implicate repair DNA systems of operation.

The human APOBEC3A and APOBEC3B encode DNA mutator enzymes the deaminate cytidine and 5-methylcytidine residues in single-stranded DNA and predispose to mutations in many cancers with a preponderance of CG->TA [10]. Mismatch repair of DNA defects is a corollary series of pathway promotional agonists in the full developmental emergence and progression of Darwinian and pseudo-Darwinian systems of promotional effect. The distributional configurations of generalizability in genetic lesion infliction would allow for multiple loci within the genome to progress as reflected consequence to mutator phenotypes. The sliding clamp enhances polymerase processivity and coordinates DNA replication with critical translesion synthesis, Okazaki fragment maturation and DNA repair [11].

Topology/Parameter Uncertainties

Molecular topology uncertainities and indefinite variability in prediction models of theoretical nature cooperatively involve the unknown oncogenesis pathways in terms of molecular biology and biochemistry of relevant systems in mutator systems of enhanced rates in tumorigenesis,

Increased expression of the interferon-inducible double-stranded RNA-activate protein kinase inhibits DNA damage response signaling and double-strand break repair, permiting mutation accumulation [12]. It is with reference to promotional increments of evolving pathways that a mutator phenotype established increased susceptibility to further Darwinian selectivity. Deregulated APOBEC3 enzymes induce a general mutator phenotype with the production of heterogeneous tumor subclones [13]. The dimensional and generalized susceptibility dynamics in tumorigenesis renders the DNA genome a series of non-sequential steps in pathway evolution. The determination of serial promotional events is allied closely to establishment of new pathway phenotypes that include mutator mutations. Hypoxia promotes transcriptional and/or translation downregulation of most DNA repair pathways, including double strand DNA break repair, mismatch repair, and nucleotide excision repair [14].

Genomic Instabilities

Sparse experimental data has led to efforts to analyze also individual tumor cell genomes, as exemplified, for example, by unidentified mutations of the p53 gene.

Inclusive formulas incriminate a susceptibility series of typology and prediction indices involving dynamics of genomic instability. If mutation rate is not constant, an expanding mutator population may include subclones with widely divergent evolutionary rates; individual genome replication events show volatility in the evolution of mutator-driven malignancies [15]. The progression of tumorigenesis is linked to the various susceptibilities of loci in DNA repair in particular. Deficient DNA mismatch repair leads to a strong mutator phenotype, microsatellite instability, a hallmark of Lynch syndrome-associated cancers [16].

The hereditary non-polyposis familial syndrome in colorectal carcinogenesis exemplifies the distributional effects arising within a series of mismatch repair defects that tend to augment the further dimensions of a mutator phenotype. Recent data have shown considerable tumor hypermutation, broadening support for the idea of a mutator phenotype [17].

One may redefine genomic instability of tumorigenic events as a system of acquired malignant transformation in the face of mutator phenotype dynamics that in turn accelerate the oncogenic mutations as systems of initiation of dynamic cell proliferation and of anti-apoptosis.

Understanding of DNA double-strand break repair mechanisms has led to targeted therapeutic approaches with display in tumors showing defects in homologous recombination-mediated DNA DSB repair [18]. The variability of metastatic evolution per se is indicative of conflicting pathways in promotion of the genomic instability itself. In this regard, proposed increments of oncogenesis are dynamics of consequence for further mutator phenotype evolution. Since Fhit loss-induced DNA damage "checkpoint blind", cells accumulate further DNA damage during subsequent cell cycling, accruing global genome instability [19].

Individual Tumor Cells

Contrasting individual tumor cells are specific variability units that emphasize the oncogenesis as terms of a parent phenomenon as dictated by the heterogeneity of the genomic instability phenotype. If unrepaired, base damaging lesions may accelerate mutagenesis with aggressive behavior in estrogen-estrogen receptor –driven breast cancer [20]. Age-incidence of tumors is itself a derivative shape modality in terms of curve configurations that is applicable even to various sub-populations of a given neoplastic lesion of the individual patient.

Clonal Expansion

Parameter uncertainty cooperatively applies in terms of typology uncertainty in outlining the properties of a possible postulated series of mutator mutations in delineating further the roles of mutator phenotype determination in oncogenesis. It may be hypothesized that the mutator phenotype in the cancer genome may represent the overuse of alternative DNA repair mechanisms, due especially to homologous recombination deficiency [21]. The distributional premises for such genomic instability are further compounded by the inherently increasing number of oncogenic driver mutations within a given tumor genome of the individual tumor cell. Hypoxia provokes base excision repair and a repair-deficient mutator phenotype in colorectal carcinoma [22]. Clonal expansion has been considered a paramount phenomenon in carcinogenesis and subsequent lesion progression and metastasis. Such premises are derivative dimensions for further increasing variability in proposed induced mutator mutations,

Contrasts of tumor cells with surrounding normal cells indicate the inherent dynamics of a mutator phenotype that is further compounded by a diversity of genomic lesions that drive the oncogenesis of lesions. Determinations based on strict criteria of genomic variability are dynamic correlates related to parameter uncertainty and also to the typology of molecular pathways.

Concluding Remarks

Per se heterogeneity is an inherently defining signature characteristic of the oncogenic pathways within an individual tumor cell and between groups of tumor cells. The further progression of such heterogeneous genomic lesions is reflected within the substrate dysfunctionality of an included mutator series of predispositions as evidenced also in pre-malignant cells that proliferate and undergo progressive increases in oncogenic driver mutations. Discriminators of evolutionary attributes resemble the evolution according to Darwin's natural selection; however, tumor cells tend to show an increased rate of mutagenesis than that seen with such natural selection of cells. In terms, therefore, of incremental dimension, the reclassified pseudo-Darwinian evolution of tumor cells is allied closely to the evidenced theoretical dimensions of a mutator phenotype that progressively increases the number of oncogenic mutations. Also, further to such evolutionary course, the individual neoplastic cell can be considered a generic sub-population index for further tumor progression in terms strictly referable to increased tumor cell proliferation and anti-apoptosis effect.

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