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A Multiplicity of possible Carcinogenetic Pathwaysarising as Genetic Instability

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Abstract: Clonality appears an essential pathogenesis for genetic instability and for aberrant cell/cell interactive adhesion contact phenomena towards creation of a neoplasm via several potential pathways of highly varied nature, including DNA strand duplication promoting mismatch repair. Indeed, a series of neoplastic type lesions ranging from breast carcinoma to thyroid, colorectal and asbestos-related neoplasms might constitute a highly varied multiplicity of pathways in carcinogenesis. Genetic instability appears centrally implicated as one paramount mechanistic pathway of progressiveness in neoplastic development and subsequent course. This would promote a highly varied mode of possible pathogenesis towards an infiltrative spread of autonomously or excessively proliferating cells. In terms of cell/cell contact promoting increasing dysplasia as seen in colorectal polyps and of inflammatory conditioning and cytokine contributory roles towards neoplasms as evidenced in asbestos related mesotheliomas, there would arise cell proliferation that both constitutes the creation of multisystem effects and also proves a strong inducer of further evolving carcinogenesis.One basic attribute of carcinogenic pathways is the initial creation of multiple promoting events that would be based on a core phenomenon of genetic instability. In overall yet specific terms, such an apparently great multiplicity in creation of carcinogenic events towards genetic instability would further induce evolving neoplasia. Such a phenomenon would depend on intercellular events biophysically determining the responsiveness of cells exposed to such highly varied potential carcinogenesis. Indeed, a strong reference point in carcinogenesis would relate specifically to the responsiveness of affected cells irrespective of actual carcinogenic agents of exposure and of action. Exposed cell responsiveness would evolve as genetic instability and altered cell/cell interactions promoting multiple injuries as inflammatory and reparative phenomena in such cellular aberrant responsiveness, this being generally of both hereditary and acquired origin.

Key words: Carcinogenetic , genetic instability, multiplicity, cell interactive

INTRODUCTION

DEFECTIVE REPAIR MECHANISMS AS SELF-PROGRESSIVE THROUGH PERMISSIVENESS, THUS PROMOTING GENETIC INSTABILITY

The concept of defective DNA repair would incorporate active injury that might prove progressive as ineffective repair together with a permissiveness that promotes progression also of defective DNA repair, including nucleotide excision repair[1] and as reflected for example in TP53 mutation rate[2]. Concurrent promoter methylation is an early and frequent event in gastric carcinogenesis, including both MSI-H and microsatellite-stable neoplasms and of especially p16 gene[3].

Within such a scheme of operative progression based essentially on permissiveness, there might develop genetic instability as a function largely to such permissiveness. This would contribute towards loss of genomic integrity as defective DNA repair pathways[4].

Such a framework would specifically enhance genetic instability as with chronic exposure to irradiation[5].

Biologic fragility might potentially predispose to defective DNA repair as affecting especially strand duplication in mismatch repair. Defective DNA strand duplication would constitute a means of progressiveness within schemes of permissiveness provoking DNA defects as related, in various ways, to impaired DNA repair. It appears reasonable to consider defective DNA repair mechanisms as progressive in their own right, subsequently enhancing the development of genetic instability through permissiveness. An intimate link exists between chromatin remodeling in particular and defective DNA repair[6].

CONDITIONING EFFECTS OF HYPOXIA IN CLONAL TUMOR CELL ADAPTATION AND AS EVOLUTIONARY TRANSFORMATIONS

The mutator phenotype hypothesis maintains that the normal mutation rate is insufficient to account for the

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multiple mutations occurring in cancer cells[7]. Hypoxia as a specific microenvironmental set of conditioning and of preconditioning elements influencing evolutionary selection of proliferative pools of tumor cells might selectively influence whole clones of tumor cells as distinct from single neoplastic cells[8].

It is important to note that incorporation of oxidized purines from the deoxynucleoside triphosphate pool appears to promote considerable genetic instability of DNA mismatch repair-defective tumors[9].

In such a setting, hypoxic effects would determine selective clonal predilection amongst various pools of tumor cells, subsequently promoting proliferative extension both locally and systemically.

Hypoxia may constitute a preconditioning influence that fosters the creation of given sets of biologic attributes as both clonal and multiclonal evolution of the neoplastic lesion. Certainly, genetic instability is a vital early step in carcinogenesis, as with transitional cell carcinoma of the bladder[10]. Clonal cell proliferation is intrinsically one that arises directly from the action of hypoxia to condition and precondition pools of cells through various systems of a proliferative and infiltrative nature and involving metastatic spread. A set of specific pathobiologic properties would perhaps intrinsically combine hypoxia with clonal selectivity in terms of relative proliferative and apoptotic rates and of evolutionary progression and transformation of the neoplastic cells.

Neoplastic clones of cells would by definition constitute multiple expanding pools in the creation of an endless series of progressive transformations implicating clonality as a means towards evolutionary determination of genetic stability versus instability as seen with gastric carcinogenesis[11].

Indices such as those of proliferation or of apoptosis might mark clonal tumor cell pools specifically related to a highly varied series of transformations as the neoplasm infiltrates and spreads systemically in relation to multi-microenvironmental conditioning influences. In such a context, marked epithelial and stromal genetic instability of chromosome 17 is associated with carcinogenesis in ulcerative colitis[12].

ANGIOGENESIS AS AN ACTIVELY MAINTAINED DYNAMIC VASCULARITY SYSTEMICALLY AND LOCALLY

Angiogenesis would actively induce a phenomenon centered on events involving intercellular adhesion and affecting mitogenesis and chemotaxis[13]. Certain aspects of endothelial cell tube formation, particularly sprouting from parent vessels, would essentially involve intercellular induction with a subsequent potential for systemic involvement.

Given a context of circulating levels of soluble intercellular adhesion molecule-1, intercellular adhesion would involve a process that progressively supplants previous vascular structures in the integral maintenance of a vascular bed. Trans-generation transfer of altered mechanics in carcinogenesis would develop as acquired genomic change in germ cells. Genetic instability would modify tumor occurrence from one cell generation to the next[14].

Angiogenesis might actually constitute extension of established vascular beds involved systemically. It is possibly not only related to inflammation and neoplasia but also comprise important host mechanisms that operate as consistently maintained vascularity and blood supply. Such dynamic maintenance of vessels would presumably constitute an intrinsic tendency for angiogenesis that induces chemotactic and proliferative phenomena via direct and indirect intercellular adhesion pathways. Reactive oxygen species would be implicated also in carcinogenesis[15].

PRIMARY COLORECTAL CARCINOGENESIS PREVENTED BY HOST MECHANISMS RESULTING OTHERWISE IN PROGRESSIVE POLYPOSIS?

Strict sequential development of colorectal carcinoma from a previous adenomatous polyp in multiple familial polyposis would comprise a spectrum of evolving dysplasia towards infiltrative neoplasia[16]. This strict concept of progression coupled to multiple lesions would operatively implicate transformation via infiltrative and metastatic spread that constitutes threshold events linked to a tendency for subsequent transformation. Within such a context, a compromised spindle checkpoint would play a key role in producing genetic instability[17].

The dual points of possible mutation of either the APC gene and of the beta-catenin gene in primary hereditary forms of colorectal cancer appear especially significant in cells of hereditary non-polyposis forms of colorectal cancer.

Gene expression profiling may offer means for classifying various types of colorectal carcinoma particularly as mechanistic carcinogenesis[18].

Such a set of circumstances might call into question an essential progression primary to etiology and pathogenesis of colorectal polyposis per se. Colorectal polyposis might constitute failed attempts at primary carcinogenesis as possible subsequent progression. Genetic instability is either of microsatellite type or of chromosomal type with gains and losses of chromosomes and with chromosomal rearrangements[19] as in colorectal

cancer. Microsatellite instability appears less important in colorectal carcinogenesis developing in the elderly[20].

The adenoma-carcinoma sequence of progression in the colorectum would tend towards progression as an expression of such a primary initial attempt at carcinogenesis.

The very manifestations of dysplasia as a field effect of evolution of the enlarging colorectal adenomatous polyp would contribute directly to infiltrative attributes and to the concurrent development of polyposis with its potential for subsequent neoplastic progression.

It is this aspect of colorectal polyposis as a phenomenon that arises directly as a potential for complete carcinogenesis that would define it as a premalignant lesion.

Such premalignancy, engineered for subsequent evolutionary development of carcinogenesis would be related especially to induced genetic instability and intercellular adhesion-mediated induction.

A targeted pathway with evolving potential in the case of colorectal polyposis would constitute transformation through the creation of microenvironmental and hereditary traits in response. An extended mitotic life span would relate to karyokinesis via nuclear budding with subsequent asymmetric cytokinesis and genetic instability; this has been referred to as neosis[21].

Polyposis and carcinogenic evolutionary endpathways of progression and transformation would constitute the prerequisites defining operative intervention of host mechanisms through cell/cell interactions of adhesion/contact type and genetic instability.

Colorectal carcinoma involves particular genetic pathways that include chromosomal instability, microsatellite instability and also none of these, as in cases of MYH-associated polyposis with defective base excision repair[22]. Carcinogenesis associated with ulcerative colitis develops within a context of marked chromosomal instability and of multiple gene amplification[23].

IS RT-PCR A POSSIBLY VITAL TECHNIQUE IN CLARIFYING THE EVOLUTIONARY PROGRESSION OF ANAPLASTIC NEOPLASMS?

Microsatellite analysis is a powerful tool in assessing the degree of genetic instability in tumor cells utilizing real time Polymerase Chain Reaction and capillary electrophoresis[24].

Molecular characterization appears potentially important in diagnosis of many thyroid nodules caused by thyroid carcinoma and also in distinguishing follicular adenoma from follicular carcinoma microscopically.

Molecular identification of increased oncofetal fibronectin as both an absolute value and also as a ratio of relative value when compared to thyroglobulin would constitute a molecular biologic marker. The neoplastic process as biologic progression would implicate molecular markers as true surrogate parameters constituting dynamic real time measurements of diagnostic and prognostic significance in terms of such progression.

Even within frameworks that are dynamically progressive, diagnosis of an anaplastic carcinoma of the thyroid would necessarily involve molecular investigation to account for poor patient prognosis.

Procedures such as RT-PCR would represent a neoplastic process that not only transforms and progresses but also incorporates amplified acceleration of such progression characterizing evolutionary set patterns of local and systemic spread in the body.

Such a phenomenon would be associated with defects at cell cycle checkpoints (such as intra-S phase, G2/M transition, spindle assembly and cytokinesis checkpoints) that normally protect cells against genetic instability during cell division[25].

VITAMIN C UTILIZATION BY A NEOPLASTIC LESION AS AN ABERRANT VARIANT OF THE REPARATIVE RESPONSE

High rates of vitamin C utilization by tumors paralleling an increase in circulating serum levels of ascorbic acid would constitute a measure of the metabolic rate of the neoplasm that allows participation also by stromal components of the lesion and related polymorphonuclear neutrophil leukocytes.

Ascorbic acid utilization would constitute an index of proliferative activity of the lesion as an integral combination of both the neoplastic cell component and of the included stromal elements admixed with the infiltrating tumor cells. In a neoplasm with some attributes of an aberrant reparative response, ascorbic acid would be an essential metabolic requirement in vascularization of the neoplastic tissue.

The dense desmoplastic stroma associated with infiltrating breast carcinoma and also the hyperplastic scar or keloid would constitute variant response as successive amplified response towards systemic involvement. Such an overall phenomenon would be well indexed by ascorbic acid rates of utilization and by serum ascorbic acid levels.

CARCINOGENESIS AS A BASICALLY ABERRANT REPARATIVE RESPONSE IMPLICATING CYTOKINE PRODUCTION BY DAMAGED CELLS

Asbestos exposure and asbestosis would constitute progression in a successive series of steps leading to a cell injury coupled to reparative fibrosis on asbestos exposure.

Asbestos exposure would constitute a tumor initiator in carcinogenesis in patients who are heavy smokers. The tumor initiator as asbestos exposure in a heavy smoker, with smoking acting as a tumor promoter, would act in a synergistic fashion and progress in stepwise manner as primary facilitation.

Many features that give rise to carcinogenesis would under a different set of circumstances result in the pulmonary interstitial fibrosis of asbestosis. What is this essential determining set of factors that apparently implicates cytokine production and the reparative process in possible carcinogenesis?

It is common for the interstitial fibrosis of asbestosis to accompany the carcinogenesis developing after asbestos exposure; such associated carcinogenesis would perhaps be conducive to a created series of pathways that allow cellular reparative attempts to promote a proliferation based on genetic instability and impaired cell/cell contact phenomena.

Carcinogenesis as a cell transformation might constitute a reparative-type process as distinctively aberrant but also conditioned pathways.

A NOVEL POINT OF ORIGN OF A TUMOR PROMOTER PATHWAY CONSTITUTING AN ESSENTIAL PARAMETER IN THE MALIGNANT TRANSFORMATION PROCESS AS PROMOTED BY TNFalpha OR IL-1

Tumor promoters as a function specifically of cytokine action would incorporate cellular response to a tumor initiator such as 7,12-dimethylbenzanthracene (DMBA).

Tumor necrosis factor alpha (TNFalpha) would induce neoplastic transformation whereby carcinogenesis first is initiated by DMBA and then replaced by a subsequent cellular response in terms of cytokine production promoted by the TNFalpha. This would result in systems of mechanistic progression. Actual transformations from novel points of origin may also develop. Malignant transformation would involve pathways of progression that once initiated would evolve as a progressively aberrant, putatively reparative process.

TNFalpha would possibly constitute a real tumor promoter linked to an initiation in a manner that involves activation or suppression of a number of transcription factors, e.g. Nuclear Factor Kappa beta and activator protein 1 (AP-1), resulting in expression of several genes as evolving genetic instability.

Malignant transformation would result from the action of a tumor promoter as progressiveness that originates at potentially multiple different points ranging from the dividing nucleus to activation/suppression systems of genetic instability. Genome-wide DNA hypomethylation in particular can enhance genetic instability[26]. Alterations of multiple oncogenes and tumor suppressor genes act together with genetic instability in gastric carcinogenesis[27]. Also, chromosomal instability and microsatellite instability may act synergistically as in endometrial adenocarcinoma[28].

It might be relevant to consider activation of the apoptotic pathway that variably promotes tumorigenesis as progression induced by the tumor necrosis factor alpha or interleukin-1 cytokine..

IS TUMOR CELL INFILTRATION A RESULT OF ABERRANT CELL PROLIFERATION?

A distinction between anti-apoptosis and active infiltration by glioma cells in an overall system that somehow utilizes phosphatase-induced dephosphorylation in an optional manner might be suggestive of systemic changes as induced cell division; this would self-perpetuate as infiltrative behavior in terms of anti-apoptosis pathways and as evolving genetic instability.

It might be valid to consider infiltrative behavior a form of anti-apoptosis that arises directly from cell mitoses distinct from excessive proliferation. The tumor cell proliferative activity would propagate tumor cell infiltration and contribute significantly to an anti-apoptosis that immortalizes the transformed cells. A proliferating cell would actively promote anti-apoptosis as dual systems of complementary induction and suppression.

A sharp distinction is also possible between normal cell mitosis and tumor cell proliferation in a manner that allows apoptosis not only to be actively suppressed but also for anti-apoptosis to be induced and sustained as inappropriate tumor cell proliferation.

An infiltrating tumor cell would constitute one that is primarily proliferative as a result of an evolving genetic instability and as multiple pathways of induced transformation of cellular responsiveness.

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