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Infiltrativeness and Proliferativeness as Mutually Enhancing Systems of Progressiveness in Neoplasms Associated with Self-amplifying Trophic Effect-Is the Individual Neoplastic Cell a Fallacious Concept?

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Abstract: Systems of progressiveness of gliomatous cells involving transformation of proliferative to infiltrative tumor cell activity primarily involving neuropil would in various ways perhaps be indicative of also systems of angiogenesis of autocrine nature. Certainly, considerations of how paracrine effect evolves as autocrine effect and also of how autocrine effect is itself a consequence of groups of active paracrine influence would perhaps implicate the individual gliomatous cell as a paradoxical grouping of such individual gliomatous cells to constitute aggregate phenomena within a truly integral gliomatous lesion. Indeed, in terms of an integral glioma made up of strictly individually proliferating and infiltrating gliomatous cells one would have to additionally consider how paracrine effect might both evolve to autocrine mechanistic pathways and conversely how autocrine systems might also evolve in their turn to mechanistic pathways of paracrine effect. In simple terms, indeed, infiltrativeness of individual tumor cells would be simply an autocrine and paracrine trophic expression of how such individual gliomatous cells would evolve as a single integral gliomatous lesion in that individual patient.

Key words: Progressiveness, glimatous cells, proliferaliveness, infiltrativeness

INTRODUCTION

Particularly characteristic of glioblastomas is the prominent presence of large, often multinuclear, tumor cell forms that are generally identified as having lost the ability to proliferate. In fact, the small tumor cell subpopulations in glioblastomas constitute the bulk of the highly proliferative tumor fraction in such neoplasms. In general, two major pathways involved in gliomagenesis involve the cell cycle and the growth factor-regulated signaling[1] in both transformation and progression.

The mechanisms arising from participation by the rather inactive giant tumor cells in glioblastomas are unclear but possibly implicate oxidative stress (for example, as induced by Nitric Oxide (NO) production)[2], mitotic cycles generated nuclear damage, apoptosis with its related mechanisms of nuclear damage . The large size and multinucleation of many of these degenerated tumor cells would be suggestive of an abnormality in cell division mechanisms such as a desynchronization between nuclear division and cytoplasmic division, in addition to abnormalities of degeneration, nuclear division involving the generation of polyploidy or aneuploidy.

A central aspect concerning the production of such degenerated tumor cells would implicate mitotic division abnormalities in mechanistic generation of the abnormal cellular forms; these would be unable to proliferate effectively because of precise attributes of such tumor cell degeneration that constitutes a neoplastically acquired system of progression.

What mechanisms of tumor cell damage would directly develop as a secondary consequence to mitotic cycle related events might be multifactorial. Certainly, with regard with multicellular tumor spheroids studied experimentally[3], there develops a fully synchronized system of zonal distribution of tumor regions, with a central necrotic zone, an intermediate proliferating tumor cell population and an outer differentiating zone. Such zonal distributional patterns of organization might indeed be suggestive of a rather senescent central tumor cell subpopulation that has undergone necrosis due to factors related to nuclear damage or mitosis-related mishaps; the intermediate zone of proliferating cell subpopulation would correspond to the small tumor cell component of glioblastomas as a neoplastic component immediately derived from the central tumor cell pool that had subsequently undergone necrosis[4].

This essentially most dedifferentiated portion of the whole tumor or tumor spheroid would develop consequent to tumor cell activity that on the one hand promoted central zonal necrosis in the tumor spheroid and on the other the creation of an intermediate tumor zone of

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high proliferative activity but with low differentiating potential.

This intermediate proliferating tumor cell subpopulation would presumably be capable of proliferating rapidly but showing little effective cellular differentiation. Such a phenomenon would perhaps be the result of various potential causative agents associated with phenomena of central zonal tumor necrosis and of processes leading initially to the generation of rapidly proliferating tumor cell subpopulations or clones. The outer zone of tumor cells would appear to sacrifice significant intense proliferative capability in an attempt to partially differentiate; these zonal patterns would perhaps arise in consequence to a dual phenomenon of tumor cell necrosis versus tumor cell proliferation that would expressly negate cell differentiation in either instance. Such systems of evolving influence would evolve as closely associated systems of strict gene level expression on the part of the gliomatous cells as these latter tend to progress to higher tumor grade.

In general terms, there might develop a dynamism involving attempts at differentiation and attempts at rapid proliferative activity in various subpopulations of tumor cells based on an essential system in terms that would refer primarily to how differentiation versus proliferation do indeed constitute mechanisms of non-progression of tumor cell necrosis. Conversely, the necrotic tumor foci, as seen in glioblastoma multiforme, would constitute subpopulations whereby the intense proliferation would result in lethal nuclear damage preventing both proliferation and differentiation of these tumor cells.

Tumor cells, as a generic pathobiologic state, would hence appear essentially to constitute either a proliferative cell pool or a tumor cell pool attempting some degree of differentiation. Failure of both of these two essential pathways of activity would result in a degenerated tumor cell state destined to progress towards necrosis. It is in such terms that an essentially inert subpopulation of degenerated tumor cells, in an otherwise highly aggressive lesion as a glioblastoma multiforme, would persist indefinitely as an integral phenomenon of participation, without the development of necrosis as a distinct component of glioblastoma progression. In this regard, also, histopathologic features and grading of astrocytomas would not invariably contribute to the identification of subsets that subsequently might progress to glioblastoma[5].

Whether in fact the degenerated tumor cell subpopulations of such a neoplasm necessarily constitute an older or earlier portion of the neoplasm would presumably depend on an evolutionary course involving several repeated cell cycle divisions. Indeed, tumor cell nuclear damage and necrosis would appear necessarily inherently progressive phenomena with consequences of spread arising from basic attributes related to clonality of progression and of tumor cell proliferation. However, on the other hand, no correlation was found between p53 immunoreactivity in glioblastoma cells and interval to tumor recurrence[6].

An endpoint for attempts at differentiation of tumor cells in glioblastoma might perhaps relate, in various ways, to infiltration as a phenomenon of strictly active incorporation within adjacent brain parenchyma; such a phenomenon might in fact possibly be influenced by trophic factors arising within the immediate microenvironment constituted by surrounding brain parenchyma and vessels around the tumor margins. In this regard, for example, PI3k/Akt pathway would appear involved in the signaling cascade required to induce cell migration. Urokinase-type plasminogen activator would, in addition, appear to regulate such tumor cell migration [7,8].

Hence, in general outline, perhaps, a highly proliferating tumor cell pool might, under influences partly exerted by surrounding brain parenchyma and also by angiogenesis and vascular differentiation, constitute tumor cell infiltration as a phenomenon of interactive paracrine and autocrine effect. Brain angiogenesis inhibitors would appear to be lost during tumorigenesis and, in addition, p53 would not appear involved in their regulation[9].

In fact, a major difference between benign neoplasms and malignant neoplasms might actually depend on strict differentiation from benign neoplasms, whereas, with malignancy, this essential attempt at differentiation would evolve as infiltrative behavior by these cells. Such an alternative process of infiltrative behavior might constitute pathobiologic attributes of the surrounding stroma or brain parenchyma and vessels involving excessive autonomous production of trophic factors, including, in particular, Vascular Endothelial Growth Factor (VEGF)[10,11]. Also, for example, macrophage migration inhibitor factor, secreted by the hypothalmo-pituitary system, would appear to correlate with VEGF production in human glioblastoma[12].

In fact, marked VEGF production, with strong immunohistochemical reactivity for VEGF in the adjacent glomeruloid vessels, would correlate closely with a high-grade for the gliomas as seen classically in glioblastoma multiforme.

Such a glioblastoma system might operate in conjunction with other forms of influence in enhancing progressiveness of tumor grade, particularly in terms of infiltrativeness; in this regard, for example, decreased

levels of cystatin C, a protease inhibitor of cathepsin B, would appear a potential mechanism involved in gradeprogression of gliomas[13]. In this regard, also, combination gene sets of glioma cells, in terms of signature genes, might contribute significantly to classification and grading of these neoplasms[14].

PROGRESSIVE GROWTH AND INFILTRATION BY GLIOMA CELLS MUST INCORPORATE A SERIES OF ADJACENT TISSUE ELEMENTS IN AN ACTIVELY AND PROGRESSIVELY PARTICIPATING MANNER

The infiltrative damage induced by glioma cells might essentially be mechanical in nature, with disruption generated by the sheer pressure as exerted by the infiltrating front of the tumor mass.

With regard to gliomas, however, the advancing tumor margin would essentially be constituted by infiltrating individual tumor cells; indeed, much of the substance of a glioma generally is in the form of individually infiltrating tumor cells, a phenomenon that is distinct from carcinomatous mass lesions.

A model of chemotaxis has been proposed involving both homotype and heterotype chemo-attraction to account for features of growth pattern evolution in glioblastomas[15].

Hence, an infiltrating individual glioma cellular front would constitute a more attenuated extension of the composed individual neoplastic cell lesion constituting the bulk of the mass. Certainly, towards the central regions of such a glioma, the native neural cell elements would become eventually largely replaced by the neoplastic process. Such a phenomenon would presumably evolve as a result of biologic aggressiveness as neoplastic cells overcome various nonproliferating elements including neurons. In fact, a rapidly proliferating tumor cell population might intrinsically constitute a phenomenon of replacement of normal cell elements that would generally evolve through various stages of proliferative and differentiation activity. In general, such a progressive replacement of normal brain (neural) substance by proliferating neoplastic cells would implicate an individual cell basis for a specific pattern of creeping substitution.

The normal neurons might actually be replaced by proliferating neoplastic cells in a manner that would actively involve mechanistic processes of infiltrative behavior and also phenomena of disruption associated with simple enzymatically released or activated events prone to evolve in damaged neural tissues suboptimally supplied by blood and oxygen.

In addition, upregulation of macrophage migration inhibitory factor expression during hypoxia and hypoglycemic stress might play a critical role for the neovascularization of gliomas[16].

The edema generated around the infiltrating front of individual glioma cells might actively serve to separate normal neuronal and glial cells in a manner that would facilitate of the individual tumor cell infiltration process itself. Perhaps, edema, as usually most marked in immediate vicinity of the infiltrating tumor cell front itself, might significantly impair viability of neurons, glia and their processes in terms of how mechanistic effects resulting directly from effects of suboptimal oxygen supply to neuropil. Such a phenomenon might be particularly significant in terms of astrocytic fibers and axonal tracts that would tend to offer most resistance to mechanistic infiltration.

Peritumoral edema[17], on the other hand, would be particularly significant in inducing damage paradoxically implicating intrinsic phenomena associated with infiltration in between individual tracts and in between tract fibers. Indeed, peritumoral edema might be a specific mechanism of neuropil involvement in its own right, linked in various ways to facilitated local tumor spread as angiogenesis on the one hand and disruption based on physical processes of microdissection on the other progressively increase in severity.

Local spread of the tumor cells into the white matter would, to a significant degree, constitute a dissectional phenomenon, based on axonal and glial participation and in a milieu of evolving edema that would continuously redirect infiltrating glioma cells as an individual cell system of multifocality in terms also of intense proliferative activity. Such involvement of white matter tracts by infiltrating glioma would appear well demonstrated by diffusion-tensor imaging[18].

The development of seizures, associated with growth of intracranial neoplasms, would develop along lines of a conceptual system of stimulation of the neurons or of its axons and dendrites that would involve mechanical pressure exerted by peritumoral edema; indeed, evolving gliomatous cell proliferation would implicate individual tumor cells as theses participate towards the growth of a single or multifocal tumor mass that progressively infiltrates.

In general terms, simple physical dynamics inducing shifts of edema fluid in the immediately adjacent white matter might facilitate tumor cell infiltration for various reasons. Also, the oxygen pressure level in peritumoral tissues might be affected by intracranial pressure, whereas the intratumoral tissue would be low in oxygen tension[19].

The edema, as a direct result of increased permeability of vessels, might constitute an expression of abnormal morphology and structure (as evidenced by the glomeruloid structures within glioblastomas) in terms of enhanced VEGF production, evidenced as proliferatingvessels. In this sense, the glioma itself would tend to fully accommodate much of the pathobiologic attributes of infiltration based on mechanisms of production of VEGF by the gliomatous cells themselves. Such a phenomenon would be significant as a intrinsically operative system subsequently involving a substitution of endothelial cells and glomeruloid vessels as the tumor cells progressively infiltrate further into the neural tissues. In such terms initially directed VEGF production by angiogenic vessels would subsequently perhaps also implicate infiltrating gliomatous cells as participants in further angiogenesis and in further VEGF production.

It is in terms of such a phenomenon of waves and shifts of transfer of biologic processes involving growth and trophic factor effect, initiated by both the neoplastic cells themselves and also by adjacent and surrounding neural and vascular tissue elements, that would allow the glioma to first grow as a tumor mass and subsequently to grow in an infiltrative manner in a strictly evolving system involving associated and incorporating neuropil.

Subsequently evolving systems of interaction of tumor cells with stroma would for example involve the chemokine receptor CXCR4 and its ligand stromal cell-derived factor-1 especially in terms of glial proliferation[20].

DOES AUTOPHOSPHORYLATION OF EGFR VIII ACCOUNT FOR AUTOCRINE PRODUCTION OF EGF IN GLIOBLASTOMA MULTIFORME?

One important factor in terms of active Epidermal Growth Factor Receptor (EGFR) -induced oncogenesis that would help account for much of the induced amplification effect might actually reside with the autophosphorylating capacity on the part of its truncated gene product, EGFR VIII. The 801 base pair genomic deletion of the wild type EGFR gene might actually directly induce an autophosphorylation system involving EGFR VIII.

Such considerations might indicate that deletion of the 801 base pair, with subsequent insertion of the glycine residue at the fusion site, would deregulate mechanics of phosphorylation of the EGFR in a way leading to an inherent tendency for autophosphorylation; this would constitute the basis for an autocrine series of active mechanisms for the same tumor cells in terms of EGFR VIII. A phosphorylated EGFR VIII in some way might stimulate the cell to produce EGF, in terms of both excess production of EGF and also in terms of autocrine production. A primary factor involved in autophosphorylation of the EGFR VIII would perhaps govern both excessive and persistent amplification in EGFR -induced oncogenesis that would account in part for malignant cellular transformation in glioblastoma multiforme[21].

Perhaps, indeed, the phosphorylated state of a growth factor receptor might play an important role in the mechanics of the receptor stimulation; such stimulation would involve production of the growth factor, as a threshold-controlled system, in terms of the phosphorylated receptor state itself.

Certainly, a rather complex situation might implicate significant degrees of autophosphorylation of the EGFR VIII. One component might involve direct stimulatory effects as exerted by the receptor autophosphorylation that would not necessitate any significant or persistent stimulation by the EGF itself. For example, EGF receptor overexpression would appear responsible for activation of protein kinase B. PTEN, on the other hand, would not seem implicated directly in dysregulation of this pathway in glioblastoma[22]. Superimposed on such a phenomenon there would develop an autocrine system of mechanics whereby the same tumor cell and also other tumor cells would further contribute to phosphorylation of the EGFR VIII.

It is such an essential combination of direct effects of EGF-induced phosphorylation acting on the already autophosphorylated EGFR VIII that would perhaps constitute significant pathways of progressiveness in terms of cellular malignancy and cellular infiltrativeness. In this regard, also, the EGFR pathway would appear to mediate resistance to radiation/chemotherapy effect in a RAS-dependent manner[23].

ESSENTIALLY ABERRANT PHOSPHORYLATION PATTERNS OF EGFR VIII MIGHT ACCOUNT FOR ESSENTIAL FEATURES OF MALIGNANT GLIOMA CELL GROWTH AND PROLIFERATION IN GLIOBLASTOMA MULTIFORME

A basic premise that would implicate essential operative systems in the origin and progression of neoplastic transformation might concern pathways of primary aberrant phosphorylation in terms of progressive cellular growth as exerted by factor receptors such as Epidermal Growth Factor Receptor (EGFR)[24] and also as exerted especially by EGFR VIII in gliomas.

In terms of an essentially autophosphorylated state for the EGFR VIII, a central deregulating series of events in tumor cell proliferation might ultimately relate to

autocrine production of EGF by that same individual tumor cell as a component of a constitutive group of similar tumor cells.

What are the possible direct tumor cell biologic effects of a constantly hyper- and aberrant phosphorylated state in terms of principal growth factor receptors? Certainly, for example, a complex relationship would appear to exist between the p53, mdm2 and EGFR expression and age in patients with glioblastoma[25]. Presumably, less growth factor would be required tostimulate the receptor concerned and this would further compound any effects produced by EGF actually combining with such a receptor.

Perhaps, in fact, it is specifically the two effects of an already autophosphorylated receptor that would combine subsequently to EGF (for example, as produced by autocrine processes) and account for the persistent proliferative activity as shown by glioma cells. Such a postulated phenomenon might evolve as a strict system of introduction of novel programmed pathways in further increasing the phosphorylated state of the EGFR VIII receptor, but also in enhancing phosphorylation of additional epitopes or residues on such receptor species.

Indeed, an essentially aberrant pattern of phosphorylation, with essentially aberrant patterns of stimulation of cell growth and division would, in strict terms, constitute simple mechanistic induction of modes of tumor cell proliferation systems that exhibit infiltrativeness as incorporated in neuropil and as patterns of progressively increasing dimensions.

A neoplasm might be defined as a process of proliferation that is non-essentially linked to aspects of progressiveness intrinsically constituting systems of infiltration and metastatic spread. In terms of such a definition of neoplasms beyond simple dimensions of either strict cell proliferation or of infiltrative and metastatic spread, one might indeed consider how cells interact within a whole series of paracrine and autocrine autonomy that is self-progressive. In terms indeed of angiogenesis and of stromal desmoplasia, in particular, it might be valid to recognize multiple systems of influence that intrinsically implicate self-progression in a manner strictly of an amplifying nature, both with regard to cellular proliferation and to spread locally and systemically.

Indeed, beyond a simple conceptual scheme of extension of infiltrative tumor in terms of metastatic tumor spread in the body, one might in various ways strictly re-define neoplasms as simply different modes of self-amplification of biologic attributes of cell proliferation and cell-related trophic effect. In fact, one might legitimately and conceptualize the integral neoplastic phenomenon as simply one mechanistic pathway of biologic and trophic self-amplification beyond any detailed attempt at biologic idealization of either excessive cell proliferation or of cell infiltration and metastatic spread.

Systems of excessive cell proliferation would in various ways be responsible for aspects of development of self-progressiveness in a way arising along pathways of inherent susceptibility to further genetic damage. However, in perhaps more realistic terms, the very progressiveness of tumor cell proliferation, infiltration and spread might constitute an effective source of evolving genetic damage as a consequence and not as a cause of neoplastic progression. Indeed, in basic terms, one might redefine the actual dynamics of evolution of a neoplastic lesion as a stereotyped progressiveness that is not only self-amplifying but also strictly intrinsic to biology of groups of actively proliferating cells.

Indeed, much of the pathobiology of neoplasia might relate to essential proliferation of groups of cells that effectively transform trophic influence even with regard to angiogenesis and stromal desmoplasia. Indeed, the essential quality of the metastatic tumor process would constitute the trophic influence arising from interactions between effective tumor cell groups undergoing actively self-driven proliferative activity.

In simple terms, one might consider a whole series of histopathologic features of a lesion such as glioblastoma multiforme as simply integral groups of neoplastic cells undergoing proliferation, necrosis, infiltration and spread via pathways intrinsic to an integral phenomenon of self-amplifying trophic series of evolving influence. In this regard, also, from a therapeutic point of view, neural stem cells might constitute effective delivery systems in glioma treatment as for example in inducing apoptosis by tumor necrosis factor[26].

The actual infiltrative process, as exhibited by neoplastic cells, might, in various ways, constitute an interactive progression in terms of trophic effect transformation. With reference particularly to autocrine and paracrine influence, one might consider how systems of infiltrativeness would constitute an active participation of stroma with proliferating neoplastic cells in terms of mechanistic progressiveness of angiogenesis and contributing, in various ways, to a stereotyped phenomenon of spread of integral tumor cell groups.

Indeed, it would essentially be with reference to strict tumor cell groups that one might better understand dynamics of autocrine and paracrine effect of a trophic nature; indeed, interactions between tumor cells and stroma as integral systems of infiltrativeness and distant spread would simply constitute modes of trophic influence integrating stromal desmoplasia and

angiogenesis on the one hand with a proliferative system of neoplastic cells that is self-progressive on the other.

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