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A Combined Scheme of Meiotic and Mitotic Events of Fusion/Hybridization Type in Neoplastic Generation

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Abstract: Even when one considers angiogenesis and a whole series of paraneoplastic events that evolve via transformation in their own right, the actual generation of a neoplastic lesion would be best viewed perhaps as a series of cell fusion/hybridization events. In such terms, DNA events would recombine and induce aneuploidy not simply via systems of aberrant proliferative activity but rather via pathways of aberrant control or loss of control at cell cycle checkpoints. Indeed, in terms especially of qualitative alterations of a meiosis-type series of events coupled to quantitative increases in cell proliferative rates, one might better view neoplastic generation a specific form of progression that develops in a setting of a whole series of epigenetic phenomena ranging from angiogenesis to stromal desmoplasia to metastatic spread. Neoplasia would constitute a de-suppression of pathways of progression in terms of aberrant cell cycle entry at checkpoints and also of aberrant cell cycle progression involving specifically cell fusion/hybridization events.

Key words: Hybridization,neoplastic,meiotio, mitotic

INTRODUCTION

Tumor necrosis as an essential hallmark of the endstage attributes of tumors: Tumor necrosis would in a real sense appear to constitute a series of events triggered by phenomena of sequence in a manner specifically unassociated with ischemia but centered on a process of evolving cellular damage primed by specific factors. It is this concept of priming that would account for tumor necrosis as a characteristic tendency to involve proliferative groups of cells that specifically are related to each other in a biologically evolving manner. In a sense, perhaps, tumor necrosis, more than being for example a distribution of effect zonally based on clonal derivation or on proliferative parameters, would actually constitute the superimposition of a full set of secondary developments that in some ways would complement processes such as clonal proliferation of tumor cells. In this regard, for example, genetic imbalance in preinvasive hypopharyngeal lesions provide evidence for cytogenetic heterogeneity. In cases of squamous cell carcinoma of the hypopharynx, there is evidence of amplification on chromosome 3q and genes on chromosomes 11q and 6p, with particular implication of chromosome 3q as a late event in the highly invasive capacity of these squamous cell carcinomas[1].

It may be even more realistic to consider clonality of tumor cells and of tumor cell proliferation as simply attributes that arise directly from etiologic factors of progression in a manner intrinsic to biology of tumors.

In this way, one might even consider tumor biology a fundamental progression that in some way paradoxically predisposes to the terminal process of tumor necrosis. Perhaps, one might actually consider tumors themselves as essentially endstage lesions in a manner that is intrinsic to all of their biologic attributes, particularly those expressed pathologically in their involvement of the patient.

Is progressiveness of cellular pathobiology a product of genomic instability and of the S phase as amplified mitotic activity in neoplasia?: Genomic stability versus instability appears largely a function of inhibition of mitotic cycle progression through the G1 checkpoint[2] In this sense, the S phase of the mitotic cycle might actually constitute a high point of genomic instability in a manner that would be controlled by p53 at the G1-S phase checkpoint.Aneuploidy and also particularly amplification phenomena might constitute systems of instability that both cause and result from a progressiveness of such genomic instability beyond considerations even of the conventional concept of homeostatic cell control.

Also, the anaphase promoting complex, although apparently functioning throughout the cell cycle as well as degrading mitotic cyclins in all proliferating cells, might or might not function during meiosis[3]. Indeed, a complex integration of epigenetic regulatory pathways with the chromatin infrastructure over target DNA loci appears to occur. Epigenetic regulation involves maintenance of states of gene expression, especially through repression,

in the face of repeated mitosis and frequently meiosis. In neoplasia, X-chromosome inactivation, imprinting, repetitive DNA silencing and aberrant methylation patterns are implicated[4]. In this sense, perhaps, beyond even strict considerations of genomic stability or instability, the mitotic cycle might be construed as the source of much of the natural progressiveness in cell biology and cell pathobiology. A multiplicity of mitotic spindles and chromocenters within a system of progressiveness seen not only in p53 null transgenic mice but particularly also in a full range of neoplastic lesions in the form of tripolar or other abnormal forms of mitotic figures, would in essence indicate amplification as a phenomenon particularly characteristic of genomic instability in terms of a system specifically concerned with progressiveness of cellular pathobiology.

Also, microtubule polymerization appears an important facet of the mammalian response to DNA damage. Indeed, microtubules play key roles in cell motility, mitosis and meiosis[5]. Microtubule-associated motor proteins appear involved in spindle formation and chromosome movements in mitosis and meiosis. Indeed, kinesin-like DNA binding protein (Kid) appears involved in regulating chromosomal movement along macrotubules during mitosis[6].

Is increased transition at the G1-s checkpoint and of DNA synthesis prime inducers of genomic instability and of concurrent increase in a poptosis: A system of p53 and p21 (Cyclin-dependent kinase inhibitor 1A or CDKN1A) expression would result not only in facilitated entry of the cell beyond the G1A checkpoint, but would necessarily also affect subsequent phases of the cell mitotic cycle in a manner particularly conducive to both general and specific manifestations of genomic instability[7].One might consider the G2/M transition checkpoint a fundamental consequence of events that would drive the cell through the initiation and maintenance of the S phase of the cycle via control of G1-S checkpoint.

Sand M phase initiation depend on the successful completion of the previous M and S phase, respectively, as well as entry into a resting state. Indeed, the S and the M cycle appear controlled by intra- and inter-cycle-dependent checkpoints in human somatic cells. Also, staurosporine sensitive kinases would act as a checkpoint network negatively controlling the initiation of S phase, M phase and cytokinesis rather than being inherent parts of a substrate-product change required for the initiation of the cell cycle phases[8].

Certainly for example, a simple mechanical model of cell cycling as a single integral system of suppressive control of entry into the S phase might actually operate by inducing DNA synthesis in actively promoting mitotic progression.

On the other hand, phosphorylation at a highly conserved serine residue (Ser-10) in the histone H3 tail is considered a crucial event for the onset of mitosis. Also, Aurora-A and Aurora-B proteins physically interact with the H3 tail and efficiently phosphorylate Ser 10. Indeed, both Aurora A and Aurora B are known to be overexpressed in a variety of human neoplasms, establishing a link between cell transformation, chromatin modifications and a specific kinase system[9]. Indeed, these two kinases may have distinct roles with different expression timing and subcellular localization during the cell cycle progression[10].

It might actually consider DNA synthesis a system of elongation of the DNA bihilar helix in terms of a mechanism allowing the cell to transverse the G2M checkpoint via systems related to net accumulation of DNA material specifically conducive to further cell division.

In this regard, also, the human PRK gene, which encodes a protein serine/threonine kinase of the polo family, plays an essential role in regulating meiosis and mitosis. In fact, PRK regulates G2/M transition and cell cycle progression and its deregulated expression would appear to contribute to tumor development[11]. The PRK kinase activity is relatively low during mitosis, G1 and G1/S and peaks during late S and G2 stages of the cell cycle[12].

A system that would also include apoptosis as a mechanism of caspase activation in cleaving CDKN1A might conversely allow cells to enter the mitotic cell cycle in a manner strongly conducive to apoptosis of that cell in terms perhaps related to abnormalities of DNA content of that cell.

Tumor cell transformation as a strict and specific property of functionality of tumor suppressor genes concerned with prevention of cell biologic progressiveness: The one fundamental axis of central participation of a tumor suppressor gene as the main inducer of transformation of events, in terms of cell growth arrest and pathways generating a predisposition to apoptotic cell death, might actually constitute an expressive effect in terms that either permit or halt progression of cell biologic processing[13]. In this regard, stable interaction between the products of the BRCA1 and BRCA2 tumor suppressor genes appear to occur in mitotic and meiotic cells, associated with the activation of double-strand break repair of DNA and/or homologous recombination. In particular, BRCA1 appears involved in

the control of recombination and of genome integrity [14] or with terminal differentiation or final rounds of cell division[15]. Dysfunction of this pathway might be a general phenomenon in the majority of cases of hereditary breast and/or ovarian cancer[16]. BRCA1 and BRCA2 are expressed in a cell cycle dependent fashion in vitro and are regulated by similar or overlapping pathways in proliferating cells; moreover, they appear to have distinct roles during meiosis[11].

It might actually be in terms essentially inherent to gene suppressive effect that one would paradoxically best understand both the nature and the delimited mechanistic pathways of tumors as essentially progressive forms of cell biologic processing. Blood cell lines show increased sister chromatid exchange and yet are capable of repairing various DNA lesions. Cell lines from Bloom mice show elevated rates of mitotic recombination. Indeed, increased rate of Loss Of Heterozygosity (LOH) resulting from mitotic recombination in vivo constitutes the underlying mechanism causing tumor susceptibility in these Bloom mice[17].

Within the strictly induced confines of tumor suppressor gene functionality, one might better define differentiation and proliferation of cells not only as arrest of cell growth or as apoptosis but as simple mechanisms that tolerate progressiveness of main pathways of biologic cell activity.

In this sense, perhaps, tumor suppressor gene activity is indeed a function of cell biologic attributes specifically preventing any progression beyond simple concepts of homeostatic control. Homeostasis is an essential series of mechanisms primarily preventing progression of cell biologic processes in terms of inducing or preventing excessive cell growth and proliferation.

Is neoplastic cell transformation a somatic cell hybridization or fusion with meiosis-type dna transfer/recombination and also mitosis-type proliferative cell activity?: Regulating p53 stability would constitute a system of controlled cycle progression within a context of enhanced cell apoptosis, presumably either as a single pathway of cell suppression or else as independent pathways of cell biologic control[13]. Considering a strict concept of cell stability as synonymous with p53 stability, it might be valid to consider cell cycle progression and apoptosis as themselves strict mechanisms concerned specifically with enhancing cell stability.

The Ataxia-Telangiectasia M protein appears to sense double strand breaks particularly during meiosis and mitosis; it directly phosphorylates p53 and interacts with many molecules involved in homologous and nonhomologous double strand break repair as well as in cell signaling as a hierarchical kinase initiating many pathways simultaneously[19].

As mechanisms of enhanced cell stability, progression via the cell cycle would perhaps be viewed as pathways inherently anti-neoplastic in terms of mechanisms of control or de-control of cellular proliferation.

In this regard the c-mos gene and its protein product mos, components of the mitogen-activated protein kinase transduction pathway, are known to be involved in the control of meiosis and mitosis. Mos appears involved in neoplastic progression of a proportion of astrocytomas and may correlate in fact with tumor grade[20].

In terms of mechanisms inducing somatic cell fusion or hybridization, one might consider proliferation of neoplastic cells as a mechanism of aberrant combination of DNA transfer (analogous to a process as normally seen in meiosis) with a proliferative activity pattern (analogous to the mitotic series of events seen in normal somatic cells). In this sense, one might consider aspects of somatic cell hybridization or fusion as a central mechanism of malignant cell transformation that would perhaps account for meiosis-type transfer of analogous DNA material and recombination within a context of a proliferative-type activity analogous to that of normal somatic cells.

When one considers meiosis involving a reduction to the haploid complement of chromosomes in each of two daughter cells, one might consider tumorigenesis as a possible mechanism inherently involving re-distribution of chromosomal material according to patterns defined by such meiosis events.

In this regard, it is interesting to note that the fission yeast protein p73 res 2 is an essential component of the mitotic MBF complex as well as a master regulator of meiosis leading to either premitotic or premeiotic DNA synthesis[21] indeed, a single transcription factor would appear involved in the control of both mitotic and meiotic progression.

It might even be valid to consider a combination of features of meiosis with mitosis that on the one hand involve re-distribution of chromosomal material and on the other hand proliferative patterns of duplication of DNA with some attempt at preservation of the diploid DNA cell content as many neoplastic cell multiplication cycles.Recombination leading to Robertsonian rearrangements of whole arm chromosomal segments is common in meiosis but rare in mitosis[22].

Indeed, in terms of redistribution of DNA in meiosis-

type events, there would be expected to develop an unmasking of recessive gene expression in a manner subsequently coupled to increased proliferative cell activity concerned with repeated duplication of such unmasked haploid complements of chromosomes. Indeed, a significant frequency of mitotic recombination occurs in human tumors[23].

Such a series of events would on the one hand involve a qualitative rearrangement of DNA material influencing the haploid versus diploid DNA complement of daughter cells of meiotic type and on the other hand, an endless series of re-duplications of such altered and re-distributed DNA material as cell proliferative activity.

One might consider malignant neoplastic transformation as incorporating qualitative aspects of a meiotic-type process with the quantitative aspects of a mitotic-type event resulting in an integral neoplastic phenomenon that is inherently progressive.

Angiogenesis and neovascularization are suggestive of aberrant biologic variations in neoplastic transformation: Angiogenesis as a phenomenon of neovascularization might be associated with tumor cell proliferation in a manner both genetically and epigenetically associated with lesion progression[24]. Processes allowing the development of the neovascularization would not only support tumor growth but also constitute an essential aspect of tumor biology in terms particularly of progressiveness of neoplastic transformation. In this sense, the angiogenesis as part of lesions such as glioblastoma , would constitute a lesion that integrally forms part of the neoplasm that is paraneoplastic rather han frankly neoplastic in its biologic attributes.

It is this aspect of neovascularization in glioblastoma that would somehow be integral to neoplastic progression without however being biologically neoplastic that would perhaps be suggestive of a range of other epigenetic phenomena. One might actually consider angiogenesis a process of significant biologic relevance even in terms that go beyond a strict distinction from pathologic processes. In a real sense, perhaps, one might regard neoplasia an aberrant variation of the same basic processes that generate and maintain biologic pathways of progression in general and which would in a final analysis help account for such processes as cell proliferation and progressiveness that are contrary to a strict concept of uniquely evolving neoplasia.

Excessive cell growth rather than cell proliferation as involved in tumor development: Cell growth as an event that is counter-analogous to cell division might actually consist of a series of systems that are primarily of an inhibitory nature and which would prevent the onset of cell cycling in a manner specifically related to prevention of gene transcription[25].

In a manner that might paradoxically assign inhibitory pathways a central role in active cell growth, one might conceive central cell biologic events as activities that evolve in the essential absence of cell division.

In this sense, perhaps, in an overall simple scheme of regulatory inhibition of cell biologic processes, one might conceive of cell division events as pathways primarily concerned also with inhibiting cell growth. Hence, one might regard nondividing cell growth as a fundamental basis for biologic progression and for pathologic progressiveness as seen classically with neoplasia. In this sense, neoplastic transformation would primarily concern itself with a facilitatory potentiation of cell growth in a manner that would only secondarily result in a subsequent phenomenon of cell proliferation; the latter would only constitute a result of excessive cell growth beyond considerations even of strict biologic relevance. In a simple scheme of cause and effects, therefore, one might consider excessive cell growth as conceptually counter-analogous to excessive cell proliferation in terms of a central axis of progressiveness in tumor biologic development.

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