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Self-Amplification of Tumor Cell Proliferation Determines Carcinogenetic Progression

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Abstract: Systems of progression of carcinogenetic pathways appear a largely acquired form of genetic evolutionary change bordering on such phenomena as hyperplasia and as manifested in dysplastic lesions. A central concept of specific cell of origin of tumors would be contrary to evolving dynamics of a stem cell population that circulates as systems of initial angiogenesis which, in turn, are subsequently established within tumor cell population confines. It is indeed in the spread of localized groups of endothelial cells as angiogenic sprouts that there would further develop a pattern of infiltrative tumor cell growth that subsequently involves lymphatic and blood dissemination of neoplastic cells. Metastases are an expression of a stem cell biology that promotes a self-amplification of systems of proliferation of tumor cells that interact with growth factors and angiogenesis in the creation of a tumor biologic milieu conducive to even further progression. There is a tendency for biologic progression in carcinogenesis that would predetermine and subsequently characterize tumor cell proliferative events as self-amplification systems of acquired genetic damage in neoplastic cells.

Key words: Carcinogenetic, tumor cell, progression, proliferation, self-amplification

SELF-AMPLIFICATION SYSTEMS

Self-amplification as an essential malignant transformation of glial cells appears frequently implicated[1], with clonal expression driven by mutation[2]. A small cell component to glioblastoma multiforme appears an amplifying system in its own right with attributes reflected in self-amplifying tumor cell mitotic progression. Mitotic activity of such small tumor cells in glioblastoma might arise largely in terms of self-amplification of a malignant transformation event that further characterizes modes of involvement of glial cell interaction with astrocytes and other glial cells and also neuropil.

Self-amplification events might strictly characterize also modes of progression of distinct tumor cell subpopulations in a given glioblastoma multiforme that arises in terms of interactions between such subsets of tumor cells with each other as specifically self-amplifying progression in transformation.

ALTERED ENDOTHELIAL FUNCTIONALITY

Endothelium appears to mark an endothelial proliferative event that is specifically angiogenic relative to highly proliferative brain tumor cell populations[3].

It seems reasonable to consider endothelial cell hyperplasia in glioblastoma multiforme and anaplastic astrocytoma as a process of invasive spread based perhaps on targeted dynamics of an endothelial cell production of endosialin. One might consider how angiogenesis is in fact a phenomenon of growth and proliferation of glioma cells in terms relative to targeting of these endothelial cells in overall tumor progression.

DISRUPTED CELL CYCLE PROGRESSION

Disrupted cell cycle progression leads to DNA damage accumulation in anaplastic oligodendroglioma[4]. Anaplasia in oligodendrogliomas appears a phenomenon linked directly to disrupted cell entry in G1→S transition phase and to dysregulated TP53 function associated with abnormal DNA repair, impaired apoptosis and also impaired cell cycle progression.

Dynamics of cell cycle progression appear an intrinsically progressive phenomenon determining functional attributes of apoptosis and of DNA repair within systems of cell injury. Tumor anaplasia would consequently represent a consequence of such dysregulated cell cycle progression in a manner that would implicate antiapoptosis and the accumulation of DNA damage.

The biologically higher grade of anaplastic oligodendrogliomas would presumably arise as an integral coexistence of accumulated DNA damage with dysregulated entry from G1→S1 phase within the added overall progression of abnormal cell cycle dynamics.

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HYPERMETHYLATION OF CpG ISLANDS

Hypermethylation of CpG islands appears an inherently progressive and aberrant phenomenon that induces a nonfunctional suppressor gene to promote tumorigenesis[5]. Tumorigenesis might prove a further generalized predisposition to hypermethylation at several aberrant sites in the cell genome based primarily on progressiveness of the genetic damage. Indeed, a predisposition to gene hypermethylation would be closely linked to a tendency for diminished repair capability of genes as primary genomic abnormalities.

OXIDATIVE STRESS AS SPECIFIC INJURY TO GENOMIC INTEGRITY

Specific localization of oxidative stress in parent cells would appear a mechanistically specific means of pathway generation and carcinogenesis that relates particularly to genomic specifications in cell proliferation[6].

Nitric oxide synthase expression and nitric oxide action are implicated in oral carcinogenesis and tumor progression[7].

Such specifically driven oxidative stress pathways might help account for ways that better integrate modes of participation of gene injury with cell cycle dynamics and mitotic spindle changes in the creation of aneuploidy as characteristic of many tumor cells. Only in so far as genetic injury is a distinct result of specifically localized oxidative injury can one further attribute genetic progression as abnormal mitotic activity in tumor cell proliferation and spread. The whole series of losses of heterozygosity and of silencing of tumor suppressor genes would equate with an oncogenic influence that promotes a progressiveness of carcinogenesis beyond simple concepts of direct transformation of the genotype of parent cells.

NEOVASCULARIZATION

Neovascularization appears an infiltrative attribute in operative positive feedback loops of glioma growth[8]. Survivin is an important member of the inhibitorof apoptosis protein family and is important in proliferation, antiapoptosis and angiogenesis of CNS gliomas[9]. Autocrine-paracrine loops would implicate a glioma cell population that perhaps is prone to positive feedback stimulation rather than to negative feedback regulation. In such terms, adrenomedullin production by glioma cells might involve neovascularization rather than simply a direct proliferating influence on endothelial cells.

Understanding how gliomas do involve an infiltrative neovascularization might imply peculiar dynamics that chiefly characterize the positive feedback systems of regulation in stimulated glioma growth. Considering proliferation of endothelial cells as only an indirect reflection of such adrenomedullin-induced neovascularization might be suggestive of modes of participation of autocrine-paracrine loops as operative systems consequent to lesions ranging from hypoxic injury to oxidative stress.

It is in trying to understand how adrenomedullin affects positive feedback pathways of neovascularization that one would better define pathways that inhibit globally a neoplastic proliferation that is primarily infiltrative.

A BASIC AMPLIFICATION-MEDIATED DISTURBANCE

Is neoplasia a basic amplification-mediated disturbance in volume and spatial dimensions of nuclei disturbing heterochromatin interactivity?[10] Expulsion of amplified MYCN from nuclei of neuroblastoma cells would appear to represent a whole group of phenomena tied up with strict control of volume/structure relations affecting particularly dynamics of mitosis and meiosis.

Mitotic activity of nuclear material would constitute primarily an apparent response to mechanical regulation of volume dimensions of a nuclear membrane-bound series of transport and relative interactions ranging in terms of amplification or upregulation of transcription and expression of genetic material.

Amplification of DNA would perhaps constitute a real basis for upregulation of proliferative activity that would further contribute to the serial setting up of whole cycles of amplified DNA.

Neoplastic transformation would appear perhaps a primary disturbance of volume and spatial relationships relative to an amplification of oncogenes that subsequently appears conducive to acentric double minutes as seen in neuroblastoma tumor cells.

Nuclear variation in size and shape of tumor nuclei and also of abnormal mitotic Figure sures in a proliferating pool of neoplastic cells might indicate a disturbance of relative interaction of heterochromatin and of membrane-bound volume/spatial dimensions. These would be relative to actual content of DNA and gene complement biophysically determining such heterochromatin interactivity.

Error-prone cell division may implicate error-prone polyerases and aberrant mitosis that are activated in a sustained stress environment[11].

APOPTOSIS AND PROLIFERATION AS BEYOND GENETICALLY ACQUIRED EVENTS

Apoptosis might relate to proliferative activity in terms that would strictly characterize neoplasia as a

system of accumulative phenomena arising as essential transformation implicating determinants of responsive adjustment to such abnormalities as infection and inflammation and genetic lesions[12].

Neoplasia appears a system of generically abnormal responses to lesions of a genetic or acquired nature that might help render feasible a better delineation of events progressing as an antiapoptotic and also as an active proliferative transformation of clones of cells. Lack of mitotic regualtion induces aneuploidy in cancer cells acting subsequently as a driving force for malignant progression. Serine/threionine protein kinases of Aurora genes family are important throughout the cell cycle[9,13]. Indeed, cellular clonality is by definition an implicit realization of the origin of cell groupings that determines in full measure how such cell groups respond to genetic and acquired systems of influence as an integral genetic/acquired series of events.

A system pathway that takes into account genetic events as an inherent system of acquired events in transformation would account for neoplasia that constitutes genetically acquired modes of transformation beyond simple concepts of suppressive or oncogenic means of perpetuation of biologic events.

Apoptosis and proliferation would counteract cyclical transformation of genetically acquired neoplastic lesions as different biologic attributes of cellular events. Heat Shock Proteins 70 and 27 inhibit apoptosis and HSP70 may contribute to hepatocarcinogenesis and also its progression by promoting tumor cell proliferation[14]. These would go beyond just categorical classification of either apoptosis or proliferation of directly induced type.

AUTOIMMUNITY IN NEOGENESIS

Ectopic lymphoid organogenesis as germinal centers would involve acquired progression in molecular mimicry whereby antigenicity acquires attributes promoting clonality and proliferative replication of such clones of B and T lymphocytes[15]. In addition, a milieu of chemokine and cytokine production would perhaps constitute amplification systems in the promotion of various T and B lymphocyte interactions involving also a possible participation by plasma cells. In this sense, one might view autoimmunity as a mode of presentation of antigens that primarily determines subsequent promoted expansion of selective clones of lymphocytes. Indeed, one might speak of clonality as a directed expansive proliferation of cells that is transformed to an autonomous production of cytokines and chemokines involving especially macrophages, antigen-presenting cells and especially follicular dendritic cells.

A full variety of inflammatory reactivities and of inflammatory responsiveness would be involved in autoimmunity promoting transformational events arising and subsequently progressing as clonal events linked inherently to neogenesis and to malignant proliferative expansion of highly selected subsets of lymphocytes.

Ectopic lymphoid follicles and germinal centers may contribute to a thyroiditis or to a synovitis in terms of modes of antigen presentation and molecular mimicry that contribute to possible generation of requisites for malignant transformation of clones of proliferating B and T lymphocytes and their interactivity.

SYSTEMIC ORIGIN OF STEM CELL COLONIZATION

Gliomas appear systems primarily originating as pathways of spread and of colonization of brain and spinal cord that subsequently progress particularly as increasing tumor grade[16]. Indeed, a conceptual origin of gliomas primarily implicating stem cells would appear consistent with the relatively common occurrence of the high-grade neoplastic types. It would perhaps be significant to note that the actual proliferative events of neoplastic progression are largely a stem cell participation in spread of various pathobiologic attributes that evolve, not as cellular events, but as biologic counterparts of tissue evolution.

Tumor biology might operate as tissue and multi-tissue biology to account for a vascularity that parallels increasing grade of gliomas that, in turn, proliferate and spread secondarily. Cathepsin S regulates angiogenesis and growth of neoplasms via matrix-derived angiogenic factors[17]. Even with regard to a lymphomatous proliferation that is beyond simple concepts of cellular origin or even of homing mechanisms of localization as in the central nervous system, one might recognize various genomic aberrations of the glioma cells as largely stem cell attributes.

One might perhaps view mechanistic pathways of progression in glioma proliferation and spread as simply phenomena of colonization beyond infiltration of adjacent neural tissues but rather directly implicating an active oncogenesis in stem cell participation. Indeed, a radical revision of a central concept of cell of origin of the gliomas would perhaps necessitate the implication of a fundamental colonization system of stem cells that originates as oncogenesis.

PERIPHERAL NERVE SHEATH NEOPLASMS

Continuity of perineurial cells with the pia-arachnoid of the central nervous system would perhaps account for a neurofibromatosis complex that parallels occurrence of meningiomas and Schwannomas, including sporadic forms of these neoplasms[18].

Peripheral nerve sheath tumors might relate to proliferative events as strict processing pathways ranging from point mutations to loss of heterozygosity and deletions resulting in a truncated protein molecular form of Merlin/Schwannomin product of the neurofibromatosis 2 gene.

Perhaps in trying to delineate involvement of proliferative transformational events in peripheral nerve sheath tumorigenesis one would consider a variety of suppressor gene effects specifically implicating often a double hit mutation. Both alleles of the NF2 gene would perhaps constitute a complex interaction that results in occurrence of meningiomas and schwannomas as counterparts of the perineurial cells and their neoplastic proliferation.

Proliferation would perhaps have to be complexed by various other component events that pathobiologically relate pia-arachnoidal structures to a peripheral nerve sheath participation in transforming progression.

Paradoxically, proliferation of pia-arachnoid and of peripheral nerve sheath would appear inherently part of various mechanistic pathways that delimit meningiomas and schwannomas from perineurial cell neoplasia both morphologically and pathobiologically.

NON-DIFFERENTIATION AND PROLIFERATION OF NEUROBLASTOMA CELLS

Increased cdc25B expression appears significant in the mediation of amplified N-myc in neuroblastoma cells both in terms of cell proliferation and also in terms of maintenance of an undifferentiated cellular phenotype[19]. This would be further significant in terms that do not relate to stage of neuroblastoma spread or stage. One might perhaps consider tumor cell proliferation a system of tumor staging that closely correlates with a firmly established and maintained state of neoplastic non-differentiation that actually progresses in degree with stage of the disease.

Neuroblastoma may be viewed as simply a variant amplification process that promotes interactive phenomena between non-differentiation and proliferation of the tumor cells in an interactively amplifying and potentiating manner.

REACTIVITY IN OVARIAN CARCINOGENESIS

Induced growth factor effect appears a mode of action of lysophospholipid and would constitute multiple levels of operability that cooperatively perpetuate a series of effects arising as predetermined mechanistic pathways of influence[20]. One might speak of how induced influence is in fact growth-factor related as a primary event, whereas subsequent processes of action are largely reactive on the part of targeted cells in eventually constituting carcinogenetic progression and spread of tumor. Metastases of ovarian carcinomatous cells would indeed be only one integral manifestation of how primary action and reaction constitute the source and consequence of a whole series of events constituting carcinogenesis.

Ovarian carcinogenesis would be considered as largely predetermined and genetically governed pathways that revolve around reactive phenomena as constituted not only by inflammatory type change but also by a series of altered receptivity for vascular endothelial growth factor and other angiogenic systems of influence.

It is in terms of growth factor action and reactivity that one might implicate ovarian carcinogenesis as integral pathways of progressive growth factor response that prove progressive.

ENDOTHELIAL CELL MIGRATION AS ANGIOGENIC SPREAD OF TUMOR

Angiogenesis in prostatic carcinoma may very well delineate disparate groups of variably aggressive neoplasms ranging from indolent, slowly growing lesions to aggressive carcinomas that spread rapidly[21]. In trying to understand dynamics of such a wide spectrum of clinical behavior of these neoplasms, spread from the primary lesion might depend largely on attributes of an angiogenic response as determined by eicosanoid production by the primary prostatic carcinoma. Vascular Endothelial Growth Factor (VEGF)-A plays a major role in angiogenesis and tumor progression[22]. Endothelial cell migration and organization as blood vessels in association with infiltrating carcinoma might implicate extracellular matrix turnover. Cathepsins of the cysteine protease family may regulate angiogenesis and invasion during neoplastic progression, implicing especially E-cadherin[23].

This would orchestrate multistep progression in the development of both local infiltration and spread systemically of the lesion. It is in terms of such conversion of an initial solid focus that is subsequently infiltratively spreading that one might recognize angiogenesis as the primary source of attributes of a metastatic process arising initially as migration of the endothelial cells in the primary lesion.

INCREASED HYPOMETHYLATION OF S100A4 IN PANCREATIC CARCINOGENESIS

S100A4 protein is associated with tumor metastases and is overexpressed in cases of ductal adenocarcinoma of the pancreas[24].

In such a scenario, it might be valid to consider the acquisition of metastatic potential as an initial step in

carcinogenesis in a way that would perhaps enhance such carcinogenesis as self-progressive. Insulin-like growth factor I has been implicated in promoting cellular proliferation, metastatic spread and antiapoptosis in several tumor types, including cervical carcinoma[25].

Metastatic potentiality might be an expression of effective self-progression in carcinogenesis linked particularly to hypomethylation of the S100A4 gene. Indeed, one might speak of how hypomethylation would evolve in terms of acquired metastatic potentiality for further progression in carcinogenesis of the pancreatic ductal cells. Eta-catenin upregulates expression of cyclin D1, c-myc and matrix metalloproteinas-7 that determine metastasis and prognosis of pancreatic carcinoma[26].

AN INTEGRAL TUMOR SUPPRESSOR GENE PATHWAY IN GASTRIC CARCINOGENESIS

An apparently distinctive molecular pathway in Epstein-Barr-Virus-positive gastric carcinogenesis might belie various systems of involvement as far as loss of heterozygosity and as inactivation of tumor suppressor genes are concerned.

Indeed, various terminal pathways of conversion of severe dysplasia to infiltrating gastric carcinoma would involve a single common endpathway of proposed promotion in genetic instability. EBV-positive carcinogenesis would presumably orchestrate a full series of effects towards a gastric carcinogenesis that is primarily resolvable as one pathway of induced inhibition of tumor suppressor genes and of inhibited promoters for such tumor suppressor genes.

SARCOMAGENESIS

The histogenesis of a sarcoma such as alveolar soft part sarcoma would represent a possible derivation that is independent of systems of the sarcomatous pathogenetic pathway concerned[28]. Indeed, whether the tumor is in fact derived from a myogenic or whether it is in fact not myogenic in origin appears to be nonconsequential as far as its biologic behavior in vascular dissemination is concerned.

It is perhaps in trying to delineate pathogenesis of sarcomatous transformation that one might better recognize alveolar soft part sarcoma as a distinct pathologic entity arising however as a sarcoma of unidentified specificity in terms of a possible cell of origin.

DOES PREMALIGNANCY IMPLICATE HYPERPLASTIC DISRUPTION OF CYCLICAL BREAST DUCT EPITHELIAL ACTIVITIES?

Deletion or mutation of Caveolin-1 gene would constitute a proliferative stimulus in the generation of mammary duct hyperplasia[29]. This phenomenon would integrally involve premalignant change in terms of proliferative excess or as hyperplastic promotion of further patterned gene deletions or mutations in carcinogenesis.

Nuclear Factor-KappaB is implicated in the development and progression of lymphoma, leukemia and some carcinomas such as breast primaries[30].

One might consider how dynamics of a dominant negative effect would result in accumulation of caveolin-1 in the Golgi apparatus of the ductal epithelial cells. Such a phenomenon would relate to disruption of cyclical proliferative activity and of excessive or hyperplastic proliferation[31]. A hyperplastic proliferation would disrupt lactational regression or the establishment of a resumed nonpregnant state after completion of a pregnancy that might occasionally prove specifically premalignant.

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