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Is Neoplastic Cell Infiltration and Spread a Differentiation of Systems in Progression?

Lawrence M Agius
Department of Pathology, St Luke's Hospital,
Gwardamangia University of Malta Medical School, Msida, Malta, Europe

Abstract: Evolving systems of developmental biology might implicate realized events that progress as cell proliferation and spread. Metastases of tumor cells appear to constitute a further characterization of such developmental systems in terms of how integrity of tissues is otherwise further maintained and supported by various contributing cell groups. Component factors appear to constitute a further development in cell biology that allow for the subsequent evolution of malignancy in terms of infiltration of a stroma that is proliferative also. Blood stream spread and lymph node deposits are further characterized as trophic phenomena within evolving contexts of either tumor cell proliferation or of stromal cell participation of such deposits. Only in terms of such evolving cell biologic systems as proliferation and hematogeneous spread can one better understand and delineate modes of interaction of proliferating tumor cells and stroma as integral representations of developmental tissue and cell systems. Differentiation is a constituent event in the evolution of pathways of development that allows for both characterization and phenotypic determination of events of malignant tumor cell proliferation and spread.

Key words: Neoplastic cell, infiltration, progression

BASAL STEM PROSTATIC CELLS OF VARIABLE DIFFERENTIATION

Differentiation of basal stem cells of the prostate either as secretory cells or as neoplastic cells may be considered as a largely bipolar form of divergent cellular development [1]. Neoplastic transformation in the prostate may be essentially relevant to biologic proliferation and derivation from basal stem cells. Malignant transformation would refer specifically to dynamics of divergent derivation from basal stem cells. The stem cell population would fluctuate biologically in terms of basal or parabasal attributes and as variable differentiation through to dedifferentiation of the stem cells. Plasma adiponectin levels appear negatively associated with histologic grade and disease stage of prostatic carcinoma[2].

Degree of differentiation of prostatic stem cells would vary with origin, derivation and progression of cells, through a series of steps in transformation of genetic attributes as upregulation or differential downregulation of gene expression.

Differentiation pathways would constitute proliferative capability spanning a full range of dedifferentiation events in terms of malignant transformation.

CHIMERIC FUSION OF GENES IN AN "INTEGRAL" GENOME

Chimera of the BCR-ABL may occur in a breakpoint cluster region of the central part of the BCR gene; this may occur in conjunction with translocation[3]. The creation of a "fusion" protein or proteins would constitute a transformation event that progresses beyond simple translocation and fusion of genes. Whole genome expression profiling may reveal signaling pathways in tumor spread, as in advanced papillary serous ovarian cancer[4].

Fusion would prove specifically chimeric beyond considerations of production of the fusion proteins. An essential chimeric mixture might resynthesize the nature of the gene region in terms of start-stop codons or promoter regions and also of abnormal protein molecular synthesis. Intergenic interactions might be disturbed due to a disturbed integrity of the genome subsequent to chimeric gene fusion.

Interactions between different genes and between different gene regions would give rise to the synthesis of abnormal protein products due to loss of genomic integrative interaction.

RECIPROCITY OF CELL PROLIFERATION VERSUS CELL DIFFERENTIATION EXERTED BY ESTROGEN

Estrogens would modulate cell proliferation and differentiation as a selective enhancement or selective inhibition of ligand binding to different isoforms of alpha- and beta- estrogen receptors [5].

This would apply also to progesterone and its A and B receptor forms in breast cancer cell proliferation and invasion[6].

Corresponding Author: Lawrence M Agius, 27 Ballarat, Guzeppi Caruana Str.tal-virtu, Rabat Rbt09, Malta Europe

Differential actions of estrogen and of estrogen receptor binding would depend on specific tissue and organ distribution as seen in the urogenital system, central nervous system and particularly in breast, endometrium and ovary.

Such a differential organ specificity of distribution of estrogen receptors and of specific isoform estrogen receptors might implicate a mechanism of established progression of the malignant neoplastic process that develops subsequent to the early carcinogenesis stage.

Neoplastic proliferation and spread would constitute a responsive series of events that evolve subsequent to the establishment of autonomous cell proliferation and of abnormal cell differentiation as a mutually reciprocal series of cause and effect phenomena.

RECEPROCITY OF ESTROGEN RECEPTOR ISOFORMS IN NEOPLASIA

Strict reciprocity of alpha estrogen receptors with beta estrogen receptors might constitute a transformational series of events involving switch activation of the receptors as primary phenomena of persistent receptivity[7].

Estrogen receptors may increase and decrease in terms of identifiable subtype as alpha and beta isoform due to reciprocity of isoform receptivity.

Reciprocity of estrogen receptivity would revolve around a series of conformational changes based on protein-protein molecular interactions. Such a main determinant would act within a context of either proximity of the receptor molecular subunits or of ligand binding and of post-binding activation/transcription of protein.

A given form of Estrogen receptor would be a source of possible modification in the establishment of fluctuation of receptivity as rhythmic establishment and progression of response of cells as in neoplastic cell proliferation and differentiation.

INTEGRAL GROUPS OF INFILTRATING TUMOR CELLS

Membrane scaffolding and transmembrane spanning domains would constitute a system of potential progression in terms of membrane signaling and growth of malignant neoplastic cells[8].

Membrane scaffolding would operate as a support system of membrane contact involved in cell-to-cell communication. Transmembrane spanning by caveolar molecules would constitute an integral biologic system.

Cellular dissociation affecting E-Cadherin/catenin complex during cell differentiation may be reversibly regulated during tumor progression and spread[9].

Infiltrating carcinomatous cells in breast primaries would implicate disordered cell-cell contact resulting in suppressive events in terms of cellular biologic progression.

Stimulated response would allow the involved tumor cell groups to progress as an integral pathobiologic focus. Type 1 insulin-like growth factor receptor signaling regulates tumor cell proliferation and differentiation and also participates in the metastasis of tumors[10].

Invasive breast carcinoma would implicate a whole integral group of transformed cells as basic units in the pathobiology of infiltrative tumor growth.

SUPPRESSOR GENE FUNCTION LOSS AND ONCOGENE ACTION

Suppressor gene function contrasts with oncogene action in terms of an individuality of fundamental biologic versus pathobiologic functionality [11]. These would refer to single integral molecules of identical or quasi-identical individuality.

A spectrum of variable action of suppressor genes might implicate pathobiologic distinction from oncogene action.

Methylation and hypermethylation of the promoter region of the Wilms' tumor suppressor gene (WTI) would account for such variability of action.

Methylation of gene promoter regions might actually implicate a mechanism of regulated exertion of dose suppressor gene effect.

Possible increase or decrease of suppressor gene effect might result from parameters of microenvironmental variables including hormones such as hyper-estrogens or age or nutritional germline factors. There might develop in particular an increased susceptibility to carcinogenesis in terms of proliferative events affecting terminal ductular-lobular units in the case of the breast.

ADAPTIVE RESPONSE TO MICROENVIRONMENTAL CHANGE BESIDES GERMLINE MUTATION

A fundamental aspect of the B1822V APC variant might relate to an intrinsic relationship with high or low fat intake in the context of germline mutations[12]. Such a relationship might call into question the validity of penetrance of such germline mutations as primary operative factors.

Such APC variants as B1822V would evolve via systems of adaptation that are distinct from operative germline mutation or of germline inheritance. Adaptive response via a number of possible pathways would not just involve a basic event of mutational change.

Hepatocyte growth factor, in particular, stimulates tumor cell interactions and migration and spread, implicating also matrix adhesion in breast carcinoma[13]. The genesis of mutational change might incorporate responsive adaptation to a wide variety of factors ranging from fat intake to phenomena depending on progression of adaptive response.

Carcinogenesis of the colon in terms of the APC gene would appear independent of any well-defined germline penetrant tendency of an APC mutation and would be regarded as an acquired change of an inherited trait. Environmental and dietary factors might condition the microenvironment of the colonic mucosa to change; persistence of such change would depend on exposure and response to such exposure.

CONTACT AND ADHERENCE INTERCELLULAR PROCESSES IN METASTATIC NEOPLASIA

A series of mechanistic steps would integrate cell differentiation processes as cell population integrity and cohesion[14]. Tumor cell metastasis would be contradistinctive to an integral cell population comprising tissues and organs.

Tumor cell metastases would implicate cell de-differentiation that disrupts tissue and organ integrity.

Vasoactive intestinal peptide regulates proliferation or differentiation of neoplastic cells[15].

Differentiation of cells would constitute tissue involvement in a manner that otherwise promotes tumor cell infiltration and metastases.

Cell integrity of whole cohesive tissues might implicate intercellular contact and adherence that influence cell differentiation and development.

A dynamically progressive process as cellular differentiation and the tissue integrity of organs might relate not simply to maintenance of intercellular contacts and adherence. CD24 is implicated in cell adhesion and tumor metastasis and with usually biologic aggressiveness[16]. A series of mechanisms would interactively allow cells to co-stimulate and co-inhibit development systems within an overall process of unity and identity of tissues. High CD40 (Tumor Necrosis Factor-alpha receptor) expression possibly is implicated in local infiltration and blood tumor spread[17].

ALLELIC AND CHROMOSOMAL INSTABILITY

Chromosomal instability might be considered as a process of progression of the carcinogenesis process and an integral event in tumorigenesis in terms of development of cell proliferation, infiltration and metastatic spread[18].

Alleleic inter-relationships and imbalance appear implicated in a carcinogenetic event involving in particular systems of progressive chromosomal instability.

Slower evolution of chromosomal instability of cells of colorectal carcinoma would be reflected in the intermediate stage of polyp formation. Increasingly variable dysplasia in the colorectal polyps would progressively transform into infiltrating carcinoma.

Progressive tumor cell infiltration and metastatic spread would actively acquire potential in terms of dimensions of instability and of interactive forces between individual cells. Contact inhibition and intercellular communication allow a progression of stromal and tumor cell participation as an active process of infiltration by the neoplastic cells.

An integral process of instability of genetic control or loss of suppressive gene expression might implicate neoplasia as progressive de-evolution. Progressive loss of genetic stability would evolve as alleles fail to counterbalance and to interactively integrate with each other.

FUNCTIONAL GENOMICS OF MALIGNANT TUMOR CELLS

Functional genomics as a differential expression profile of genes would be central to malignant cell proliferative, infiltrative and metastasizing activity[19]. Increased preferential gene expression would be involved in translation and protein synthesis.

Gene expression would relate to actual production of proteins within schemes of both transcription and translation. These would account for phenomena such as lymph node metastases involving colonization of proliferating tumor epithelial cells without an essential stromal component.

Functional genomics would be an expression machinery as interactive forces of facilitation and inhibition that constitute shifting of expression profiles that increase and decrease in terms of dynamics of the carcinomatous cell biology.

Selective advantage of carcinomatous cells would implicate proliferation, invasion, tumor angiogenesis, anti-apoptosis and spread. A high proliferative cell rate promotes infiltration by tumor cells within an overall context of both progressive anti-apoptosis and of advancing metastatic spread.

Malignancy is a pathobiologic process that constitutes a strong predisposition towards pathologic progression beyond simple concepts of cell biology.

STROMAL COLLAGEN DEGRADATION BY MATRIX METALLOPROTEINASES

Suppression of synthesis of matrix metalloproteinases would constitute inhibition of effective degradation of stromal collagen, largely in terms of action of retinoids as vitamin A analogs[20]. Matrix metalloproteinases mediate a broad range of effects on infiltrating tumor cells that include cell growth and differentiation, apoptosis and motility. Tumor cells would appear integrally involved in a growth phenomenon that arises primarily as infiltration of collagen and of stroma. Angiogenesis as a further component of stroma would implicate a series of events that degrade collagen including basement membrane, collagen types I and III. The Vascular Endothelial Growth Factor (VEGF)/VEGF-RII pathway regulates angiogenesis, local growth and spread of pancreatic carcinoma cells[21].

It is perhaps in terms of how collagenous stroma degrades that infiltration and angiogenesis would integrally comprise alternate aspects of tumor growth involved in cell proliferation and subsequent spread via metastases.

Expression of tissue inhibitors of matrix metalloproteinases depends on degree of tumor differentiation in laryngeal squamous carcinoma and these contribute to neoplastic progression[22].

CELLULAR PROCESS EXTENSION IN INFILTRATIVE SPREAD

Motile protrusions of the cancer cell membrane may very well prove a biologic basis not only for the active process of stromal infiltration but particularly for the established initiation of processes of conversion of the cell as a mechanism of induced autonomy[23].

One might view an essential aspect of cellular autonomous growth as largely a system of involvement that progresses largely as the elaboration of ruffling and of cellular extensions that allow prolonged interaction with stroma. A series of subsequent processes of modified intervention might develop that promote possible progression of the infiltrative process.

CLONAL ATTRIBUTES OF THE INFILTRATIVE TUMOR PROCESS

Inhibition of matrix metalloproteinases would appear an effective approach to eliminating a subsequent propensity for proliferation of tumor cells that are specifically infiltrative[24]. Stroma and epithelial cells of the prostate as a source of matrix metalloproteinases would promote further neoplastic infiltration in cases of prostatic carcinoma.

Fibronectin ligation supports survival of dormant breast cancer clones[30] as in bone marrow.

Infiltrative tumor would proliferate specifically in terms of both stromal and epithelial components of the neoplastic lesion. Specificities of interaction of stromal elements with epithelially derived components of the neoplasm might constitute a reactivity that progresses. E-cadherin is closely related to systemic neoplastic metastasis and proliferation of brain metastases[25]. E-cadherin expression in primary lung adenocarcinoma correlates with neoplastic differentiation and spread[26]. Clonal progression is an expression of such interactivity of stromal and epithelial components of the tumor and in metastatic deposits.

COORDINATING AUTOCRINE/PARACRINE ACTION

Lysophosphatidic acid (LPA) would act both in a paracrine and autocrine fashion on adipocytes and preadipocytes in a manner that includes a number of organs such as bowel, myocardium and muscle[27]. Dynamics of influence may coordinate a number of cell-growth related events on the basis of action of lysophosphatidic acid. Alpha2-adrenergic action might be based to an important extent on autocrine and paracrine action of LPA that thus coordinates myocardial with skeletal muscle action.

Coordinating autocrine/paracrine action would involve a tissue and organ functionality that transcends even cellular functional physiological concepts.

Leptin influences cellular differentiation and progression of carcinoma cells of the prostate and is a biomarker of total body fat[28].

CELL ADHESION IN THE PREVENTION OF METASTATIC TUMOR SPREAD

Cell signaling would correlate with cell adhesion and junctional complexes in terms of tumor suppressor function[15]. Id-1 protein is over-expressed in metastatic breast cancer cells [26]. Phakoglobin appears to constitute an essential function in terms of which the tumor cell would acquire, in its absence, the ability to invade or infiltrate and spread systemically. Various systems of intercellular communication would implicate a variety of cell adhesion functions that expressly result in tumor suppression.

ANGIOGENESIS INCORPORATES TUMOR CELL CLUMP SPREAD

Angiogenesis would constitute an integral component of the metastatic tumor process whereby

matrix metalloproteinases enzymatically breakdown matrix protein to induce the formation of new blood vessels[30].

VEGFR1+ hematopoietic progenitors are implicated in the regulation of metastasis[37], dictating also organ specific tumor spread.

Angiogenic tumor cell spread would culminate in invasion of the stroma and involve angiogenesis as concurrent invasion of the vessel wall and lumen by clumps of tumor cells.

A series of proteolytic events affecting stroma would entail tumor cell spread as a phenomenon of progressive angiogenesis.

INFILTRATING TUMOR CELLS INTERACTING WITH STROMA

Peritumoral stromal desmoplasia would incorporate a responsiveness to the stromal invasion[32]. Receptor ligand interactions are implicated especially in this process[33]. Neoplastic cell proliferation further promotes desmoplasia of the stroma. Peritumoral stroma would actively induce stromal invasion as a series of proliferative events. Proliferation of the neoplastic cells appears one facet of the infiltrative process of neoplastic cell growth. Transforming growth factor suppresses early tumor cell proliferation but promotes neoplastic progression and spread in advanced disease[34].

Gene expression would be a differential attribute of interactions of proliferating neoplastic cells that are actively infiltrating peritumoral desmoplastic stroma.

Various pathways characterized by receptor ligand binding may enhance modes of interactive participation of stroma with proliferating tumor cells.

Aberrant expression of trophic factors or their receptors (for example basic Fibroblastic Growth Factor and Platelet Derived Growth Factor) may affect tumor differentiation and support spread[35].

Enzymatic and receptor binding events would constitute endpathway events that are actively conducive to further creation of translational changes leading to overt transformation of infiltration to metastatic spread. Nitric oxide synthases enhance tumor cell proliferation and are implicated in spread of gastric carcinoma[36].

Likewise, the chemokine monocyte chemoattractant protein-1 promotes breast tumor growth and metastatic spread[37]. Increased stromal syndecan-1 expression together with its loss from the surface of cancer cells, may enhance tumor cell infiltration and spread[38]. Syndecans regulate cell adhesion proliferation and differentiation involving matrix binding[39].

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