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# Dynamics of Metastasis of Breast Carcinoma to Brain

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**Abstract:** A metastatic cascade appears to operate as a non-random predetermined system of selective advantage implicating initially a sieving effect by the first capillary beds in an organ of spread. A seed-soil predilection appears to constitute a released system of promotion enhancing progression of tumor cell proliferation as a critical step in the metastatic cascade. One might redefine events in terms of promotion of pathways influencing subsequent acquisition of attributes. Permeation and embolic spread via vessels would constitute a realized idealization of events primarily characterized in terms of ongoing changes in phenotype of tumor cells both as genetically unstable cells and as increasingly self-progressive pathways of strictly sequential type.

**Key words:** Dynamics, breast carcinoma, proliferation

## A MULTISTEP PROCESS

A multistep process integrally promotes a progression of the metastatic process of malignant tumor cells based primarily on an ability to locally invade matrix. Matrix metalloproteinases are thus of primary significance in the establishment of metastatic tumor foci beyond the step of extavasation from lymphatics or capillaries. It is perhaps significant that a whole assorted or heterogeneous system of influences effect the development of a cellular phenotype that further evolves as metastatic tumor deposits[1].

A clear definition of evolving influences in the characterization of events might further delineate the development of metastasizing deposits largely in terms of vascularization or angiogenesis of the stroma. High density angiogenesis appears a primary pathogenic factor in the further promotion of an extravasated clump of tumor cells that subsequently metastasizes in its own right. Angiogenesis appears to comprise an inherent tendency for promotion of metastasis based largely on the ability of tumor cells to bridge extravascular sites of deposition via a process of infiltration of the stroma.

## STROMAL INFILTRATION

Stromal infiltration as a local spread pattern of tumor cell dissemination appears a central mechanism that redefines systemic metastasis in terms largely of ongoing subsequent hemodynamics. It is significant that intravascular spread of tumor cells allows for the subsequent establishment of cell signaling pathways via systems such as integrins and basement membrane laminin[2] that recapitulate cell cyclical activity and cell receptivity pathways.

A balancing system of promotion versus inhibition pathways allows for the progression or otherwise of pathways that further delineate processes of induced transformation in cell cyclical activity. Indeed, extravasation of infiltrative changes of tumor cells is a basis for further promotion of cell cyclical activity based on cell signaling or cell communication systems[3].

It is significant that trophic factors further specialize the environment in terms of a seed/soil interaction as shown with metastasis of melanoma to the brain.

## THE BLOOD BRAIN BARRIER

The blood brain barrier constitutes a fundamental mechanism involving a barrier effect in transfer of tumor cells from the intravascular compartment to the cerebral interstitial space[4]. A complexity of multiple barrier effects involving cerebrospinal fluid, endothelial cell layer, astrocytic foot processes would revolve around targeting mechanisms implicating transfer or nontransfer of tumor cells from the systemic circulation. A particular tendency for involvement of the leptomeninges rather than the dura in brain metastasis would implicate a rich anastomotic system of capillary type vessels that

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perfuse the subarachnoid membranes. Perfusion dynamics of blood supply of the brain and leptomeninges appear particularly implicated in a progression of pathways that reemphasize a density of vascular systems that deliver tumor cells or tumor cell clumps to multiple regions of the central nervous system and enveloping membranes.

Risk factors in brain relapse of patients suffering from metastatic breast carcinoma would promote a redistribution of tumor cells based on systems of perfusion to the brain[5]. One might recognize negative estrogen receptivity of tumor cells that progresses particularly with regard to the establishment of lung metastasis. Indeed, the blocking of capillaries by tumor cell clumps would relate to a stasis in blood flow that hemodynamically increases pressure on the vascular bed.

Extravasation of tumor cells is a process that appears determined to a significant degree on a subsequent progression of the cells to establish metastatic deposits in the extracellular /interstitial compartments of the central nervous system.

## ONGOING STRESS PHENOMENA

The blood brain barrier might relate particularly to ongoing stress phenomena that hemodynamically alter progression of systems that in multiple ways involve either deposition or else passage of tumor cells to multiple extracellular foci. Proliferation of tumor cells as metastatic deposits in the central nervous system might significantly correlate with a tendency for non-receptivity for estrogen on tumor cells. It appears highly significant that multiple heterogeneous models of clonal cell populations would refer to a tendency for selectivity of an inefficient metastatic process of neoplastic cell spread.

## CIRCULATORY SYSTEM

Breast carcinoma as a form of neoplasia primarily spreading via lymphatics and to lungs might significantly compromise the circulatory system supplying the central nervous system. It appears highly probable that obstruction of passage flow of blood through multiple capillary beds constitutes a progression step in the establishment not simply of extravasation pathways but of the deposition of proliferating metastatic foci of tumor cells. The brain microenvironment really constitutes a full series of transformation events in reconstituting conditions of proliferative spread of carcinomatous cells involving brain interstitium[6].

## NON-RANDOM EVENTS

It appears highly significant to consider non-random events linked in a strictly sequential pattern of progression of metastatic spread. P53 indicates a patient subgroup with breast carcinoma at high risk as may also Epidermal Growth Factor, receptivity[7]. Hemodynamic turbulence may prove a particularly efficient mode of progression in the development of subsequent metastatic deposits linked to ongoing variability of blood flow patterns in capillary beds.

Integrins and laminin[2] appear significant particularly in terms of cell-cell adhesion and signaling pathways mediating tumor cell migration and invasion. This is perhaps in terms specifically implicating a migratory pathway of progression.

Heterogeneity models of cell proliferation and of angiogenesis particularly characterize neoplastic cell systems that specifically predetermine metastatic potential immediately following sequential steps of extravasation of the tumor cells.

## PARAMETRIC REDEFINITION

Parametric redefinition of metastatic potential might relate particularly to ongoing dynamics of influential progression in metastatic spread within the brain interstitium[8]. The implications of matrix proteases such as metalloproteinases[9] would perhaps help resolve one aspect only in the evolution of metastatic spread subsequent to immediately precedent extravasation of the tumor cells.

It is in the realization of events borne out by a full depiction of steps contributing to heterogeneous patterns of abnormal capillary blood flow that further characterization of tumor cell spread further promote proliferation of the tumor cells. Heterogeneity of clonal attributes of neoplastic cells appears a determining factor that particularly empowers the development of selectivity forces in further tumor cell spread. Death associated protein kinase may function as a metastasis suppressor by inducing apoptosis[10].

One might recognize events in breast carcinoma spread that implicate not only the establishment of pulmonary metastasis but also a concomitant tendency for systemic spread to especially the central nervous system[11].

Proliferation of pathway events would allow for a fine selectivity that further progresses as proteolysis of extracellular matrix. It is in this sense that local infiltration of tissues is a primary determinant in the establishment of metastatic deposits subsequent to tumor cell extravasation[12].

## MICROENVIRONMENTAL PROGRESSION

Indeed, microenvironmental progression would relate to ongoing heterogeneous systems of involvement of tumor cells that proliferate clonally and evolve especially as selective advantages biologically and pathobiologically[13,14]. Metastasis indeed is a further recharacterization of such dynamics of matrix proteolysis[9] arising in terms of clonal heterogeneity of deposits of tumor cells that nonselectively extravasate and selectively proliferate subsequently. Nonrandom selectivity of further pathways of production of injury may account for a particular propensity for invasion of the brain interstitium by tumor cells.

## GENE SILENCING

Gene silencing appears a constitutive system involving methylation[15] or histone acetylation in the regulation of metastasis suppressor genes[16]. The NM23 gene is a conspicuous metastasis-suppressor gene[17]. Metastasis appears a process of involvement that self-progresses in terms of conditions allowing self-amplification. One might further characterize events in terms of ongoing systems that selectively redefine conditions of microenvironmental progression in metastatic spread[13].

Angiogenesis appears also a particularly selective process of a negative control system in angiogenesis that appears particularly applicable as a means that heterogeneously promotes further characterization of evens in clonal determination of metastatic foci of tumor cell proliferation and spread[14].

## PREDETERMINED SUSCEPTIBILITY

Pathobiology of a full array of attributes of tumor cells might predetermine susceptibility in subsequent progression of events linking nonselective extravasation to a highly predilected system of interstitial cell deposition and spread[18]. Inhibition and promotion pathways in tumor cell spread might specifically correlate with angiogenesis that densely populates the interstitium infiltrated by metastatic tumor cells. Predictive events in the production of pathways selectively conducive to metastatic spread would relate particularly to ongoing transformation of microenvironmental conditions of selective spread of tumor cells[19].

A multiplicity of tumor cell deposits appears a strict predeterminant in progression of spread of neoplastic cells in terms of trophic effect. The blood-brain barrier appears a particularly preselective system that allows discrimination of cellular attributes conducive to subsequent steps in transformation of tumor progression. Nonrandom transformation is indeed a characterized predetermination of pathways borne out by metastasis suppressor genes on the one hand and a whole host of matrix proteases and other events in interstitial space infiltration and spread in the central nervous system, on the other.

## MICROENVIRONMENTAL SELECTIVITY

Microenvironmental selectivity allows for the promotion of events in the creation of promoting influences in subsequent spread of the tumor cells via interstitial and angiogenic pathways[20]. A multiplicity of foci of involvement might help determine requisites for spread arising in terms of concurrently evolving pathways of infiltration of the interstitium. Tissue specificity and general metastatic competency genes might cooperatively implicate a recognized set of operative pathways in the execution of both pro- and anti-tumor cell proliferative events.

Proliferation and spread appear inherently evolving steps in characterizing further definition of tumor cell clonality. Clonality and heterogeneity models may prove an effective representation of modes of interactive pathway progression determining a multiplicity of events that subsequently self-resolve as metastatic spread of actively proliferative cells represented in particular by density of neoangiogenesis[21].

## BIOMOLECULAR TRANSFER IN CELLULAR METASTASIS

Blood-brain transfer refers to an integrative process of manipulative transfer involving particularly a tendency for recycling of macromolecules[22]. In terms of a microenvironmental progression that evolves particularly as ongoing processes of such transfer, the blood-brain barrier might primarily in the central nervous system.

The blood vessel (neurovascular)-capillary network might entail an ongoing process of dynamic turnover involving a reversion to simple transfer mechanics in studies of overloading of the blood-brain barrier by numerous metastatic cells from the systemic circulation.

One might view the evolution of the metastatic cascade in terms not simply of a strict sequence of linked steps all essential as a metastasizing event but particularly in view of ongoing transformation in the handling of macromolecules that in turn further redefine transfer dynamics across the blood-brain barrier. In such terms, indeed, one might recognize the onset and further

progression of events of transfer in terms arising directly from hemodynamic flow mechanics that critically determine evolving subsequent steps of molecular transfer.

## STATISTICAL VARIABILITY

Variability and statistical fluctuations in incidence of ongoing interactions between molecular and neurovascular units of integration might allow for the development of a series of subsequent transformation events in the evolving possible metastasis process. Central nervous system compromise implicates in particular a dual process of evolving dynamics that promotes further development of cellular/neuropil or cellular/stromal interaction with blood vessels.

Metalloproteinases MMP2, MMP3 and MMP9 appear implicated in breast cancer metastasis[23].

Increments in the use of biomolecular species that modify survival of metastatic cells focally and systemically might account for an ongoing evolution in biophysical modification of events that primarily transform the blood-brain barrier mechanics.

One might consider the full complex disorder of evolving change in terms of how metastasis is an integral event in its own right. It is reasonable to consider a full development of statistical events that variably modify in a fluctuating fashion a whole series of transformations in the initiation and execution of pathways of linked consequence. One might recognize ongoing events as dynamic consequences of interest to a whole array of involved participants in the metastatic cascade[24].

## SEQUENTIAL CONSEQUENCE

Pathways of sequential consequence as linked events might incorporate a realization of modes of interaction of cellular components that biomolecularly evolve. In terms of such interaction, one might recognize a full diversity of consequences possibly redefining progression of such processes[25].

Metastasis are a realized interactivity of biomolecular species that progress as cellular phenotypes but that self-resolve eventually as focal groups of proliferative events both of tumor cells and of angiogenetic sprouts of endothelial cells[26]. Modeling pathways that schematically outline such evolution might help account for metastases that redefine dynamics of transfer across the blood-brain barrier with accumulative impact of biomolecular species.

## SYSTEMIC DISSEMINATION

Breast carcinoma spreads primarily as lymph node metastases that subsequently convert to a predominantly hematogeneous mode of spread via intervening cascades of intravasation within capillary and angiogenic vessels of proliferative potential[27]. Proliferation of cells particularly implicating interactions between neoplastic and endothelial cells appears a central operative mechanism in the dissemination of systemic metastatic deposits. Such neoplastic cell spread appears to originate in terms of consequence of events arising as stimulated proliferation of angiogenic vessels[27].

## MICROVESSEL DENSITY

Microvessel density within primary breast carcinomas would correlate with at tendency for promotion that underlies metastasis as a trophic event.

Cell receptivity might allow for a progression of events apart from strict dynamics of ligand binding. Estrogen induced transforming gene securin is abundantly expressed in breast carcinoma and associated with metastasis. Securin regulates sister chromatid separation during mitosis and induces bFGF-mediated angiogenesis[28]. It might prove significant that events of change in receptor modulation underlie the onset of a developmental progression that characterizes metastatic spread as a pathobiologic modification of stem cell biology. An increased activation of the Stat3-Bcl-2 pathway in estrogen receptor-negative metastatic breast cancer cell lines appears to contribute to chemoresistance[29]. Stem cell cultivation in bone marrow would represent a recharacterized series of processes that eventuate in pathobiologic transformation of metastatic spread of primary malignant neoplasms[30].

A reconstitution of events borne out by a metastatic process of spread as cascade events might underlie consequences that primarily develop as a full array of participating agents in promoting neoplastic progression[31].

## EXPRESSED METASTATIC PHENOTYPE

A fully expressed metastatic phenotype appears a constitutive derivative of functional hemodynamics that promote evolving cascades of spread of tumor cells[32].

Such a phenomenon would be an expression of modes of possible interaction between metastasis suppressor genes and a phenotypic determination of interactivity with endothelial cells. An evolving

endothelial cell reactivity appears as a possible basis for developing consequences of events related to spread of tumor cells both via the lymphatic and blood vessel route. It is apparent that a consequence of such evolving consequences might implicate a relative interactivity that temporarily increases in terms of progression. It is significant that temporal consequences of metastatic potential are a realization of modes of progression of cells via the circulatory system. A unique association exists between E-cadherin, systemic metastasis and proliferation potential in metastatic brain tumors[33].

Endothelial cells are a fully expressed series of interactivities that promote the evolution of pathways as evidenced by an array of operative factors of consequence mainly as evolving features of metastatic disease. Permeation and embolization of tumor cells are illustrative of events that indicate consequences marked by progression.

Interactions of endothelial with tumor cells would allow for the development of cellular phenotypes that delineate the subsequent expression of events borne out by thrombogenicity and hemodynamics as two expressive profiles of circulatory system progression.

## HEMODYNAMIC TURBULENCE

Indications of a metastatic potential would allow for the evolution of pathways borne out by hemodynamic turbulence in particular. Turbulence would allow for the development of interactive phenomena between endothelial cells and neoplastic cells that further differentiate. Differential divergence between endothelial and tumor cells would be in keeping with evolving consequences of eventual injury particularly to capillary beds and perivascular tissues as a secondary site of progression of such injury.

## ENDOTHELIAL INTERACTIVITY

Realized phenotypic expression of consequences of endothelial interaction with neoplastic cells might account for the development of a sequence of linked eventual steps that allow progression to phenotypic transformation. Included interventions in the progression of endothelial reactive patterns of interaction with neoplastic cells would perhaps be indicative of a whole array of events linked particularly to hemodynamic turbulence. It is in terms of such interactivity that progression will eventually prove a mainstay distinguishing factor in tumor metastasis.

A resolving issue in terms of metastatic potential relates to how primary tumors grow and enlarge in relation to their own supplying vessels[34]. One might view the consequences of increased size of organs by proliferating tumor masses a relative indication of modes of progression of the metastatic potential. One might allow for a tendency for invasion of blood vessels concurrent with increased proliferative size of the primary neoplasm[35]. In this manner, perhaps, progression of primary tumor size is a critical determinant in the subsequent intravasation of tumor cells within vessels.

Thrombogenicity and hemodynamic turbulence would potentiate a self-tendency for increased endothelial interactivity with circulating tumor cells in a manner particularly conducive to metastatic deposition of neoplastic cells. Vascular Endothelial Growth Factor appears related to relapse-free survival and overall survival in primary node-positive breast cancer after adjuvant endocrine treatment or adjuvant chemotherapy[36]. It is in terms arising from such considerations that hemodynamic spread evolves both as an original source of turbulence and as a final consequence of endothelial reactivity with metastatic clumps of tumor cells.

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