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Paradoxical Systems of Patterned Autonomy in Uncoupled Neoplastic Cell Proliferation and Spread

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Abstract: Essential uncoupling of substrate metabolic and oxidative systems of supply and utilization by clones of neoplastic cells might correlate with various uncoupled phenomena of neoplastic cell proliferation and spread in specific patterns of carcinogenetic derivation and subsequent evolution. In this sense, the clonally based distributional patterns of intratumoral hypoxia and of various other pathobiologic effects of induced transformation ranging from angiogenesis to infiltrative spread of the neoplastic cells might constitute active modulation as exerted by active and passively acquired pathways of lost suppressor gene function. Indeed, one might speak of quantitative and qualitative systems of evolved influence that parallel each other and mirror fundamental uncoupling disturbances leading to a paradoxical series of systems characterized as patterned autonomous proliferation of malignant orimmortalized cells.

Key words: Paradoxical system, uncoupled, neoplastic, cell, autonomy

INTRODUCTION

A fundamental relationship appears to exist between sensitivity to chemotherapeutic agents on the one hand, and accumulation of tumor cells within a specific phase of the cell cycle such as for example the G1 phase checkpoint on the other[1]. In this sense, cis-platin sensitivity might actually be an inducible factor dependent for example on the actual percentage of tumor cells in a neoplasm that are in the S phase or else at a G1S checkpoint of progression to the S phase.

A simple concept whereby certain specific phases of the cell cycle are inherently constituted by a specific cell pattern of activity would necessarily appear to constitute a mechanism of increased susceptibility to a series of chemotherapeutic agents. On the other hand, mitochondria are an important target in overcoming resistance to TRAIL-induced apoptosis in colon carcinoma[2].

Sensitivity of tumor cells to a particular chemotherapeutic agent or regimen might actually constitute a system of lesion induction as this relates and affects pathways of progression of certain specific cell cycle phases of the tumor cells.

Also, for example, certain glioma cell lines may involve uncoupling of Epidermal Growth Factor Receptor (EGFR) autophosphorylation from signaling through AKT and ERK (extracellular signal-regulated kinase) and thus allow the establishment of resistance to specific EGFR inhibitors[3]. In this manner , human ovarian carcinomatous cells that are resistant to cisplatin invivo might be cells that have integrally suppressed pathways in preference to others, allowing such cells to bypass normally operative checkpoints in their cell cycle. In a basic sense, beyond even a concept of checkpoints in progression from one phase to another in the cell cycle, it might even be valid to consider an a priori cell cycle progression as itself a parameter in its own right and irrespective of any consideration of specific phases as the G1 or S phase. Indeed, a cell cycle progression might be a parameter that induces or suppresses any possible relevant role of specific checkpoints relating for example to malignant transformation process in terms of its origin and progression as purely carcinogenetic events.

Endothelin-1 overexpression as in ovarian carcinoma promotes tumor cell proliferation, survival, neovascularization and infiltrativeness through decreases in gap junctional intercellular communication, with escape from growth control[4].

Tumor cells as an integral tumor cell mass would constitute basic sets of distinctive parametric progression of the cell cycle that are largely independent of specific phase checkpoints of individual neoplastic cells.

Hypoxia in tumors determines threshold levels of autocrine loop operability in terms of growth, proliferation, apoptosis and anti-apoptosis: A concept of cellular adaptation to hypoxic conditions might implicate an integrative utilization of available oxygen in a manner that would promote metabolism derived as a direct

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function of insulin and insulin-like growth factor[5]. On the other hand, calcitriol, the hormonal form of vitamin D, interacts with Tumor Necrosis Factor alpha at the level of mitochondria in enhancing cell death that is mediated by reactive oxygen species[6].

Metabolic utilization of oxygen and of glucose would be pattern systems of adaptation to hypoxic effects on cells that would render them responsive even in terms of facilitated receptivity to trophic effect. Substrate availability, cellular enzymes carrier proteins and proton leak may be influenced by uncoupling protiens, peroxisome proliferator activated receptors[7].

Cells would be structured as mechanistic rendering of hypoxic sensitivity selectively inducing or suppressing pathways prone to integrally couple various systems of substrate utilization and metabolic rate control. Altered respiratory capacity and enzyme activities of tumor cells develop as a result of changes in cell size with cell cycle arrest as triggered by cell-death signaling pathways[8].

Malignant cells, with their high metabolic rate in often significantly hypoxic conditions might actually constitute terms of evolution that are responsive or highly responsive to such hypoxic adaptations. Vascular endothelial growth factor as a system of angiogenesis would perhaps evolve as an induction paradoxically based on responsive elements to hypoxia subsequently culminating in autonomous tumor cell proliferation and apparently equally autonomous systems of tumor cell apoptosis/antiapoptosis

It is significant that pharmacologic uncoupling of androgen receptor-mediated prostate cancer cell proliferation from prostate-specific androgen secretion is possible as a diverse system of androgen receptor-mediated transcription events[9].

Perhaps apoptosis of tumor cells would constitute a real rendering of autonomous autocrine loop operability whereby hypoxic conditions would determine specific threshold levels of such dynamic loop autocrine operability.

Hypoxic conditions might actually be a main determinant in operative modulation of a number of autocrine loops of responsive operability that would include in some paradoxical fashion also pathways of evolution involving tumor cell growth, proliferation, apoptosis, and anti-apoptosis. $Ca^{2}+$ plays a significant role in apoptosis and energy metabolism and appears affected by transforming growth factor beta 1; mitochondrial function promotes thus apoptosis of prostatic carcinoma cells[10].

Regeneration of cells through self-replication is deregulated in malignant cell transformation: A conceptual framework whereby cell proliferative activity incorporates an inherent suppression of apoptosis in a manner beyond defining influences of anti-apoptosis would perhaps constitute integral expression of trophic growth induction as effective manipulation of cell cycle dynamics[11].

Mitogenic activity may be an expression of a phenomenon that integrally induces anti-apoptosis in a specifically directed manner towards active participation of transforming biologic cell regeneration.

Small DNA virus proteins EIA and EIB from human Adenovirus and other oncoproteins such as E6 and E7 from human papillomavirus, and large T and small T antigens from SV40 can disrupt gatekeeper cellular functions at checkpoints that operate at multiple levels, and also caretaker functions. This would disrupt cell cycle and apoptotis, resulting in mitotic abnormalities and genomic instability[12].

Perhaps a concept of cell senescence might actually be suggestive of a series of biologic mechanisms that constitute pathways of regenerative activity of the cell through various mitogenic cell proliferative influences. In this sense, malignant transformation of cells might actually constitute mechanisms of such regenerative processes that are deregulated in terms of uncoupled trophic effect of anti-apoptosis.

The actual identity of the malignant transformation process might be a constitutive series of steps whereby cell biologic conversion evolves as progressiveness of amplified uncoupling of events of cell regenerative and proliferative type. Such a phenomenon may also be reflected in a phenomenon of uncoupling of otherwise overlapping systems of cancer immunity and autoimmunity[13].

Malignant cell transformation would involve a progressiveness of self-regeneration as self-replication within a context of anti-apoptosis that somehow self-sustains itself beyond any genetic induction or suppression.

Cellular pathways related to oncogenic transformation may arise as deregulation of signal transduction pathways with their subsequent uncoupling[14].

Suppressor gene function as parallel mechanisms of positive active induction and of passive mirroring in modulating gene expression: Chromatin remodeling, particularly as a phenomenon that modulates heterochromatin in a manner that involves histone deacetylases, might constitute systems of controlled gradation of activated gene expression related to overexpression as would be expected in blast crises of chronic myelogenous leukemia[15].

A normal phenomenon of maturational acquisition of controlled suppression of gene expression might actually be reflected in and indeed mediated by suppressive gene

activity by for example the Ikaros gene. Also, the zinc finger protein KRC that binds to V(D)J signal sequences interacting with kappaBeta motif, when lacking, increases cell proliferation, anchorage independent growth and uncouples nuclear/cell division. It thus acts as a tumor suppressor gene[16].

The actual validity of dominant negative isoforms of Ikaros might revolve around the reality or non-reality of suppression as an actively exerted modulatory effect. It is in this sense perhaps that one might have to consider suppressor gene function as a mechanism that actively incorporates both positive and negative modes of action. In this manner parallel events of fusion gene creation would evolve due to translation events as an insertion mutation or as a deletion mutation.

It is in this sense that one would conceive modulatory control of gene expression as in fact a phenomenon that somehow integrates a series of mechanisms paradoxically actively induced to mechanistic operability and also passively induced in terms of a reversal or mirror image of a positively active system of suppressor as exerted by that gene. Also, disruption of GRB2 protein complexes by high affinity molecules may effectively uncouple GRB2 adaptor protein with the Bcr portion of the Bcr-Abl fusion protein[17].

Are regionally heterogeneous hypoxia a marker of clonal proliferative pools of neoplastic cells?: Tumor environmental hypoxia appears essentially a regionally heterogeneous system based on a series of dynamic distribution of oxygen diffusion based primarily on vascularity of the lesion[18].

In a fundamental sense, the marked heterogeneity in degree of hypoxia in different regions of a neoplastic lesion might actually constitute an identifying marker of the actual growth of that lesion as this relates in turn not only to oxygen availability but also to a full variety of substrates such as glucose and blood supply.

In fact, a phenomenon of uncoupling of oxygen delivery reflected in peculiar blood supply distribution patterns would relate to fundamental disturbance in utilization of oxygen as neoplastic clonal proliferative events.

It is perhaps possible to recognize a simple series of mechanistic disturbances held accountable for a marked heterogeneity in distribution and degree of hypoxia in different regions of a neoplasm as derived attributes of uncoupled clonal proliferative events and subsidiary events of insufficient responsive effect.

It might even be possible to demonstrate not simply a heterogeneous scale of hypoxia but an actual fundamental disturbance in utilization of oxygen by different regions of a neoplastic lesion independent of blood supply; clonality of tumor proliferation superimposed on a basic background of aberrant angiogenesis would perhaps relate not simply to hypoxic stimuli but especially to a full array of phenomena inherently characterizing the neoplastic process itself as primarily uncoupling of metabolic and proliferative events.

Resistance to radiotherapy and tumor recurrence rate after surgery would constitute parameters arising directly from degree of spread of the neoplasm at time of presentation in a context of shifts of disturbed oxygen and of glucose utilization. Aberrant blood supply patterns in the neoplasm would also reflect directly active clonal evolution of tumor cell subpopulations that are inherently autonomous and largely independent of trophic induction. In further measure, the hypoxic microenvironment in many regions of such a neoplastic lesion would tend to create systems of subsequent utilization of any available oxygen as different regions of a clonally heterogeneous proliferative series of phenomena.

A fundamental paradox of qualitative transformation in quantiative terms as a process of carcinogenesis: A germline imbalance resulting in induced transcript expression of hMHL1 and hMHL2 alleles might actually represent a full category of conditions that in one way or another constitute a system of predisposition to, and also of potential origin for, full malignant transformation of colonic epithelial cells in the development of hereditary nonpolyposis colorectal cancer[19].

A system of evolution that is, in a significant sense, distinct from the two hit theory of carcinogenesis might actually consist of a systemic disturbance in the germline whereby mismatch DNA repair gene transcripts are expressed at a reduced level. A defect in gene expression such as this would be considered an integral operative system analogous to pathways possibly leading to cellular or neuro-degeneration. Possible predisposition of the individual to malignant transformation of tissue might directly implicate germline defects of repair genes as transforming events. A phenomenon of essential defect in mismatch transcript expression that is inbuilt in the germline of the individual's cells might operate in an interactive manner with a series of mutational changes in these same DNA mismatch repair genes in a mode that would allow progression to occur according to specific parameters of germline attributes.

It might be relevant to consider expression levels as a parameter that allows interactions between somatic and hereditary factors somehow conducive to progression along a pathway of evolving transformation to a

malignant phenotype. Hepatitis B virus frequently targets cellular genes involved in cell signaling and some of these may be preferential targets of the viral integration[20] .

It might even be relevant to consider progression as a relationship of threshold values that transcends quantitative aspects in qualitative terms. In a basic formulation of qualitative transformation it might be relevant to consider quantitative levels of expression in terms of levels of gene transcript expression that convert gene products to a distinct pathobiologic form of self-sustainment in production of such gene products. Resistance to mitochondrial and Fas-mediated apoptosis in leukemic cells develops with acquired resistance to 9-beta-D-arabinofuranosyl guanine with increased levels of Bcl-xL and a lack of Fas; this resistance to apoptosis may account for a general resistance to a number of anti-neoplastic drugs[21].

A stepwise progression in malignant transformation involving generic and histopathologic organ-specific categories of tumor suppressor genes: The concept of a system cluster of suppressor tumor genes on chromosome 4, both q and p arms, that is important in carcinogenesis of different type ranging from malignant mesothelioma to squamous cell lung cancer, to esophageal cancers and those of head and neck and skin besides neoplasms of bladder and of cervical, colorectal and hepatocellular type, might actually constitute a system that more than protects against such carcinogenesis even as a core of progressiveness for such carcinogenesis in genotypic terms[22].

Hence, perhaps, one might consider a series of target sites of allelic losses in multiple regions of chromosome 4 as the fundamental step in transformation of a cell that would subsequently be programmed to undergo further carcinogenesis in a progressive fashion.

Also, in this regard, pleiotropic drug resistance may be related to low mitochondrial membrane potential and the use of nonglucose carbon sources for mitochondrial oxygen consumption. There are also high levels of mitochondrial uncoupling protein 2 in drug resistant cancer cells[23].

In fact, the very progressiveness of carcinogenesis in both transformational genesis and in subsequent course of the neoplasm might be fully consonant with a series of programmed events arising from specific patterns of allelic loss on the p and q arms of chromosome 4. In this sense, perhaps, it might be valid to consider carcinogenesis itself as a primary pathobiologic event affecting a more different array of primary organ sites potentially causing a histopathologic variety of neoplasms.

In this sense, perhaps, one might actually categorize tumor suppressor genes into two main groups, one that is generic and another that is specific to a particular histopathologic or organ-type of neoplasm.

However, one might envisage a generic set of mutations or of allelic loss as a substitute for a series of secondarily affected tumor suppressor genes in a process of the stepwise progression of malignant transformation.

Uncoupling of intra-loop and inter-loop pathways of amplified progression in neoplastic cell interactivity and proliferation/cycling: Breast carcinogenesis appears to relate to a ductal/lobular proliferative series of events that constitutively progress not as transformation of either cell cycling or of cell-cell/cell-matrix interactivity but more as an amplified system of tight loop operability. Indeed, a working conceptual operability would perhaps be regarded as forms of intraloop progression and as systems of amplified interactivity that become essentially uncoupled from cell cycling. It would perhaps be in terms of such a progressively amplifying series of events that arise as uncoupled pathways of cell proliferation and of cell responsiveness that one would in various ways perhaps better understand how increased neoplastic cell division in fact constitutes integral tumor cell infiltration of the stroma in a manner that is clonal. Indeed, clonal cell division of neoplastic type would specifically involve infiltrative spread within contexts of amplified involvement.

Indeed, neoplastic tissue would somehow develop as an interactivity of cellular and matrix components that perhaps even promotes progressive uncoupling of a reactive nature.

One might speak of autonomous proliferation of neoplastic cells that would allow a progressive uncoupling of cell-cell and cell-matrix interactivity. Even in terms of such interactivity, however, one would perhaps recognize an amplification of intraloop and interloop participating roles towards trophic events of progression.

It is in terms of a progression intrinsically transforming that one might realize how cellular genetic aberrations develop and do become subject to interactivity of progressive intraloop components. Indeed, progressiveness of tumor cell proliferation and spread might correlate strictly with tighter loop operability in inducing an amplification of interactivity of intercellular and cellular matrix participation.

It is perhaps largely as a system of amplification based on progressive uncoupling and on progressive simplification of loop-interloop operability of such pathways as apoptosis/antiapoptosis, of cell cycling, of

cell adhesion related phenomena, and of participating pathways of trophic factor receptivity that one might better recognize neoplasia as a biologic simplification of amplified effectiveness toward increasing interactivity uncoupled from cell proliferative/cycling events.

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