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Epigenesis of Carcinogenesis as Inflammatory Cytokine Mechanics

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Abstract: Epigenesis in malignant evolution would transform mechanics of development of genetic mutation in terms of failure of DNA repair pathways. Genetic instability would be an expressed result of the development of mutagenesis that includes such failed DNA repair mechanisms. The cytokine/chemokine axis of influence in terms of carcinogenesis might particularly implicate proliferation of cells and infiltration of stroma involving also targeted action of trophic factors. Epigenesis would be an expression of a malignant transformation event that incorporates various modes of evolution in DNA mutagenesis. DNA mutations that develop as multiple pathways of impaired subsequent mutational repair mechanisms would both account for and extend the influence of genetic instability systems in carcinogenesis. One might recognize a full array of mechanistic events inherent to a concept of transformational processes both originating and subsequently promoting various systems of tropism and trophism even as the cellular clonality is itself extended beyond the initial carcinogenetic focus.

Key words: Epogenesis, carcinogenesis, Malignanl, DNA, mutations

INTRODUCTION

Clonal proliferation as a developmental system would enhance a transforming role of cell biologic systems, including possible mitochondrial uncoupling[1], that subsequently evolve as excessive cell proliferation. Genetic instability results from a high rate of mitochondrial DNA mutation in liver tissue[2] and hepatocellular carcinoma, when it develops, almost always arises in chronically inflamed livers[3]. Stromal infiltration would attest to such evolving transformation in terms of spatial dimensions of matrix-cellular interaction. One might recognize the development of various genomic repair mechanisms that are incorporated as pathways of possible DNA mutagenesis in their own right. Understanding interactions of DNA reparative pathways in terms of a trophic series of evolutionary events might help link cell proliferation to a persistently transforming phenotype of carcinogenesis. Host genetic susceptibility may influence gastric carcinogenesis associated with Helicobacter pylori infection[4]. It is in terms of such evolving influences that cytokine/chemokine action[5] would further promote an initial step in epigenetic definition of carcinogenesis[6] that would incorporate also transformation as a failure of DNA repair.

In high-grade CIN lesions, the epigenetic changes become less sensitive to growth and modulating influences as mediated by cytokines and cell-cell and cell-matrix adhesions[7].

In such terms, cell biologic transformation would be a sustained mechanics in the evolution of pathways borne out by dynamics of an epigenetic control of DNA mutagenesis.

WHOLE POOLS OF CELLS ARE CONTROLLED BY CELL CYCLE DYNAMICS AND APOPTOSIS OF INDIVIDUAL CELLS

A phenomenon that includes cell-cell cohesion as a mechanism of controlled regulation of cell phenotypic expression might actually revolve around mechanisms influencing cellular growth and proliferation[8]. Interleukin 1 beta regulates cyclooxygenase expression in colorectal carcinogenesis[9]. Whole pools of cells may relate to origin and to subsequent inter-relationships of the constituent cells. In a system whereby whole pools of cells are not clonally related to each other, there might still operate a system of control both in the generation and subsequent biologic behavior of cells. In such a manner effective control of pools of cells would develop as integral components of a single corporate population of cells of an organ.

There might exist a phenomenon that supersedes the individual cell status but rather evolves largely as an integral cell population.

Pools of cells would however operate in a manner that is susceptible to control along terms dictated by mechanisms of single cell growth and of single cell cycle dynamics and kinetics.

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It might be relevant to consider a whole pool of cells as an integral unit that although non-clonal, would still constitute a system regulated by cell proliferative rate, cell growth and cell apoptotic rate. Promoter hypermethylation of adhesion genes in silica-induced carcinomas indicates a role for epigenetic mechanisms[10]. These would be directly determined, in turn, by mechanisms beyond individual cell kinetics. Transforming growth factor beta 1 in particular would override its tumor suppressive effect even at early stages of skin carcinogenesis[11].

Pools of cells would constitute a series of mechanisms of control that are largely independent of single cell regulatory mechanisms; these would be analogous in their operability to cell cycle and apoptosis mechanisms that are conventionally associated with biologic evolution of the individual cell.

IMPAIRED DNA RECOMBINATION REPAIR AS A CAUSE OF SIGNIFICANT DNA DOUBLE STRAND BREAKAGE

A concept of hypersensitivity inherently associated with increased susceptibility to DNA double strand breakage and of impaired recombination- repair would constitute a system of enhanced damage[12].

The direct cause of actively induced double strand DNA breakage would prove to implicate the defective recombination-DNA repair mechanisms themselves.

A system may evolve whereby the repair mechanisms are an active cause of DNA strand breakage. Double strand involvement would promote disruption especially of impaired homologous recombination.

Mutation of BRCA1 and BRCA2 are markers of a familial predisposition to breast carcinoma that revolve specifically around such an impaired series of DNA recombination- repair mechanisms. Induced accumulation of further mutational events would develop.

Mutational events may cause impairment of DNA repair mechanisms with accumulative DNA damage and a failure of events beyond correction of damage as induced additionally by ionizing radiation.

In this context, a system of operative DNA damage such as by ionizing radiation as a perpetuating series of directly accumulating DNA mutations would promote self-amplification because of a significant impairment of DNA repair mechanisms that contribute to DNA mutagenesis.

INFLAMMATORY CYTOKINES AS AN ACTIVE SERIES OF MECHANISMS THAT ARE COUPLED TO THE MALIGNANT TRANSFORMATION PROCESS

Inflammatory injury to cells would constitute a basic pathobiology incorporating not only progressive lesion infliction but also patterned effects that evolve concurrent with dynamics of the inflammatory reaction[13]. Pancreatic cancer appears a multi-gene-controlled malignancy involving also transforming growth factor-beta and Smad proteins that interact in a variety of cellular signal pathways[14]. Transforming growth factor-beta regulates homeostasis of lymphoid cells[15].

The actual role of an inflammatory reaction, as seen for example in sclerosing cholangitis, in the possible induction of a series of changes conducive to possible malignant transformation, might revolve around set patterns of DNA damage that implicate also DNA repair enzyme systems. Interleukin 1 beta upregulates the inflammatory response and is implicated in malignant transformation, growth and spread of tumor cells[16]. Impairment of DNA repair systems as a primary target of inflammation-induced cellular damage would largely prove a consequence of such direct damage to the DNA repair enzyme systems.

Within a context of production of large amounts of inducible nitric oxide by phagocytes, it might be relevant to consider cytokine production as a basic response mechanism primarily aimed at influencing cellular evolutionary pathways. In various ways, such mechanisms would transcend simple concepts of homeostatic control or even of directly induced pathobiology. In particular, neovascularization in carcinogenesis appears environmentally controlled[17]. Inflammatory cytokines are an operative mechanism whereby biology is often transformed to pathobiology within the context especially of reparative cellular responses and of malignant transformation. Inflammatory cytokines might constitute active mechanisms that directly drive the malignant transformation process within a context of cell injury and of cell reparative response.

GENETIC DESUPPRESSION INHERENTLY PROGRESSIVE BEYOND MECHANISMS OF GENETIC INSTABILITY

Wrn (Werner) mutation would appear not only to act synergistically with the p53 null state within an overall process of enhanced tumorigenesis of progression, but to actually induce inhibition of apoptosis by the p53 null state and promote progression beyond simple accumulation of genetic damage and mutation[18]. Transformation would intrinsically incorporate progressiveness in a manner strictly characterizing such transformation event.

Dysregulation of cytoskeletal, integrin, protease and adhesion molecules affects interactions with the microenvironment and progression of the cellular immunophenotype[18].

Progressiveness as a genetic instability would bypass checkpoints in cell biologic mechanisms of mitotic cell cycle and of genetic repair. A system of programmed

activity would operate beyond control systems that are operative particularly via a sophisticated and selective suppression of gene function.

Malignant transformation would evolve beyond enhanced genetic instability in a manner that enhances genetic damage in terms of cell biologic systems that self-progress as desuppression.

Gene desuppression is inherently a system of progressiveness beyond mechanics of implied genetic instability.

MALIGNANT TRANSFORMATION AS PROGRESSIVENESS WITHIN THE CONTEXT OF TROPHIC GROWTH FACTOR MECHANISMS OF INDUCTION AND SUSTAINMENT

The actual nature of the malignant transformation process is provoked and sustained by loss of deletion of a 20-amino acid sequence of the beta domain of the von Hippel-Lindau (VHL) tumor suppressor gene. This might be intrinsically tied up with an inherent tendency for VEGF-sustained angiogenesis directly transferring growth factor effect[19].

Malignancy is strictly a correlate of a series of growth factor effects that transform cell biologic attributes in terms of progressive desuppression of genetic control. Nuclear Factor-kappaB would bridge the action of growth factors and inflammation in hepatic oncogenesis[21,22].

The tumor angiogenesis would not simply constitute a manifestation of induced effect concurrent with malignant transformation but in terms of genetic deregulation and instability that self-engender progressiveness.

Malignant transformation as a progressiveness of cell biology would prove a manifestation normally harnessed in a number of ways. It is perhaps in terms of such progressiveness as induced and sustained by trophic growth factors that malignant transformation would evolve as an event of immortalization of cells within systems of cell proliferation, infiltration and spread.

CHIMERIC TRANSFORMATION OF GENE EXPRESSION CENTRAL TO TRANSLOCATION GENE FUSION EVENTS

A chimeric fusion based on chromosomal translocation would incorporate transcriptional activation that transforms the fusion event via a series of steps allowing facilitated expression of genes or of fused genes[23]. Is a chimeric fusion of genes essentially a facilitated form o f transformation in terms of gene expression?

Within the context of the Ewing's sarcoma gene product, it might be relevant that chromosomal translocation controlling chimeric fusion would constitute facilitated gene expression via mechanisms that inherently provoke the production of novel protein.

It might be reasonable to equate chromosomal translocation events as essentially facilitated gene expression systems in the creation of novel fusion proteins beyond any dynamics of such fusion protein products.

These would form part of an induced pathway that integrates activation with disinhibition via mechanisms that translocate genes directly, leading to a fusion chimeric transformation of the expression profile rather than primarily of the gene.

EPIGENETIC FIELD EFFECTS IN CARCINOGENESIS

A multitude of genetic pathways in carcinogenesis might constitute an essential mechanism of evolution or de-evolution that allows clonality of proliferation to integrate as field effect via a series of epigenetic influences[24].

It might be relevant to consider the strict concept of multiple pathways of carcinogenesis to be fully dependent on an associated variety of epigenetic influences exerted as field effect.

Multifocal urothelial carcinoma may have a unique clonal origin from independently transformed progenitor urothelial cells, supporting a field-effect theory of carcinogenesis[25]. Hypermethylation of CpG islands near gene promoter regions may induce gene silencing and act epigenetically with DNA mutations and deletions to disrupt tumor-suppressor gene function[26].

In such a scenario, it would perhaps be relevant to consider carcinogenesis as inherently epigenetic in large part, a concept that would be suggestive of normal cell biologic processes of proliferation and differentiation to be epigenetically influenced or acted upon within an overall context of field clonality.

Field carcinogenesis would be suggestive of an epigenetic series of events that substantially account for neoplastic transformation even in terms of cell biologic attributes of proliferation/replication and of cell differentiation. Leptin has been associated with carcinogenesis tumor migration and invasion and enhanced angiogenesis; it may mediate adverse prognostic effects of obesity in breast cancer[27].

Responsive/reactive and autonomous types of cell replication would necessarily differentially progress as differentiation or dedifferentiation within a shifting

context of maintained developmental circumstances of such differentiation or dedifferentiation.

CONCLUSION

An integrative approach in terms of both genesis and epig04enesis of transforming carcinogenetic events would extend mechanistic scope of development of multiple pathways of inflammation and repair systems of tissues and cells. Some malignancies involve sequential acquisition of mutations whereas certain oncoproteins in chromosomal translocation may not require additional mutation to induce tumorigenesis[27].

Developmental evolution of clonality would represent a prototypical series of events in evolving transformation beyond simple definition of tropism or of trophic factors. One might further redefine transformational events in carcinogenesis beyond a realization of simple phenotypic traits. Lack of surface Fas expression is a main route for antiapoptosis in tumorigenesis and tumor progression[29]. One main defining attribute concerns the realization of clonality as both a consequence of developmental transformation and also as a source of further evolving change in carcinogenesis. In such terms, perhaps, a full realization of epigenesis in carcinogenesis would strictly necessitate a multiplicity of developmental pathways of change that paradoxically maintain a state of enhanced or evolving genetic instability.

Tumor promoting action of prostaglandins may stimulate cell proliferation and migration, inhibit apoptosis and increase angiogenesis and invasiveness[30]. Dynamics of interactivity predetermine mode of involvement of a neoplastic process that developmentally recreates conditions that are conducive to biologic progression.

One might view relative participation of stroma[31] as evidence of a biologic continuum that evolves in terms of different modes of transforming influence. The chemokine stromal cell derived factor 1 promotes infiltration by glioma cells through the action of MT2-matrix metalloproteinase[32]. There is an apparently irreversible change in development of pathways that induce pathogenic predetermination of cell proliferative events and of stromal/metastatic spread. Multiple types of stromal cells, including macrophages, mast cells, adipocytes and fibroblasts contribute critically to carcinogenesis[33].

Biologic predetermination in neogenesis reconstitutes embryologic developmental conditions that promote progression of a tissue-related event in cytogenetic derivation. There is a central role for physiologic versus pathologic cell death pathways that tend to redirect transforming influence in its own right.

Tumor Necrosis Factor apoptosis-inducing ligand appears a potential extrinsic suppressor mechanism[34]. Multistratified interactivity of biologic progression and of cellular reactivity would allow the creation of loops of operability that would promote genetic instability in terms of subsequent transforming effect[35]. Host genetic factors, including the Interleukin-1 gene cluster, play a key role in determining the long term outcome of Helicobacter pylori infection in gastric carcinogenesis[36]. Interleukin-1 gene cluster polymorphisms also affect risk of lung cancer[37]. The great degree of variability in progression of a neoplastic lesion is in contrast with developmental pathways of morphogenesis and of biologic evolution. Indeed, one might recognize an associated genesis of the neoplastic phenotype that is derived from assumed developmental progression of stem cells giving rise to that particular organ and tissue[38].

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