International Journal of Molecular Medicine and Advance Sciences 1 (4): 369-374, 2005
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Perivascular Attributes of Transformation and of Amplification in Tumor Cell Infiltration

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Abstract: Many attributes of a neoplastic proliferative and spreading phenomenon appear to directly arise as perivascular processes and as transforming and amplified response of infiltrated stroma. Growth factor participation would operatively interact with neovascularization in subsequently inducing progression of a neoplasm that spreads both locally and systemically. Such patterns of transformation would self-amplify in the subsequent evolution of a tumor that is characterized by paracrine and autocrine effect. It is in terms of such lesions inherently infiltrating stroma that metastatic spread implicates clonal groups of tumor cells in participation with neovascularization and endothelial proliferation and migration.

Key words: Tumor, cell infiltration, transformation, amplification

INTRODUCTION

INFILTRATED WHITE MATTER AS INCREASED GRADE CREATION OF GLIOMAS

Intracranial neoplasia constitutes an increase in intracranial pressure that compromises primarily vascular blood supply to the brain tissues. Such a problem is accompanied, in the case of high-grade gliomas, by a high degree of intra-tumoral vascularity that particularly promotes an intractably severe degree of cerebral edema. Dynamics of involvement of the tumoral vessels themselves are a progressive source of transforming change in fluid shift between the two main hemispheres. Understanding how endothelial cells of brain tumors differ from normal endothelial cells may be useful in determining abnormalities of the blood brain barrier and in treating gliomas in particular[1]. Lobar white matter expansion appears to initiate a further tendency to even more cerebral edema formation. The ipsilateral compression of the cerebral hemisphere is a compressive phenomenon that affects many regional vascular beds surrounding the region of neoplastic growth. Coupled to this is a shift of midline structures compromising blood supply to the opposite hemisphere.

This peculiar combination of vascular proliferation within the lesion and the associated compression of blood vascular supply further afield appears especially conducive to the cerebral edema and a tendency for interstitial accumulation of fluid derived from disturbed cerebrospinal fluid circulation.

Increased interstitial pressure gradients and the much larger and chaotic interstitial space arrangement of a tumor contrast with the very tight architecture of normal brain tissue[2].

In terms that would perhaps involve a strong tendency for active accumulation of fluid especially in the cerebral white matter, one might view neoplastic vascularity as an integral component of neoplastic evolution. This would further enhance pathologic effects of a neoplasm not only as a space-occupying lesion but also as a transformation of equilibrating attributes of fluid transfer across the wall of many blood vessels both within and beyond the actual tumor.

Vasogenic cerebral edema accumulation involves therefore a complicated integration of cerebral tissue shifts that transfer particularly significant forces on blood vessels including those of the neoplasm itself. It might very well be relevant to associate neoplastic vascularity with a series of ischemic changes affecting the white matter. This would create an actively participating role on the part of tumor cell infiltration. The considerable pathologic sequences in development of a microenvironment that actively supports tumor cell growth would implicate accelerated growth factor stimulation as a central mechanism in neoplastic progression.

Also, the host angiotensin II type 1 receptor pathway appears involved in tumor-related angiogenesis and growth and supports macrophage infiltration with enhanced vascular endothelial growth factor production[3].

The highly characteristic tendency for recurrent gliomas to increase in grade would perhaps relate closely to vascular dynamics of endothelial proliferation that implicate cerebral edema and protein exudation in the cerebral white matter.

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Shifts of the cerebral hemispheres would participate with an accompanying expansion of a tumor mass that is both hypervascular and itself edematous. Cerebrospinal fluid production as a mechanism of further potential compromise of fluid dynamics might specifically call into operation a series of compensatory pathways relative to tissue herniation through the tentorial opening and beneath the falx cerebri and especially as a phenomenon that is prone to become intractable.

Endothelial vascular hyperplasia in gliomas is perhaps a potent source of growth factor stimulation as tumor cell infiltration of the edematous white matter in cases of high-grade glioma. Vascular endothelial growth factor, besides its promotion of angiogenesis, also inhibits dendritic cell maturation[4].

Platelet-derived Growth Factor and Vascular Endothelial Growth Factor (VEGF) appear centrally axial processes in the production of pressure effects by a tumor mass that is specifically prone to edema formation. Modulation of the extracellular matrix, in addition, operatively regulates tumor growth[5].

In such a scenario, ischemic effects on white matter would paradoxically cooperate with an intratumor hypervascularity that is self-progressive even in terms of distortion of many regional vascular beds. With meningiomas, Tissue Factor as a cell-surface glycoprotein regulates tumor growth, proliferation and angiogenesis, and reflects tumor malignancy[6] . One might understand how ischemia of tissues somehow promotes further growth factor production in a highly dynamic milieu of progressive injury to an neoplastically infiltrated white matter.

Ischemic effects on edematous and compressed white matter surrounding an actively proliferating neoplasm would constitute a material source for growth stimulation of the lesion tied up with a series of phenomena implicating enhanced growth factor production and effect. The innate and adaptive immune systems have tumor-promoting as well as tumor antagonistic effects. Hence, CD4+ T cells and certain matrix metalloproteinases favor tumor progression, whereas CD8+ T cells and certain heat shock proteins exert antineoplas0tic action[7].

It is only in terms arising from enhanced proliferative and infiltrative behavior of the neoplastic cells that there tends to subsequently develop a propensity not only for progressively higher grade but also for enhanced injury to white matter further afield. In this sense, infiltration by high grade gliomas combines with a series of injuries to white matter that is integrally edematous and ischemic. Hypoxic induction of vascular endothelial growth factor may create a proangiogenic microenvironment facilitating endothelial cell recruitment[8].

A perivascular creation of neoplasia: The creation of a microenvironment involved in the active progression of anaplasia of gliomas appears intrinsically associated with a high proliferative cellular rate and with ischemic and edematous white matter. The engagement of the receptor for advanced glycation end products (RAGE) on the cell surface induces cellular dysfunction in cases of vascular disease and tumor cell invasion[9]. In a sense, the high degree of cellularity of high-grade gliomas is both a product of such hyperproliferative state and also a cause of further progression in grade of the neoplasm.

A grade III astrocytoma is one particularly prone to further increase in grade because of a potentially wide variety of mechanisms ranging in effectiveness from maintenance of neoplastic proliferation and infiltration to interactions with macrophages during angiogenesis[10] and with Transforming Growth Factor-beta[11]

Considerations of a general hyper-proliferative activity within a high- grade glioma would appear to implicate glomeruloid hyperplasia of endothelial cells that promotes neovascularization. Such neovascularization is a reliable reflection of how a lesion constitutes a high-grade tumor. Human TRAIL can effectively kill tumor cells and activate NF-kappaB, induce expression of E-selectin, Intercellular adhesion molecule-1, and Interleukin-8, and promote leukocyte adhesion. These actions induce apoptosis and inflammatory gene expression in human endothelial cells[12].

No doubt, it is a series of observed attributes of the neoplasm, as determined for example by microscopic examination, that astrocytomas implicate trophic influences related to florid endothelial cell hyperplasia of the vessels. Given the impetus for generation of more daughter neoplastic cells, the tumor would constitute a phenomenon of enhanced responsiveness in the creation both of hypervascularity and of subsequent grade deterioration.

The activating protein-1 (AP-1) family of transcription factors plays a potentially significant role in glioma progression by inducing uncontrolled production of VEGF-D and other compounds in glioma cell proliferation and spread[13].

A size-grade relationship would thus evolve that dynamically constitutes a mainstay in further neoplastic generation and infiltration. It is in terms largely of attainment for a certain tumor size that ischemia of the white matter develops and that edema progresses with increasing hypervascularity of the glioma.

AN AXIAL VASCULAR SYSTEM OF TRANSFORMING PROGRESSION IN GLIOMAGENESIS

A high degree of biologic heterogeneity appears a cardinal mode of transformation in gliomagenesis as revealed also in experimental model systems such as Rat C6 glioma[14]. A strictly astrocytic lineage to the neoplasm

would belie transition to a full range of heterogeneity implicating also vascular and extracellular molecular species. It might be relevant that a non-integral lesion such as an infiltrative high-grade glioma would constitute a highly heterogeneous grade to the individual neoplastic cells. Such a tumor microenvironment would also transform the white matter relative to tumor progression.

This may include alphavbeta3 integrin that would promote proliferation of tumor and endothelial cells and their migration in glioma growth[15].

A representation of high-grade glioma around axial vascular tributaries would correlate with development of proliferation of the tumor cells that migrate outwards from nearby blood vessels. This supply of growth factors would be provided by a blood vascularity that progressively becomes incorporated with increasing grade of the neoplasm. A deeply infiltrative nature to the glioma might be relevant to a neoplasm as a central pathway of transformation that supplies, sustains and further converts gliomas to higher grade.

The matrix metalloproteinases degrade extracellular macromolecules and lead to tumor cell infiltration. Matrix metalloproteinases 7 and 10 contribute to the worse prognosis of astrocytomas when compared to oligodendrogliomas whereas matrix metalloproteinases 2 and 9 are important in neo-angiogenesis and tumor vascularization[16].

In general terms, neoplasia would evolve as angiogenesis involving the participation of hematogeneously arising processes both in the creation of the malignant transformation itself and also in the subsequent expansion, grade progression and subsequent spread of the same lesion.

Nitric oxide regulates vascular endothelial growth factor expression in many systems and possibly modulates tumor angiogenesis[17].

Platelet-derived Growth Factor and Vascular Endothelial Growth Factor involvement in tumor sustainment may very well be directly implicated in a sequence of mechanistic pathways leading to further subsequent tumor evolution. VEGF inhibits dendritic cell maturation as induced by lipopolysaccharide, and this may depend on the maturation status of the dendritic cells[18].

Stem cell biology as an inherently body-wide process of spread and proliferation of cells would appear to closely parallel in analogous terms a tendency for blood and vascular spread of malignant neoplastic cells. Even the highly varied differentiation sequences in tumor progression would reflect fundamental aspects of a stem-cell phenomenon centered on axial pathways of pathobiologic progressiveness.

The expression of NG2 and GD3 antigens on glial precursor cells would correlate with specific functions in the malignant progression of human brain tumors[19].

MONOCLONAL TUMOR PROGRESSION IS BOTH PARACRINE AND AUTOCRINE INVOLVING INTEGRAL INTERACTIVITY OF NEOPLASIC CELL GROUPS

A molecular mechanism of cell-cell adhesion appears to paradoxically promote a whole series of events that drive invasive behavior of neoplastic cells often specifically tied up with metastatic spread. With aggressive uterine endometrioid carcinomas, vascular invasion is associated with a diffusely infiltrative growth pattern, solid growth, necrosis and deep myometrial invasion[20]. N-cadherin appears especially implicated in invasive infiltration that proteolytically alters stroma and matrix proteins. The transition to an infiltrative phenotype appears one that derives largely from cell-cell adhesion implicating in turn not only interactive communication between cells but also a growth pattern of amplifying type. In this regard, abnormal endothelial caveolin 1 plays an important positive role in regulating pathological angiogenesis[21].

Molecular attributes of cellular adhesion might operatively involve modes of adhesion beyond simple interactive participation between cells. Indeed, surface expression of vascular cell adhesion molecule-1 and of intercellular adhesion molecule-1 is dependent on cycling of the actin cytoskeleton of endothelial cells[22]. Invasion as a group phenomenon of tumor cells would interactively promote further secondary waves of amplified effect that are specifically metastasizing.

Neovascularization would perhaps implicate such secondary waves of responsive participation of stromal elements in a manner primarily based on adhesion between groups of cells. Tumor angiogenic activity is an important prognostic factor in many human tumors[23].

A phenomenon of neovascularization might implicate modes of interactivity with a stroma dominantly influencing infiltrating cells and a whole series of progressive evolutionary changes that is evidenced by metastases of whole groups of infiltrating cells.

Proteolysis appears to function as an attribute of tumor cell infiltration in a manner that implicates neovascularization as an attribute also of the infiltrating tumor cells. Infiltration of stroma by groups of neoplastic cells appears a powerful transforming event that also adds directly to a metastasizing potential of amplified dimension.

Defining neoplastic amplification as a whole series of events that inherently transforms dynamics exerted by growth factors would go beyond simple concepts of tumor cell progression and of static idealization of cell-cell adhesion and interactivity. It is perhaps instructive to consider even cell-stromal interactivity as an incomplete representation of specific groups of tumor cells that

infiltrate as metastasizing and neovascularization phenomena.

In tumors in general, inflammation during the microvascular phase of cancer cell infiltration is prometastatic through vascular cell adhesion molecule-mediated capillary arrest of tumor cells[24].

Only insofar as it is possible to consider modes of participation of endothelial cells as integral neovessels can one in addition realize how whole groups of neoplastic cells infiltrate as specifically designed metastatic deposits. Hypercoagulability contributes to the pathogenesis of tumor growth and metastasis by promoting angiogenesis. A cross-linked fibrin network provides a provisional proangiogenic matrix that facilitates blood vessel infiltration[25].

Infiltrative tumors cells as a specific phenomenon of neovascularization and as amplified metastases could be further defined as interactive groups of cells acting as paracrine and autocrine systems of transforming progression. Stroma infiltration and vascular maturation are an important checkpoint linking the angiogenic switch with initiation of tumor progression[26]. A transforming series of paracrine events would self-progress as systems of transforming autocrine effect. Interleukin-15 produced by metastatic colon carcinoma cells contributes to angiogenesis and disease progression[27]. A close characterization of stromal infiltration might help redefine such transforming events as a neovascularization that is itself inherently clonal.

Interpretation of neoplastic transformation would implicate a process of clonally-based paracrine effect. Indeed, it is with regard to such a redefinition of clonality related to neovascularization that a derived process of infiltration of stroma would progress in the first instance.

Also, one might recognize modes of interactive adhesion as whole groups of tumor cells that function in the evolution of clonal neovascularization and of a clonal metastatic phenomenon.

Increasing neutrophil recruitment by inducing endothelial cellular adhesion molecule-expression may potentially optimize vascular targeted anticancer treatment [28].

Clonal and interactive phenomena of paracrine and autocrine progression would constitute a schematic representation of mitotic activity potentially involving transformation of cell-cell adhesion and of cell-cell interactive events.

Interactions of clonal groups of tumor cells might further implicate the neoplastic cells as progression from a microscopic focus to a macroscopic potentiality for system amplification. Growth of neoplastic cells that spread as clonal neovascularization and neoplastic infiltration would constitute a transformed profile of molecular interactivity that progresses as groups of tumor cells.

A monoclonal basis for mitotic tumor cell division would reflect a strict process of autocrine effect and of a clonal paracrine system of amplification. Events that specifically progress as self-transformation would incorporate amplification of tumor cell cycle dynamics as integral participants in tumor cell infiltration and as a clonally based neovascularization.

Growth factor stimulation as exerted by Platelet-derived Growth Factor would act with Vascular Endothelial Growth Factor in terms of an endothelial cell proliferation that participates in the stromal response. Endothelial cells appear a powerful source of the singularly amplifying attributes of both tumor cell proliferation and spread locally and systemically. It might be relevant to consider endothelial cells as related not only to organization of the stromal neovascularization but also to a clonal derivation of the neoplastic cells as progressive transformation of cell dynamics.

In such a scenario, endothelial cells would induce neovascularization as clonally derived dynamics of tumor cell infiltration. Multiple modes of interaction of whole integral groups of neoplastic cells would progress in amplifying fashion and in a manner that transforms growth factor responsiveness.

Growth factor action as self-amplifying events might involve modes of interaction that progress as paracrine processes and as subsequently transforming autocrine systems of participation.

Hence, cycles of transforming paracrine and autocrine progression might alternate as basic mechanistic dynamics of groups of tumor cells that are in turn self-transforming with neoplastic progression.

Monoclonal groups of tumor cells would refer to a constitutive neoplastic cell autonomy that progresses in terms of metastatic potential affecting cell cycle dynamics and also interactive adhesion of cells with stroma.

Tumor cells that spread as integral groups involve a monoclonality that progresses as a proliferative event and that transforms the whole neoplastic focus.

Endothelial cells form a pavement pattern of lining cells to neovessels in a manner dominantly characterizing neoplastic cell infiltration of a stroma that is proteolytically transformed. It appears significant that clonal tumor cell proliferation is a strict characterization of cell-cell interaction and of cell-stromal participation in tumor progression.

Participating vascular- and growth factor-related events not only progress monoclonally but also help further characterize neoplasia as a transforming series of

induced responses. Interleukin-1, as a multifunctional proinflammatory cytokine, enhances expression of IL-6, IL-8 and VEGF and intercellular adhesion molecule-1 and may facilitate metastatic spread of tumor cells[29].

Responsiveness and progression as events integral to a neoplastic monoclonality might involve paracrine systems not only as transforming processes but especially as mechanistically amplifying systems.

Response and autonomy as inherent biologic attributes of neoplastic infiltration and as a neovascularization-driven process of progression might help account for a transformation implicating monoclonality as combined autocrine/paracrine effect.

A stromal desmoplastic response to infiltrating tumor cells appears primarily a proliferative mechanism that enhances spread of the neoplasm. Transformed cell-cell adhesion reflects characterized progression not only of proliferative events but also of cell differentiation. Desmoplasia of a stroma incorporating such transformed cell-cell adhesion would constitute mechanistic responsiveness as evidenced by neovascularization of the stroma and by the infiltrative behavior itself of the tumor cells.

Infiltration of stroma is a responsive phenomenon that characterizes tumor cell-cell interactivity. Such cell-cell interactivity primarily evolves as paracrine systems determining subsequent progression as autocrine pathways of influence.

Such transformation of progressive paracrine systems to autocrine-driven phenomena would promote mechanistic evolution as tumor cell infiltration of the desmoplastic stroma. In addition, the potential for metastatic spread is inherent to such paracrine transformation to autocrine effect in terms of a responsiveness that predetermines neovascularization as part of the monoclonal derivation and progression of the neoplasm.

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