International Journal of Molecular Medicine and Advance Sciences 1 (4): 324-331, 2005

Disturbed Cell Cycle Dynamicsin Clonal Progressiveness Andclonal Necrosis of Neoplastic Cells- Chromatin Remodeling Versus Genetic Instability in Carcinogenesis

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Abstract: In terms of essential mechanics of development of the malignant phenotype, systems of evolutionary-type progression might specifically relate to chromatin-remodeling disturbances as a basic framework in inducing states of self progressive genetic instability. In view of the subsequent accompanying features involving progressive dedifferentiation and high mitotic activity, neoplastic lesions might paradoxically evolve as specific systems of interaction with a stroma of fibroblastic participation towards further enhanced genetic instability. Indeed, in a real sense, mutagenesis of tumor cells would appear to involve active participation of a stroma that both maintains and further induces increasing mutagenesis in terms of an increased mitotic activity of the tumor cells. In addition, apoptosis and necrosis of neoplastic tissue would themselves arise and evolve as additional mechanistic effects of such increased mitotic activity together with evolving genetic instability. Indeed, in simple terms, perhaps, systems of disturbed chromosomal segregation and of spindle disruption together with disturbed cell cycle checkpoint dynamics would account for both genetic instability and mutagenesis in a context of increasing mitotic activity involving also stromal participation towards infiltrative growth and spread of the neoplasm.

Key words: Disturbed cell cycle, chromatin, remodeling, neoplastic tissue, carcinogenesis

INTRODUCTION

CLONALITY OF GLIOBLASTOMA TUMOR CELLS AS THE CENTRAL BASIS FOR MOST OF THE PROPERTIES AND MANIFESTATIONS OF THIS LESION

Disruption of normal mechanisms for cell cycle regulation would appear particularly central to evolving carcinogenesis. In this connection, for example, the polo family mitotic regulators SAK and PLK are both aberrantly expressed in colorectal cancer[1]. However, in a more global sense, with regard to gliomas, for example, clonality of glioblastoma tumor cells would constitute a phenomenon intimately linked to the various sets of processes making up much of the histopathologic manifestations of the lesion including in particular the endothelial cell proliferation, the zones of tumor necrosis with their peripheral pseudopalisading, the marked nuclear pleomorphism and high mitotic rate and even the gemistocytic appearance of some of the tumor cells. It is in this context that one might consider the essential clonality of the tumor cells in terms of the parent tumor giving rise to various modes of manifestation arising directly as a consequence of dynamics of cellular proliferation and necrosis.

Indeed, in general terms, in various types of neoplasia and as exemplified well by neuroendocrine tumors, a multiplicity of genetic pathways might be deregulated towards the predisposition of neoplastic cell proliferation. Indeed, multiple endocrine neoplasia, von Hippel Lindau, Carney and even Recklinghausen and Tuberous Sclerosis syndromes would constitute a full panel of genetic disorders relating deleterious mutations to mitosis, DNA transcription, extracellular matrix production and transcriptional control of apoptosis and response to hypoxia and cellular stress[2].

The zones of necrosis would reflect in particular an impaired viability of clones of tumor cells arising from peculiar attributes of the clonal proliferative phenomenon—the derivation of a progressively enlarging cell pool from a single cell of origin in itself might perhaps tend to promote exposure to the effects of certain genetic defects within systems of single stem cell origin and of strict clonal expansion leading directly to progressive deterioration of cell genome with successive cell divisions. In this regard, for example, N-methyl-N-nitro-N-nitroso-guanidine (MNNG)

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during the initiation stage would induce G2/M arrest and apoptosis with increased expression of wild type p53, p27 and GADD45 proteins and down regulated mRNA level of cyclin B1 and upregulated mRNA level of cyclin G[3].

Indeed, the endothelial cell proliferation itself might essentially evolve as a clonal type form of cell proliferation. The mitotic figures often assume an abnormal configuration and would particularly tend to promote a phenomenon allied to that of tumor necrosis evolving also along clonal lines. Hence, clonality of tumor cell proliferation might itself manifest powerful mechanics of evolution in terms not only of progressive genetic injury to the tumor cells but particularly of exposure of these cells to either the progressive acquisition of increasing biologic aggressiveness or to generic forms of progressive deterioration in biologic viability of such tumor cells.

Whether in fact increasing aggressiveness is itself linked to impaired viability as strict forms of reference evolving biologically in terms of decreased potential to further potential malignant proliferation is unclear. Certainly, for example, high degrees of aggressive cellular injury might effectively constitute several different, even contrasting, sets of biologic attributes potentially detrimental to viability of such cells especially as phenomena of short versus long term evolving effect.

Certainly, within shifting frameworks of strict tumor cell clonality in glioblastoma multiforme in particular, the gemistocytic tumor astrocytic cells might actually involve directly consequences of cell division—as phenomena that would implicate specific subsets of the neoplastic cells as distinguished even morphologically.

Indeed, the monstrous, predominantly degenerated, tumor cells with their grotesque nuclei and abundant cytoplasm might actually implicate stages of consequence in terms specifically of mitotic activity on a strictly clonal basis of initiation and progression. Also, for Mxi1 (Mad family member involved in cell proliferation and differentiation) appears capable of acting as a tumor suppressor in human glioblastomas through a molecular mechanism involving the transcriptional down-regulation of cyclin B1 gene expression[4].

Indeed, in the same general terms of an evolving progression that is strictly neoplastic, closed communities of high cellular interaction between closely related clonally derived cells might essentially constitute an effectively high rate of emergence of expression of several genetic traits of disease, involving dynamic consequences of several successive cell divisions on a strictly clonal basis. Indeed, a strict concept of the single cell of origin for integral lesions such as a glioblastoma might paradoxically have to account for a whole spectrum of manifestations characterizing the lesion itself in terms of appearance and biology of highly heterogeneous patterns of evolution and consequence.

It is indeed in such terms of a strict recognition of clonality as a basic phenomenon pertaining initially to the actual derivation of whole subclones of tumor cells from a single parent cell and subsequently to a whole panorama of manifested effects, that both microscopically and biologically would evolve as an effectively integral glioblastoma multiforme, that one might especially recognize a suitable model for pure tumor cell kinetics and for subsequent development as a phenomenon of progressive aggressiveness that pathobiologically is subclonally based on necrosis versus proliferative consequences. In this regard, for example, mutations and decreased expression of mitotic checkpoint genes including hsMAD2 (mitotic arrest deficient 2) have been reported in cancer cell lines[3].

IS CLONAL CELL DIVISION A RESULT OF INITIAL PARTIAL DE-DIFFERENTIATION OF THE CELL, WITH SUBSEQUENT CLONALLY-INDUCED FURTHER PROGRESSIVE DE-DIFFERENTIATION LEADING TO T RUE MALIGNANT CELL TRANSFORMATION?

It I s perhaps essential to assume aspects of strict clonality of neoplastic cells as possibly central to tumorcell proliferation in terms that automatically would equate with a diagnosis of neoplastic systems of pathobiologic progression.

On the other hand, is a strictly nonclonal form of cellular proliferation necessarily always non-neoplastic? Is it possible in fact to have a proliferating neoplastic cell pool that is non-clonal?

Certainly, it would perhaps prove conceivably true that a number of different cell lines of origin in a specific region of an organ might occasionally undergo neoplastic transformation. Certainly, such lesions might more commonly give rise to systems of a hamartomatous-like nature rather than to morphologically typical systems of neoplastic proliferation. However, for example, with choristomas, where certain tissue elements exceed in amount, both absolutely and relatively, that of the tissue elements in the normal tissues, there are indeed features of excessive cell proliferation reminiscent of neoplasia.

A hemangioma, for example, might more closely resemble a neoplasm than a malformation. Certainly, for example, a stronger growth factor- induced effect coupled with certain intrinsic genetic attributes of endothelial or vascular-type cells might be directly implicated. A

distinguishing feature of ahemangioma, however, is its closely developmental type attributes. Indeed, certain of the processes responsible for the genesis of a hemangioma might actually closely evolve as systems closely allied to the genesis of a true neoplasm.

A particular feature of hemangiomas might in fact actually implicate essential arrest of the lesion in terms of a phenomenon theoretically evolving as a consequence of a wide variety of causes, ranging from intrinsic attributes of the proliferating cells themselves to failure of extracellular systems or cues of controlling influence. Is it possible to postulate, in fact, the characteristic arrest of growth of a hemangioma to a failure of extracellular cues in stimulating cell proliferation?

An analogous situation might apply in terms of benign intradermal melanocytic nevi—in these lesions there would actually evolve systems of migration of melanocytes from the dermo-epidermal junction down into the dermis, a phenomenon however that characteristically would implicate lateral symmetry and cytologic manifestations of maturation in the deeper regions of the nevus. Some factor might indeed constitute systems extrinsically evolving outside of the cells themselves. In terms in fact of factors successively operative in accounting for the strict lateral symmetry of the nevus, one might perhaps conceive of a phenomenon that would in addition become biologically or pathobiologically linked to actual systems of migration of the nevus cells from the dermo-epidermal junction down into the dermis.

It is indeed in terms of such a phenomenon of controlled cell migration within systems of evolving cell maturation applies to implicating whole populations of melanocytes within an integral lesion that an effective phenomenon capable of controlling and eventually arresting the growth and migration of nevus cells might progress in terms of subsequent full maturation that would strictly apply not only to individual cells but also to the entire group of nevus cells making up the lesion. One might perhaps conceive paradoxical systems of control as exerted by extracellular matrix somehow evolving themselves however as attributes of the proliferating and migrated cells themselves as seen with melanocytic nevi.

Hence, it might be valid to consider the existence of whole series of mechanistic pathways that are often successful in controlling and eventually fully arresting cell division and migration of integral groups of cells as melanocytes in a nevus. It is here that the essential difference between a lesion like a benign melanocytic nevus or a benign hemangioma so drastically differs from a population of truly neoplastic cells capable of malignant aggressive behavior; indeed perhaps, a concept of integral preservation of a melanocytic nevus or of a hemangioma would help a ccount for attributes of non-neoplastic proliferation drastically contrasting with the essential lack of lesion integrity with neoplasms so well typified by glioblastoma multiforme.

In this sense, aneuploidy could arise as a possible system of progression in malignant transformation, as a consequence of a phenomenon of genomic instability implicating in particular functional inactivation of pRb[5]. Also, for example, with hepatocellular carcinoma, aggressive biologic behavior such as vascular invasion and recurrence correlates with markedly altered apoptosis/mitosis ratio and with progressive accumulation of multiple genetic abnormalities[6].

In this regard, it is particularly interesting to consider the possible development of malignant transformation in a previously benign melanocytic nevus. Is this a real phenomenon? If so, what happens to allow for its development? Such considerations might have to be made in the context of the classical examples of spontaneous regression of malignant melanomas sometimes arising from melanocytic nevi.

Certainly, within a full scope of operative dynamics of a truly regional phenomenon affecting entire groups of cells within a lesion such as a melanocytic nevus, it is perhaps valid to consider the vital importance of the single nevus cells as individual constituents of the true integral nature of the nevus as a whole lesion.

Essentially programmed series of mechanisms[7] might possibly be operative that would allow strict interactions of whole cell populations with the immediate extracellular environment. This would appear particularly relevant in a context of mitosis as the potentially dangerous event in the cell cycle in terms of a driving foce in tumorigenesis and as a period of vulnerability of the cell to evolving chromosomal instability[8]. Also, for example, stromal fibroblasts would appear to activate p21 to induce increased transcription of secreted factors with mitogenic and anti-apoptotic activities[9]. Only by considering the essential operation of strictly coordinated systems of interaction can one perhaps account for the extraordinarily stereotyped patterns of behavior of all nevus cells as seen for example with typical benign melanocytic nevi.

In an important sense, of course, it is the nature of an essential phenomenon of nevus cell migration from the dermo-epidermal junction, through proliferation of such nevus cells that are allowed to evolve, that one might better recognize the melanocytic nevus as a distinctly integral lesion. The congenital melanocytic nevus would

attest to the possible proliferative activity not only of the junctional melanocytes but especially of epidermal elements and of adjacent follicular components as well. It would appear that cell proliferation is such a central abnormality in conceiving an integral identity to the melanocytic nevus that such cell proliferation would essentially directly implicate extracellular factors of influence in terms of peculiar attributes of the migration process of the nevus cells into the dermis.

Such considerations would appear to implicate also systems such as polo-like kinases (PLK) in regulating several stages of mitotic progression. Indeed, PLK1 overexpression is a negative prognostic factor in patients suffering from neoplasms ranging from non-small cell lung cancer, head and neck tumors, esophageal carcinomas to melanomas[10].

In other words, the containment process with melanocytic nevi would perhaps evolve in terms of strict relative consequence of extracellular mechanisms acting essentially as biologic mechanisms of the migratory process of the junctional melanocytes still capable of proliferating but controlled as effective systems of maturation, as evidenced by the deeper dermal melanocytes. In this sense, it is interesting to note that overexpression of cyclin D1 would enhance taxol induced mitotic death in MCF 7 human breast cancer cells via M2/G arrest related to reduced clonogenic surviva[11].

Perhaps, proliferating pools of melanocytes might constitute an integral nevus that is non-clonal and not derived from a single parent cells, simply as a consequence of attributes of an original whole lesion that evolves as a specifically nonclonal system. Indeed, the nature of the cell proliferative process might constitute an effectively benign melanocytic nevus only as far as an essential pattern of orderly cell proliferation is expansile and nonclonal beyond even strict considerations of melanocytic proliferation itself. In this sense, for example, Nedd 5 appears cell cycle dependent and increased in G2/M phase ; its interference would appear to affect cytokinesis and cell division[12]. What is the essential difference? What are the essential attributes arising from a purely clonal pattern of cell proliferation, linked consequently with the highly characteristic loss of control in orderly expansion of the lesion and subsequently with essentially defective cell differentiation and progressive growth of a lesion that is not integrally whole or integrally preserved but prone to infiltrative spread. In this regard, for example, Hepatitis B virus x protein that has been implicated in hepatocarcinogenesis, activates the p38 mitogen-activated protein kinase pathway in dedifferentiated hepatocytes as distinct from differentiated hepatocytes; indeed, px expression in the less differentiated hepatocyte 4 px-1 cells activates signaling pathways known to be activated in regenerating hepatocytes[13].

Certainly, a central phenomenon arising directly from the very nature of clonal dynamics of unrestricted infiltrative behavior of such clonally derived neoplastic cells might necessarily implicate the acquisition of true infiltrative behavior, a phenomenon that is distinct from the migratory behavior of melanocytes into the underlying dermis. Such considerations might account for benign nevus cells in axillary lymph nodes from a primary melanocytic nevus in the ipsilateral breast as simply variable degrees of loss of such a conceptual framework of integral whole of a lesion such as a melanocytic naevus.

Is it after all true that an important quantitative difference in the biologic properties as exhibited by neoplastic cells would contrast with normal melanocytic nevus cells simply as expressions of evolving systems of pathobiology that primarily are concerned with preservation or loss of integrity of lesions that are benign and nonfiltrative or less infiltrative and metastatic? Indeed, integrity of a lesion that is proliferative would constitute a benign versus a metastasizing lesion perhaps in terms of dynamics of evolving systems that would influence clonal patterns of such preservation or loss of integrity of the lesion biologically or pathobiologically.

Also, for example, the melanoma differentiation associated gene-7 would appear to potentially exert inhibitory effects in melanoma progression through induced apoptosis and G2/M cell cycle arrest, but not in normal human melanocytes[14].

Certainly, in a true sense, clonal proliferation is a progressive phenomenon, in a way in which a melanocytic nevus is not. Clonal cell proliferation would appear to be an essentially progressive lesion largely and primarily because it is clonal. A cell that persistently continues dividing apparently would develop into a clonal population of cells and would consequently progress in terms especially of preserved or lost integral identity of that proliferating lesion.

Persistent and intense cell proliferation in some way might achieve a certain threshold value at which point loss of cell controlling mechanisms might result in such phenomena of infiltration and of possible development of aggressive metastatic behavior largely referable to a conceptual loss of integrity of the lesion as a single whole. In this regard, for example, human Aurora A mitotic kinase when overexpressed in NIH 3T3 cells would lead to tumors in nude mice[15]. Also, increased mitotic

phosphorylation of histone H3 attributable to AIM-I Aurora B overexpression would contribute to chromosome number instability[16].

In this sense, it would appear true perhaps to consider clonal cell populations as indicative of the prior occurrence of intense proliferation of a single parent cell subsequently persisting or else progressing in terms of proliferative activity and of other attributes of a truly malignant lesion.

Such lines of reasoning might imply a primary phenomenon of persistently intense cell proliferation, in terms specifically that are clonal but somehow progressive pathobiologically. Such clonally expanding populations of cells would apparently evolve specifically as stereotyped loss of integral preservation of pathways of proliferation as evidenced by infiltrative spread.

Retinoblastoma gene, for example, would function as a tumor suppressor in terms of multiple biologic functions related to chromatin remodeling that would influencemitotic progression, faithful chromosomal segregation and structural remodeling of mitotic chromosomes. Indeed, the essential tumor suppressive action of Retinoblastoma gene would appear to arise directly as fundamental cellular functions in control of cell growth and differentiation[17] .

Hence, it might be in terms specifically of significant degrees of cell proliferation constituting a de-evolving or de-differentiating phenomenon that much of this de-differentiation would effectively prevent suppression of uncontrolled autonomous cell behavior and infiltration as seen with malignant neoplasia. As such, a truly malignant neoplasm would arise in terms of cell proliferative events that specifically would constitute de-differentiation of such cells—indeed, such processes of initial de-differentiation would apply beyond conceptual frameworks of suppressive influence but rather as de-evolution of clonal proliferative origin.

Hence, de-differentiation and de-evolution would seem to constitute essentially staged phenomena, driven beyond a certain threshold of control as reflected presumably in terms of quantitative degrees of the de-differentiation itself and leading to the generation of a malignant neoplasm. In this regard, for example, Rad6 would appear an important ubiquitin-conjugating enzyme that might play a significant role in maintenance of genomic integrity of mammalian cells. Deregulated expression of Rad6 might be important in phenotypic expression of malignancy as a key player in postreplication repair and induced mutagenesis[18].

The clonal nature of a truly malignant neoplasm might itself involve a particularly reliable marker for the neoplastic nature of the lesion, in terms of influence developing through previous staged processes of de-differentiation[19] of cells that subsequently undergo further clonal cell division.

In a sense, perhaps, a vicious cycle relationship might evolve specifically as clonal division and de-differentiation in terms of an initial cell proliferation, subsequently persisting as clonal proliferation of self-progressive severity. In this regard, for example, deregulated DNA polymerase beta would appear to induce chromosome instability and tumorigenesis through he genesis of aneuploidy, abnormal localization of the centrosome-associated gamma-tubulin protein during mitosis and deficient mitotic checkpoints in nude immunodeficient mice[20]. Also, overexpression of B cyclins in particular would appear to result in alteration of the spindle checkpoint and to chromosomal instability[21].

DOES A CLONAL PHENOMENON OF APOPTOTIC CELL DEATH OCCUR, INVOLVING ENTIRE SUBPOPULATIONS OF TUMOR CELLS?

What is the essential link between apoptosis and necrosis? Is there a possible pathway of progression from a state of individual cell death that is self-programmed by that cell and a phenomenon of conglomerate groups of cell death showing morphologic evidence of such cell death?

Is it reasonable to suppose, in other words, that whole subpopulations of cells can self-program their own death first and foremost as a paradoxical phenomenon involving whole confluent groups of cells rather than occurring on an essentially individual cell basis? In this regard, also, a fundamental difference appears to exist at the gene expression level between the molecular mechanism of reversible G2 delay that follows mild DNA damage and the mechanism of permanent G2 arrest that follows more severe DNA damage[22].

In other words, can mechanisms exist that would essentially induce a whole regional phenomenon of cell-directed death of these same cells?[23]. Such a situation might conceivably arise if one assumes that whole subpopulations of cells do carry a basic defect that would specifically promote cell death on a clonal basis.

It is conceivable that clonal tumor cell death might in actual fact constitute a real phenomenon and that this is essentially dependent on genetic defects of a stem cell that are transmitted to all its daughter cells and that such genetic defects would expressly tend to promote apoptotic cell death on a clonal or confluent regional population basis. In this regard, an inverse relationship

appears to operate between apoptotic and mitotic index[24].

Indeed, it might be true that the apoptotic death phenomenon is essentially one evolving within the context of the individual cell, but specifically progressive in terms essentially of entire subpopulations of tumor cells. It is in such terms perhaps that a conceptual framework of phenomena of a clonal nature in terms of occurrence and evolution would perhaps constitute an effective pathobiology of progressiveness in neoplasms that both arise and evolve as a clonal system of lost integrity of the single lesion of origin. In simple terms, malignant neoplasia constitutes a pathobiologic loss of integral identity of the lesion that clonally progresses.

CLONAL TUMOR CELL NECROSIS AS A FUNCTION OF ILL-PREPARED CELLS WITH INCOMPLETE DNA REPLICATION AND THEIR SUBSEQUENT DISASTROUS MITOTIC PHASE ENTRY

It might be valid to consider apoptosis as at least partly due to suicidal entry of cells into the cell division cycle. Cells for example that would not have completed DNA replication might implicate many neoplastic cells, in terms specifically of entire subpopulations of embryonic cells during development subsequently induced to enter mitosis with disastrous consequences for those cells.

In general terms, apoptosis might simply evolve itself often as a primary disturbance in the regulation of entry of cells into the cell division cycle. In terms indeed of a situation that would implicate a disorder affecting primarily the cell cycle control mechanism, cyclin protein kinase or cyclin itself might be central players of mediated influence even in clonal progression of neoplastic proliferation. Also, for example, genetic and epigenetic inactivation of mitotic checkpoint genes hBUB1 and hBUBR1 would appear to contribute to a specific driving force in tumor metastasis and progression as a result of nonmutational as well as mutational events[25].

With regard to malignant neoplastic proliferation, such an occurrence of premature entry of the cells into the M or mitotic phase might simply reflect a widespread disturbance among the neoplastic cells in terms of disrupted DNA replication, rendering as a consequence previous mitotic cycles of the parent cells chief determinants of dynamics of subsequent clonal proliferative activity of the affected cells[26].

Clonal zones of necrosis of tumor cells might themselves be explained in terms of disastrous entry of tumor cells that are ill-prepared to sustain the integral process of mitotic division. Such a phenomenon would depend to an important extent on the characteristics of the mitotic division giving rise to the parent cell subsequently proliferating as a clone of defective cells with incomplete DNA replicative capability. In this sense, for example, compound haplo-insufficient (WD repeat proteins) Rae 1/Bub3 mice, although viable, would exhibit greater rates of premature sister chromatid separation and chromosome missegregation than single haplo-insufficient cells; in addition, such mitotic checkpoint defects would render cells more susceptible to dimethylbenzanthrene-induced tumorigenesis than wild-type mice[27].

CONCLUSIONS

It is with respect to systems of mechanistic progression as classically typified by mitotic cell division that one might better understand pathways of enhanced and amplified nature in the development of infiltrative and metastatic spread of neoplastic cells. Indeed, a conceptual framework of disordered chromatin remodeling might perhaps account for features of self-progression of the cell phenotype in terms of such features as aneuploidy and of genetic instability that are central to a mutagenesis in carcinogenesis. It is in such terms of disruption of systems ranging from centrosome disturbance to chromosome deseggregation that one might better appreciate the phenotypic characteristics of neoplastic cells ranging from increased and abnormal mitotic figures to large pleomorphic cell forms to systems of tumor necrosis within a contextual framework of evolving dedifferentiation and spread locally and systemically. In simple terms, a basic concept of disturbed mechanistic progression directly involving chromatin remodeling and segregation might perhaps best account for most of the phenotypic hallmarks of a self-progressive neoplastic lesion that is both proliferative and infiltrative in terms of genetic instability and enhanced mutagenesis.

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