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Is Neoplasia a Sequential Progressiveness in Terms Of Quantitative Variability of Qualitative Cellular Attributes?

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Abstract: Fundamental acquisition of the cardinal attributes of a neoplastic lesion might concern the evolving transformation quantitatively of qualitative systems of a sequentially progressive nature. The highly increased proliferative rates of activity of neoplastic tissues would in various ways constitute an integrally sequential series of pathways also actively incorporating the local infiltration of tissues and the complex interplay of involvement constituting metastatic tumor spread in the body. It is indeed in terms of an essential sequential progressiveness that is primarily a biologic attribute of cells that is also potentially an axis of involvement in terms of a neoplastic transformation that one might realize multiple potential pathways of evolution even as an integral carcinogenetic event. It is with regard to a strict definition of carcinogenetic transformation that one might conceptualize a cell proliferative activity as part of an integral sequentiality leading to activated progressiveness of cell biologic attributes. Such sequential progressiveness of cell biology would perhaps be strictly characterized as a true form of pathobiologic transformation of neoplastic type simply in terms of induced quantitative variability influencing paradoxically qualitative determinants of cellular activity. In such terms, malignant cellular transformation would specifically arise as an integral system of pathologic evolution inherent to distinct biologic progressiveness of various cellular attributes referable to metabolic, proliferative, membrane physiologic, oxidative and genetic type as quantitatively variable but sequentially progressive even as transformational events.

Key words: Neoplasia, qualitative, sequential quantitative, quantitative variability

INTRODUCTION

A fundamental phenomenon of oncogenesis might be conceptualized not in terms strictly of transformation but of threshold variability as would be induced by a series of suppressor gene and oncogene pathways. Defects might presumably be exerted via such systems as dietary and environmental factors in cases of colon carcinogenesis. Indeed, alterations in the control of gene expression is a key event in neoplastic transformation that would probably implicate homeodomain protiens as revealed by reduced malignant nuclear DLX4 immunoreactivity and loss of HB9 expression in breast carcinomas[1].

Even the high degree of variability in expression of extracolonic manifestations in patients with APC gene mutation or of Gardner's syndrome might actually be related in some way also to fundamental variability in the degree of bowel polyposis in individual patients[2].

One might consider colon carcinogenesis as simply one facet of a developmental progressiveness within a whole panorama of landscape changes constituting not only effects exerted on cells and cellular genomes but in terms of a fluctuation primarily influencing baseline manifestations. In this regard, neoplastic transformation may develop even if telomeric length is decreasing in the face of downregulated telomerase activity. On the other hand, anti-telomerase strategies have been suggested against neoplastic transformation[3].

One might interpret most of the known attributes of carcinogenesis as simply pathobiologic correlates of a variability of expression of baseline fluctuations as related to rate of cellualr proliferation, of anti-apoptosis or apoptotic reate, of cellg rowth itself arising from pathways of induced instability and of a responsiveness that is autonomous in relation to cellular biologic dysregulation. Complex chromosomal aberrations and quantitative expresion of monosomic cell clones might for example constitute a continuous spectrum of progression from hyperplastic to dysplastic epithelial cells[4].

Even a concept of strict clonality of tumor cell derivation and progression might only constitute an effect arising simply from a polyclonality that progresses subsequently in terms of a clonal proliferative activity.

Also, in particular, stromal interactions with infiltrating neoplastic cells would critically modulate various central phenotypic attributes of the neoplastic lesion in terms ranging from angiogenesis to growth factor receptivity to regulation of tumor cell proliferation and spread[5].

A loss of communal cell identity and characterization of individual cell groupings without distinctive biologic attributes primarily related to neoplatic transformation and progression: A complex activity that in some ways promotes[6] transformation of normal phenomena of DNA segment translocation would in turn perhaps characterize such transformation affecting both oncogene and suppressor gene function towards oncogenesis as a specifically integral dysfunctional process pathobiologically. Such a dysfunction might perhaps be related to a progressiveness not sdimply of either cell proliferation or of cell apoptotic/anti-apoptotic rate but more to attributes of a community of cells specifically differentiated from essentially individual cell groupings that are biologically autonomous. Increasing acquisition of mutations and abnormal expression/function of various cell cycle regulators would appear principal factors in operative oncogenesis[7].

One might distinguish an essential phenomenon of individual cell groupings from one of communal cellular biologic attributes whereby the individuality of the constitutent cells is itself one superceded or actually transformed as identifiable traits of integral participation biologically or pathobiologically. Indeed, for example, susceptible to various types of neoplasia such as prostatic adenocarcinoma would appear to implicate not a single gene but several genes in the cell genome[8].

It is perhaps in terms inherently arising from such distinction between groups of essentially individual cells on the one hand and of groups of communal cell phenomena on the other that one might perhaps better appreciate fundamental attributes of a basic neoplastic transformation event, as would apply for patients with neurofibromatosis[9]. Neoplastic transformation might actually relate to a process of basic dimensions whereby individual cells with germinative capability in terms arising from cellular biologic potentiality would involve evolutionary lack of biologic apparatus of functional communal cooperation and communication. Such normal communal cellular participation might relate to not only concepts of tissue and organ integrity but particularly to concepts of integral biologic characterization progressing especially as proliferative action in transformation.

In terms specifically arising from differentiation dynamics that subsequently influence clonal selectivity of proliferating cell pools, one might perhaps consider malignant transformation as primarily biallelic mutation of suppressor genes[10].

Biologic and physiologic processes as an ever-active series of insults in terms of either progressiveness or nonprogressiness: Metabolic stress as a process constituting an aspect biologically of chronic inflammation in terms also of acute exacerbations of such inflammation of long standing (OMIM 147620) might constitute a phenomenon of autocrine effect paradoxically inhibiting such processes as growth of the individual as seen for example with juvenile rheumatoid arthritis. Such a phenomenon of metabolic stress would appear to constitute an induced effect of the inflammatory process especially as a phenomenon whereby an induced effect and response would specifically characterize inflammation both biologically as well as pathologically. In terms of fundamental aspects of biology as evidenced by the inflammatory response, one might actually consider biologic processes as well as physiologic processes as inherently arising form pathologic disturbances and from induced pathologic effects.

In this regard, cancer cachexia might constitute an expression of proteolytically generated peptides released from the neoplasm[11].

It might be valid to consider pathologic effect or lesion creation not simply as a variation in biologic processes but as itself a fundamental inducer of what would be recognized strictly biologically and physiologically arsing from regulation and of induction events[12]. Even beyond the conventional concept of pathobiology, one might perhaps better realize a process of altered disturbance as a fundamental mechanism of induction and of effect within strict systems of integral biologic and physiologic proliferative events related inherently to persistent series of insults of a pathologic nature. Ultimately, progressive or nonprogressive events would evolve in terms of individual organ tissue or cellular patterns of potentially variable transformation of integrally participating events of carcinogenesis. Particularly significant would appear an essentially global gene expression progressing in terms of accumulation of multiple forms of genetic change or damage[13].

Is apoptosis concerned primarily with interactions between different community groups of cells–parenchymal, stromal, epithelial or immune cells?: Programmed cell death as a mechanism of regulation might actually constitute a mechanism of translation of cell number control in terms of mechanisms of suppression of such systems as mediated by immune surveillance or conversely of lymphoproliferation[14]. Indeed, within a single system of cell death and of variable degrees of cell proliferation, one might appreciate a system of dysregulation that at one and the same instance would concern itself both with persistence of cell numbers and an increase in cell numbers in a context of systemic immune suppression as characteristic of neoplasia. Multiple overalapping mechanisms affecting promoter and suppression pathways of carcinogenesis might operate in many instances on a variable background of mutator phenotypic characterization[15].

In trying to define the biologic mechanisms of neoplasia not simply as excessive cell proliferations but particularly as a system whereby anti-apoptosis is itself a system of variable dysregulation in certain patients with neoplasia, one might actually consider neoplasms as effective imbalance between apoptosis and anti-apoptosis of dysregulatory nature[16].

In a manner that might account for excessive tumor cell proliferation in the strict context of suppression of the immune response to such excessively proliferating tumor cells, one might consider mechanisms of apoptotic cell death as themselves a common target of differential dysregulation in a manner specifically concerned with excessive numbers or suppressed mechanisms of reactivity in an overall system variably influencing cells as community groups of individual cells.

Indeed, one might consider apoptosis itself as a fundamental expression of homeostasis within a single axis of pivotal relationship and control between different groups of cells beyond considerations even of strict regulation of cell numbers or of cell life span but related ultimately to variable characterization of interactions between different community groups of cells constituted by parenchymal cells, stromal cells and immune cells of effective dimension. Different cell types would appear to have adopted different mechanistic systems to halt cell proliferative activity and potential transformation in response to telomere attrition [17].

Beyond cellular progression as an attribute of interactive natural and therapeutic resistance in neoplastic development: A fundamental property of 17p deletion that intrinsically contributes to the resistance to treatment of the acquired medulloblastoma might actually concern a distinct phenomenon of predisposition that is itself an attribute of acquired resistance as a basis for the carcinogenesis process[18].

One might consider certain traits of pathobiology as not only responsible for a poor clinical response to treatment but especially as a poor response to such treatment integrally reflecting essential attributes of the malignant transformation process. Indeed, a simple mechanism of carcinogenesis would essentially form a series of acquired mechanistic processes of acquisition of biologic resistance of the tumor cells.

In this sense, perhaps, carcinogenesis as a series of steps of progression within a single integral pathway of malignant transformation might actually progress simply as acquired pathways of resistance in terms of both simple and complex attributes.

Indeed, it would be with reference to attributes that persistently progress simply resistance to a whole series of mechanisms normally preventing onset of evolving carcinogenesis that one best interprets carcinogenesis itself as a failed series of system pathways actively implicated in normal function of a distinct progressiveness biologically.

In such a sense, one might consider carcinogenesis as simply a graded series in susceptibility to the development and progression of neoplasia simply resulting from an acquired set of traits. Even an essential process of fusion of different cell types would perhaps constitute effective systems of potential interference and deactivation /activation of multiple genes promoting neoplastic transformation[19]. Such traits would be inherited in a manner that would constitute resistance to both natural and therapeutic attempts at preventing or curtailing malignant transformation. It is in terms of such systems of susceptibility that owe their very progressiveness to a direct interaction between acquired and inherited traits determining therapeutic resistance pathobiologically that one might consider neoplasia itself fundamentally a series of developmental-type events in transformation concerned with both natural and induced cellular progression.

In terms beyond simple considerations of natural or induced or acquired attributes of communal cellular interaction, one might consider even systems of participation within conceptual frameworks of transformation as strictly quantitative variability influencing qualitatively a distinct integral attribute of progressiveness in cell biologic terms.

Progressive sequentiality in neoplastic transformation and development within a specific sequential progressiveness defining carcinogenesis and neoplastic spread : Li Fraumeni syndrome might be construed as a specific type of susceptibility to tumor development arising directly from sequential series of mutations that are concerned specifically with sequential carcinogenetic events[20]. A situation might actually develop in a setting of Li-Fraumeni syndrome function that is specifically not related to neoplastic transformation but to a strong susceptibility to sequential development or evolution of such neoplastic transformation.

Given such a contextual definition of Li-Fraumeni syndrome that is specifically concerned with an essentially sequential susceptibility to neoplastic transformation one might legitimately regard neoplasia as concerned with phenomenal attributes essentially concerned with sequential progressiveness, arising initially as carcinogenetic transformation and subsequently progressing along very similar lines of such sequential progressiveness.

In the Li-Fraumeni syndrome, such an attribute of neoplasia evolving as a phenomenon of strict sequential progressiveness would be concerned as a neoplatic

process predisposing to subsequent development of susceptibility to potentially different neoplastic transformations affecting a range of histologic and organ tissue types from sarcoma to breast carcinoma, to ovarian, pulmonary and even to diverse undifferentiated tumor subtypes. Neoplasia might actually be considered as expression of specific tendencies towards sequential progressiveness of events integrally constituting and strictly defining such neoplastic lesions as exclusive phenomena of progressive sequentiality. Also, in this context, tyrosine phosphorylation and dephosphorylation as systems regulating normal and abnormal cellular growth might actually constitute pathways of transformation in sequential carcinogenetic progression[21].

Biologic aggressiveness and anaplasia reflect the primary nature of glioblastoma rather than its strictly grade nature: Glioblastoma multiforme as highest grade glioma might constitute a system of progression not simply as a culmination of the neoplastic process but as a system that develops within boundaries of definition of a lesion that either develops or else does not develop along a pathway of developmental progression[22]. In this sense, glioblastoma multiforme, more that simply a Grade IV glioma, is a neoplasm that paradoxically constitutes progression via multiple pathways of pathogenesis involving integration of neoplastic processes with events of etiology and pathogenesis. Indeed, etiologic and pathogenetic pathways of disturbed development and of pathologic transformation would directly relate to neoplastic transformation and progression simply as events of sequential progressiveness characterizing strictly cellular proliferation as infiltrative and metastatic lesions. One might speak of glioblastoma multiforme simply as a progression through integration that more than just

culminates in terms of a high grade glioma but rather as multisystem involvement in etiology and pathogenesis via pathways activated at multiple points of progressive evolution/de-evolution in sequentially progressive fashion.

Various alterations in rate limiting steps involving angiogenesis, cellular proliferation and antiapoptosis would perhaps progress parallel with tissue stromal remodeling and infiltration by tumor cells[23]. Genomic instability as expressively manifested in terms of amplification of specific gene fragments would constitute a characteristic mechanistic pathway of progression in neoplastic transformation[24].

Chromosome 17q in pilocytic astrocytoma, chromosome 17p in astrocytoma Grade II, and chromosome 10 in glioblastoma multiforme might perhaps help better characterize aspects of various systems of malignant development that are a priori central in defining the generic neoplastic process itself but that would subsequently account for such malignant aspects of the neoplasm as sequentially progressive.

With glioblastoma multiforme, the malignant aspects of this high grade glioma as reflected in its biologic aggressiveness and infiltrativeness but also in terms of its cellular anaplasia would indeed constitute paradoxically a strict definition of the neoplastic transformation and progression of glioblastoma multiforme not simply as the highest grade form of glioma but especially as a reflection of the generically neoplastic nature of this lesion in terms of a sequential progressiveness of uniquely biologic origin reflected consequently as pathobiologically acquired lesion attributes.

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