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Integrative Systems of Trophic Modulation Centrally Evolving as Interactions Between Neoplastic Cell Proliferation, Stromal Infiltration and Angiogenesis

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Abstract: In terms of a distinctly delineated attribute of actively acquired progressiveness of cellular activity ranging from mitotic and meiotic division to cell infiltration and spread, one might strictly relate neoplastic cell division itself to an expression of subsequent pathologic neoplastic spread. In terms indeed of mitotic cell division that constitutes transformed meiotic cell division dynamics, it would perhaps be relevant to consider neoplastic progressiveness beyond simple cell dynamics of proliferative spread. It would indeed be simply within a context of evolving influence arising directly from mechanistic pathways of infiltrative growth that one might envisage proliferative neoplastic cell an integral axis of potential progressiveness particularly conducive also to multi-stratified increase in tumor grade and of subsequent tumor stage. It is perhaps in this sense that proliferative activity as an essential variation of basic schemes of meiotic division would relate to a diploid set of chromosomes ultimately related to a self-progressiveness of dynamics of such proliferative cell activity.

Key words: Trophic modulation, neoplastic cell proliferation, angiogenesis

INTRODUCTION

Indeed, one might perhaps further conceptualize inherent attributes of cellular infiltrative behaviour as intrinsic systems of progressiveness arising from such proliferative systems giving rise in the first instance to potential subsequent pathways of infiltrative and metastatic spread.

In simple terms, it is interesting to note an intensive mitotic cellular activity of neoplastic cells that inherently constitutes subsequent mechanistic evolution to local infiltration of spread of tissues in a context paradoxically that is systemic in terms of metastatic spread via lymphatics and blood vessels to various multiple organs in the body.

Progressiveness is the attribute primarily acquired with neoplastic transformation as with meningiomas: Increased expression of p73 with increasing grade of meningiomas[1] would be suggestive of an increased gene expression resulting from acquisition of various mechanisms contributing to increasing aggressiveness as exhibited by the meningioma. In this sense, particularly in view of the inherent tendency for any meningioma to infiltrate locally, the increased expression of p53 in parallel with increased aggressiveness but in the context of absent mutations of p73 would be suggestive of the infiltrative cell behaviour constituting a central pathway of progressiveness of such aggressiveness. This would be generally reflected in hypercellularity, atypical mitotic figures and brain infiltration[2]. Indeed, a direct gene target for p53 appears to be RTVP-1 (mRTPV- 1 , related to testes-specific, vespid, and pathogenesis proteins) with proapoptotic activities in cancer cell lines[3]. Also, in this regard, for example, differences in glycosylation state of fibronectin with reference to cell attachement and collagen binding domains in certain carcinomatous cell lines would appear related to progressiveness of the neoplastic process[4].

In simple terms, indeed, biologic aggressiveness of meningiomas as an essentially progressive attribute of the lesions would inherently progress as an attribute arising from the transformation event itself originally giving rise to the meningioma as a neoplastic lesion in the first place.

Therefore, increasing p73 expression concurrent with increasingly acquired aggressiveness of meningiomas would, contrary to a concept of suppressor gene function, actually constitute a marker of progressive. Such progressive transformation might actually go beyond simple delineation of concepts of simple neoplastic transformation in development of meningiomas as such. It might hence be valid to consider neoplastic progressiveness as forms of infiltration and metastases arising as directly evolving attributes of the neoplasm in terms strictly of a mechanism of proliferation determining phenomena of characterized transformational pathobiology. In this regard, for example, inducible nitric oxide synthase would appear implicated in the control of early malignant change as seen apparently in some cases of breast carcinogenesis[5]. In overall terms, perhaps, a concept of suppressor gene function and of strictly active oncogene function as phenomena of neoplastic

transformation would perhaps constitute a pathobiologic series of events operating in parallel with increased expression of other genes such as p73.

Such essential gene expressivity would somehow progressively develop in terms of lesions acquired primarily in the initial neoplastic transformational stage and progressing as essential pathogenesis of neoplastic pathways as manifested biologically in meningiomas and also particularly in recurrent cases of this tumor type [6].

It is certainly in view of the infiltrative nature of a meningioma that is generally recognized as benign but particularly as a lesion capable of an evolutionary progressiveness even of such infiltrative attributes constituting transformation that one might envisage active mechanistic pathways of acquisition of such essential progressivenes as primarily neoplastic. This attribute of progressiveness might in real terms constitute one primary event central to the essential neoplastic transformation giving rise to a lesion recognizable as a meningioma in the first place[7]. Also, DNA ploidy and S-phase function would appear to reliably indicate meningioma subtypes with a higher degree of aneuploidy and hence different biologic meningioma behaviour[8].

Is variability of growth factor effect central to a disordered trophic phenomenon involving an integral neoplastic transformation and progression event?: One simple pathway of variability of effect through manipulation of suppressing effect as exerted by Neurofibromin in terms of RAS-GTP action might in a unified fashion help explain the phenomenon of neurofibromatosis type 1 (NF1) in a manner to account for neoplastic development linked in various ways to a full spectrum of manifested developmental phacomatosis. Indeed, in a general sense, developmentally induced variability or noise might create systems of susceptibility that could subsequently promote cancerous change[1].

Certainly, one particularly interesting aspect is the phenomenon of a system development of benign Schwannomas and neurofibromas in NF1 that would incorporate especially a system characterized in part by dynamics of a malignant degenerative series of events as progressiveness affecting a previously present benign Schwannoma or neurofibroma.

It is perhaps in terms of strict dynamics of operability and transporation of various modifying factors influencing neurofibroma suppressive effect on RAS-GTP at multiple levels ranging from genomic DNA, RNA, and protein that one might better help explain aspects also of a highly dynamic variability in phenotypic expression in neurofibromatosis type 1. Indeed, in a manner linked inherently to a phenomenon of neoplastic development and also of malignant tumor development, one might perhaps regard meningiomas as aberrant expressions of growth versus infiltrative spread bordering conventional concepts of benign versus malignant neoplastic progressiveness.

Certainly, one might even consider the strict term malignant degeneration of a neoplasm as a phenomenon that would implicate besides degradative pathways particularly also an essential high degree of variability of effects in terms of cooperative interaction of growth factor (eg. Nerve Growth Factor) and RAS-GTP through disturbed transportation at DNA, RNA and protein level of variable suppressive action of neurofibromin. Indeed, for example, vascular neogenesis associated with cerebral tumor metastases would appear to parallel the degree of malignancy of the proliferative cells[9].

Also, it would appear highly significant that a paramount feature in determining biologic activity of a lesion lies largely with stromal infiltrative capabilities of the neoplastic cells, as seen for example with endometrial adenocarcinoma[10].

Is benign neoplasia distinct from those benign-behaving neoplasms potentially capable of subsequent malignant transformation in progressiveness?: A system of variability of effect that is either patterned or essentially unpatterned but created within a system of multi-level effect might actually directly implicate an interactive series of changes that beyond considerations of induced effect of suppression or of enhancement would actually constitute effective progressiveness as characteristic of neoplastic transformation. In this specific context, it would appear that tumor-stromal interactions would operate to significantly promote neoplastic progression apparently arising from aberrant growth factor receptivity. Such abnormally induced trophic effects might indeed implicate especially hematopoietic growth factors and inflammatory cells in the presence of also progressive angiogenesis[11,12].

Certainly, the phacomatosis complex of neurofibromatosis type 1 would appear to incorporate a spectrum of lesions that is primarily characterized by aspects of growth disturbance that would relate in various ways to tumor growth.

In this sense, for example, neoplastic growth and progression even in terms of neoplastic transformation, might not be understood specifically in terms of individual cellular phenomena but more definitively in terms of a phenomenon of body growth and of a lesion of disturbed growth characteristics within systems of body development and maintenance. Also, immune and inflammatory responses as constituted particularly by

prostaglandins and leukotrienes would potentially target specific clonogeneic progression of tumor transformation events[13].

In this sense, for example, the nerve sheath tumors of either benign or malignant nature and of brain gliomas in patients with neurofibromatosis of either type 1 or 2 would in addition involve aspects of localization of such disturbed growth phenomena as patterns that allow some characterization related to histologic attributes in terms of combined specific localization and histologic type as with of bilateral acoustic nerve Schwannoma.

Certainly, therefore, it might be true to consider neurofibromatosis as simply an integral manifestation of a phenomenal predisposition specifically in terms of neoplastic development and as applicable to a setting of inherent predisposition to definite but variable degrees of malignancy developing either as a denovo phenomenon or as a malignant transformation step of a previously benign behaving neoplasm.

Certainly, for example, malignant transformation of a previously established benign behaving neoplasm such as a Schwannoma or neurofibroma might actively constitute an essential property present from the start of development of that Schwannoma or neurofibroma in a manner that would help delineate a distinction between a truly benign neoplasm from a benign behaving one with however the added inherent predisposition to subsequent malignant transformation in progressiveness. Such considerations should however be kept in contextual frameworks of various modulatory type, including in particular modulated L-selectin ligand expression on endothelial cells in developing carcinogenetic foci[14].

A system of essential acquisition of predisposition that is nongenetic in the establishment of progressiveness in carcinogenesis: A system of non-genetic effect on lung cancer mortality might constitute a pathway that somehow allows nonsmoking itself to operate also in systems of development of lung cancer via mechanisms of predisposition versus nonpredisposition[15].

In this sense, for example, it might be relevant to consider systems of development as mechanisms that either allow or prevent to variable degree the development of a lung cancer within pathways that would essentially be classifiable in terms of either progressiveness or nonprogressiveness. In more general terms, vascular endothelial growth factor for example would modulate infiltrative attributes of neoplastic lesions arising within a context of operative interactions with nitric oxide, edema, hypoxia and active necrosis[16].

Within such a conceptual framework, perhaps, one might consider pathways of carcinogenesis not as primarily genetic but of a series of systems that either permit or actively cooperate in an overall mechanistic progression versus nonprogression in the development and establishment the neoplasm.

Also, however, p53 suppressor gene would induce apoptosis and suppress both cell growth and angiogenesis within specific operative systems of reduced matrix metalloproteinases and tumor invasiveness[17].

Even in basic terms, one particularly crucial mechanism in carcinogenesis might relate specifically to a step in establishment of the progressiveness of a lesion as it develops definitive attributes for further potential transformation.

Hence, within a system that is primarily nongenetic, as evidenced by a lack of increased incidence of lung cancer among monozygotic twins when compared to dizygotic twin pairs, one might consider the actual predisposing set of factors specifically related to the establishment of progressiveness of a pathologic lesion undergoing carcinogenesis as essentially acquired through various pathways of exposure to agents of interactive and cooperative nature in lesions such as primary adenocarcinoma of the lung. In terms of regulated morphogenesis and cellular differentiation, it would appear for example that cell-matrix interactions directly modulate the neoplastic process of growth and indeed perhaps the actual ongoing processes central to malignant transformation in progression[18].

Antiapoptosis cooperating with growth factors and oncogenes in tumor cell infiltrative action in an overall system of malignant transformation and progression: Cooperative action with oncogenes might constitute a system of divergent neoplastic transformation in a manner that might account for anti-apoptosis as a chief mechanism specifically concerned with malignancy rather than simply with neoplastic development.

In this sense, for example, malignant transformation might itself constitute systems of integration of anti-apoptosis within overall pathways of neoplastic cell proliferation as applicable to constituent groups of tumor cells.

Indeed, malignancy as a mechanism of acquisition of anti-apoptosis both by individual tumor cells as well as by groups of tumor cells might actually revolve around axes of progressiveness chiefly determined by character and dynamics of such acquired anti-apoptosis. On the other hand, TRAIL has been shown to effectively induce tumor cell death and even to kill human tumor xenografts in mice[19].

Indeed, for example, infiltrative behaviour and metastatic spread by malignant tumor cells might only partly be inter-related and as such only through such an axis of centrally operative anti-apoptosis[20]. For example, disturbed regulation of Helicobacter pylori-induced cell turnover of gastric mucosa would appear linked to malignant transformation within a context of reduced apoptotic activity and increased cellular mitoses[21].

Indeed, for example, metastatic spread of tumor cells as a constitutive phenomenon of metastatic tumor cell deposition in various tissues might actually constitute systems of progressive tumor cell growth within operative anti-apoptosis and operative tumor cell proliferation and infiltration.

Indeed, tumor cell infiltration as one essential pre-requisite for both metastatic tumor cell spread and metastatic deposition might in real terms constitute in itself anti-apoptosis operating through mechanisms of cooperative action with growth factors and oncogenes.

Considerations of apoptosis and anti-apoptosis via systems of both evolution and progression as patterns that would be pathologic rather than simply biologic: Growth factor-mediated protection through apoptosis might in a sense constitute instances whereby the initiation and progression of anti-apoptosis would evolve as a single type of pathway in a manner whereby apoptosis itself would integrate as a single system of mechanistic progression. Indeed, double strand DNA breaks would at times evolve as pathways implicating atypical mitoses of tumor cells as well as mitotic cell death pathways[22].

Certainly, within any system of evolution that is both suppressible and also actively suppressed, it might be in fact true to consider aspects of promotion and of report of a mechanism such as that of Bag1 (BCL2-associated athanogene 1) to constitute a central axis for both apoptosis and anti-apoptosis in purely biologic terms[23].

Indeed, it might be valid to consider Bag1 itself the agent that secondarily would biologically engender actual evolution of both apoptosis and anti-apoptosis within an operative axis that might embrace biology and pathobiology in terms of intergral pathologic dimension.

In this sense, one might better appreciate both apoptosis and anti-apoptosis as mechanisms of pathologic development and as mechanisms essentially beyond biologic constitution of life systems. It is in this sense, perhaps, that growth factor-mediated protection arising from apoptosis would constitute anti-apoptosis in a manner that is more fully pathologic rather than as a biologic form of cell protection within systems that both evolve and progress. In this regard, for example, hepatocyte growth factor/scatter factor would induce a microgliosis related to glioma infiltration and possibly chemokine-related mitogenesis of the tumor cells[24].

Certainly, in simple terms, cell system evolution along a course that progresses would perhaps technically and specifically distinguish a truly pathologic process from one of truly biologic nature in terms of protection or of lesion infliction. It is perhaps in terms of opposing modulatory influences as exerted by cytokines on angiogenesis and leukocyte/macrophage recruitment on the one hand, and on pathways of progressive tumor growth modulated by infiltrative behaviour that one might envisage active malignant transformation itself an inherent attribute of such neoplastic progressiveness[25].

Is cell cycle activity itself a paradoxical mode of prevention of cell cycle progression in terms also of completion of cell cycle activity?: Cyclins as partners of cyclin-dependent kinases might operate not simply in terms of regulatory functionality in cell cycle progression but as a system that would allow the development of stages of mRNA influence[26].

Indeed, perhaps, concepts of peak expression and of oscillation of influence in both the progression of stages of the cell cycle and also in the permissive progression from one stage to another of this cell cycle, would appear to depend on a single central axis of cyclin binding and unbinding.

In addition, it would appear that dysfunctional cell cyclical activity would critically disturb signal transduction systems as evidenced by caspase-3-dependent apoptosis caused by an immunosuppressant FTY720 on lymphocytes[27]. In this sense, for example, Hodgkin's disease would appear to progress both as mitotic and also as amitotic multiplication of neoplastic cells with reference to such systems as activation of cytokines and oncogenes and suppression of DNA repair genes[28].

In basic terms, somehow, incorporation as permissive development that paradoxically is conducive to a strict completion of the cell cycle might be considered as strict completion of the cell cycle in terms of only a secondary consequential nature.

It is perhaps reasonable to consider cell cycle activity as permissively progressive in terms that are contrary to a concept of strict completion of the cell cycle, and that progression of cell division is inherently one of biologic significance as far as cell cycle completion can or cannot be achieved in that particular instance of cell cycle activity. Furthermore, in terms of progressive DNA ploidy and of degrees of proliferation or as the S-phase fraction size, lesions such as breast carcinoma would appear to

parallel such parameters obtainable with flow cytometric analysis of the neoplastic cells[29].

Indeed, in terms that would simply have to take into account both an essential progressiveness of the cell cycle and also of the strict completion of such cell cycle activity, it might be true that cell cycle activity is an alternative form of completion of cell cycle activity in terms of prior and subsequent cell cycle progression as applicable to processes such as DNA coding, protein synthesis, enzyme activity, and other cell biologic processes of receptivity and induced action.

Also, proliferative rates of tumor cells as with prostatic carcinoma, would carry prognostic significance as reflected in terms of the monoclonal antibody Ki-67 staining reaction[9] of the tumor cells.

Mitosis as an abnormal perversion of the process of meiosis in preventing dna material exchange between cells: Checkpoint kinase 2[30] as a mechanism of induced cell cycle nonprogression secondary to DNA damage and replication blocks might actually constitute a biologic bridging point between meiosis as seen in testis, for example, and mitosis as seen in spleen, colon and peripheral blood leukocytes.

Certainly, as a system that would implicate cell mitosis as a modified form of meiosis, it might be reasonable to consider such mitosis as a progressiveness in terms of an extra DNA division stage in a process that allows preservation of the diploid complement of chromosomes.

In this sense, meiosis as a mechanism that is centrally of significance in terms of cell biologic evolution, and as a modification implicating mitotic events in terms of a necessity for DNA replication would be coupled strictly to a cell division as an integral event.

In this sense, perhaps, one might consider meiosis as simply a mechanism of preservation of DNA material that is primarily concerned with subsequent fertilization and the creation of a zygote. Mitosis as itself a mechanism of preservation of the diploid complement of chromosomes, would constitute a perverted form of meiosis whereby chromosomal interchange of DNA material fails to take place and to progress.

In such terms, perhaps, one might consider mitosis as an abnormal perversion of meiosis as the latter would normally constitute an effective pathway of DNA material exchange in the evolution of life forms in an added context of potential species preservation.

Multistratification of tumor suppressor gene function as reflected also in loss of such multi-stratification in cancer development and spread: Telomeric loci of tumor suppressive effect that specifically influence suppressor gene loci more centromerically situated might constitute a system of stratified suppressor effect in a manner that is integral to the often observed stepwise progression in carcinogenesis depicted for example in progressive degrees of severity of dysplasia to carcinoma in situ and to progressively higher grades of a given neoplastic lesion such as with an adenocarcinoma of the colon.

In this sense, for example, the general phenomenon of progression through successively higher grades of cancer in successively metastatic lesions of a given primary carcinoma, a phenomenon of telomeric influence exerted on suppression tumor genes such as the TP53[15] might actually help explain dynamics of metastatic spread of tumors.

Metastatic tumor spread might itself constitute successive steps of progression that integrally involve progressive loss of tumor suppressor gene function in a de-stratifying pattern of de-evolution. Indeed, also, for example, leukemic cells would tend to respond strongly to growth factors within a context of dysregulated growth control and/or of normal immunoregulatory mechanisms[31].

Indeed, tumor suppressor gene function might best be viewed as intrinsically a multi-stratification of effect allowing also a phenomenon of potential progressiveness of tumor cell growth and proliferation and of spread in an evolving context of successively higher grade and stage of tumor involvement.

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