International Journal of Moleculer Medicine and Advance Sciences., 1 (3): 262-267, 2005

Essential Uncoupling of Proliferation and Differentiation in Neoplastic Transformation

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

Abstract: An either/or integration of proliferative tumor cell events would perhaps relate to a stromal desmoplasia that strictly reflects also angiogenesis and metastatic spread. Indeed, it would be perhaps be in terms of a responsiveness to actively proliferating cells that one might define neoplastic cell infiltration and spread as simply an uncoupling of cell cycling and of gene expression. Indeed, a basic formula towards understanding neoplastic transformation might lie specifically with essential uncoupling of various phases of the cell division cycle and of the various forms of cell responsiveness conducive ultimately to an amplification of self-progressiveness. One might indeed recognize uncoupling of various systems of proliferative interaction as both arising and progressing in terms of neoplastic cell infiltration and metastatic spread. Even beyond simple equations of gene silencing and of programmed cell death, various mechanistic pathways of system uncoupling promote neoplastic progression in terms of transformation.

Key words: Prdiferation, neoplastic, transformation, uncoupling

INTRODUCTION

Phagocytosis as a mechanism linked to active individual cell apoptosis might actually convert the latter process to one inherently involving whole pools of cells with a potential for clonal attributes[1]. A mechanism that encompasses transformation transfer between different individual cells via phagocytic cell participation might actively transform a pool of cells into a clonogenic system of progressive cell proliferation; such clonal proliferation would tend to increasingly promote apoptosis within a context of rapidly expanding cell pools. Also, tumor suppressor gene products inhibit tumor cell proliferation by participating in activation of tumor cell differentiation. With impaired tumor suppressor gene function, differentiation stops with sustained proliferation of the cancer cell[2].

Determination of tumor cell clonality that integrally promotes not only apoptosis of individual constituent cells but especially in terms of transfection of genetic material intercellularly, might implicate phagocytosis as a mechanism of participating transfer of such genetic material.

Indeed, clonality would itself evolve largely as a phenomenon of both derivation and progression of cell processes dependent on systems of communication and transfer/exchange between clonally related cells. Also, for example, thymic stromal lymphopoietin is a cytokine that facilitates B lymphocyte differentiation and also costimulates T cells but is insufficient for cell proliferation through Stat 5 activation[3].

Neoplastic cell infiltration and spread would perhaps carry an inherent tendency for progression in terms of both grade and stage of that neoplastic lesion. It is in terms of a whole series of mechanisms allowing not only transfer and interchange of various genetic attributes but particulalry also a tendency for genetic reprogramming that one might realize holistic systems of carcinogenesis that integrate malignant transformation within frameworks of essential neoplastic progression. With endometrial carcinomas, P_{16}, P_{21} and Rb appear uncoupled from normal cell-cycle inhibiting function and cyclin E and cyclin B1 are directly implicated in proliferation and reduced differentiation of these neoplastic cells[4].

Does gene transmutation parallel analogous fusion/translocation events in malignant transformation?: A normal process of effects analogously paralleling translocation genetic events would appear to necessarily occur; for example, a family of p300 transcriptional coactivators would perhaps constitute one mechanism whereby translocation-like effects would implicate binding and fusion events between different transcription/expression sites in the genome at differential expression levels at signal response sites[5]. In this sense, perhaps, genomic transcription activities at both basal and differential expression levels might constitute a phenomenon integrally controlled and activated by one simple mechanism of binding proteins; these latter would

Corresponding Author: Tel: 356 21451752/ 356 25951663 Fax: 356 21224286

coactivate different sites in the genome in a way that normally would be specifically signal responsive. GADS as an adaptor protein involved in CD3 signaling links SLP-76 to LAT. It deficiency results in a severe block in proliferation of mature T lymphocytes that however still differentiate[6].

Androgen receptor mediated transcription of several genes determining cell growth and differentiation, on the other hand, may become uncoupled from induced prostate specific antigen expression in cases of prostatic adenocarcinoma[7].

In terms of fusion gene products as associated with 11, 16 translocations between MLL gene and the CBP gene, a phenomenon of superimposed progressiveness would involve gene transcription activation essentially independent of signal responsiveness. In myelodysplastic bone marrow, a distinct pattern of significantly increased proliferative activity becomes uncoupled from differentiation-associated gene activity[8].

Leukemogenesis might be characterized as a series of effects of genomic translocation that besides gene fusion would also entail disruption at the site of breakage/fusion of the two genes. This would contrast with the role of Stats in the regulated survival and proliferation of immature hematopoietic progenitors[9] and also in differentiation commitment related to endstage cell functionality. Failure of any re-established maintenance of continuity of the DNA strands or of integrity of the genome as a structure would perhaps implicate dynamic physical and biochemical events that perhaps are nonrandom in nature.

In a real way, perhaps, genomics fundamentally pivots on a degree tendency for instability not only in terms of transcriptional expression but especially in terms of a basic predisposition towards breakage-refusion of constituent genes that relate activator sites to other parameters of gene expression.

Somatic hypermutation may be involved in lymphomagenesis. Ongoing hypermutation during B cell proliferation occurs in post-transplant lymphoproliferative disorders in a setting of Epstein Barr virus infection. In Hodgkin's disease, unfavorable somatic Ig gene mutations of B cells appear to render immunoglobulin genes nonfunctional[10]. Also, in acute myeloid leukemia, there is uncoupling of proliferative from maturational signaling pathways as induced by granulocyte colony-stimulating factor receptor[11].

Actively programmed dedifferentiation versus apoptosis of the differentiated cell via systems of either/or: Peroxisome proliferator-activated receptor Y with its ligand binding would essentially appear to constitute a mechanism that actively reverts mechanistic pathways of dedifferentiation[12].

Cell differentiation appears a process involving active participation of many evolutionary cell biologic pathways converging in a predetermined manner on that cell genome that is inherently developmental in nature. In this way, a differential mechanism of regulated enterocyte proliferation and apoptosis is implicated in the adapting intestine[13]. With regard to hormone responsive cells, steroid-metabolizing enzymes may create an uncoupling of the microenvironment, often dominating systemic estrogens[14].

Perhaps, in an equally emphatic manner, it might be valid to consider dedifferentiation in neoplastic transformation as a truly acquired phenomenon of active dedifferentiation. In such terms, an alternative possible pathway to active dedifferentiaton on the part of a differentiated cell would constitute apoptosis that effectively terminates cellular biologic progressiveness and transformation. Negative growth control as either growth arrest or apoptosis may be uncoupled from differentiation via p53 dependent or independent pathways[15]. With regard to normal lymphoid homeostasis, however, CD95-based downregulation of activated B cells does not necessarily result in apoptosis of B cells[16].

Cell differentiation would perhaps primarily evolve as a phenomenon that is essentially individual to that cell in terms also of apoptosis. In this way, also, for example, p107 (a cell cycle regulatory protein) appears involved in terminal differentiation but not in proliferation of quiescent preadipocytes following hormonal stimulation[17]. Indeed, with regard for example to hematopoietic cells, agonist stimulated lineage commitment can be uncoupled from development[18] .

In a real sense, it might be realistic to consider dedifferentiation processes in neoplastic transformation and progression as the active acquisition of new biologic cellular attributes that become activated in terms of mitotic activity, hypertrophy and metaplasia in a manner determining even neoplastic progressiveness and further malignant transformation events.

Entry of T-lymphocytes into the cell cycle at the G0_G1 transition commitment point may uncouple the early expression of effector molecular functionality. In this way, clonal proliferation may occur during G0_G1 transition in a manner that also permits T cells to grow in size prior to initiation of T lymphocyte-mediated immune responses[19].

Is upstream deletion/mutation a common pathologic mechanism of transcriptional silencing of genes in neurodegeneration or neoplastic transformation?: Hypermethylation as a system that in some way regulates gene expression by a silencing mechanism might also be pathogenically related to a gene deletion constituting a more permanent form of mechanistic gene silencing[20] .

A concept of controlled genetic expression in terms of gradation in genetic silencing would perhaps implicate promoter sites for gene expression susceptible to hypermethylation as well as to deletion. In this sense, perhaps, the deletion of CpG islands, which constitute the promoters for some 60% of human genes, might actually be a major form of pathology exerting a full range of genetic silencing events in conditions ranging from neurodegeneration to neoplasia.

A particularly attractive aspect of a deletion of CpG islands might directly implicate inactivation of tumor suppressor genes that are inherently difficult to detect biologically.

Basic concepts of transcriptional promoter silencing that are independent of actual gene deletion might constitute mechanisms revolving around not only reversible states of hypermethylation but especially of more permanent forms of genetic silencing implicating even events upstream to the gene in question.

In this manner, Ras/extracellular signal-regulated kinase signaling appears dispensable during early CNS stem cell differentiation in the development of the post-mitotic neuronal phenotype[21].

Is a cycle of methylation-induced silencing of the mgmt promoter a determinant of genomic stability?: G to A transition mutation generation in K-ras would tend to persist in the presence of methylation inactivation of the promoter region of the DNA repair gene, O6-methylguanine-DNA methyltransferase, as seen with colorectal carcinogenesis[22]. In this sense, methylation might constitute a series of wave effects as methylation mutation O6 of the methylguanine DNA methyltransferase (MGMT) subsequently leads to serial genetic mutations of a non-random type.

DNA mutagenesis that, on the one hand, involves methylation of MGMT promoter region, and on the other, involves subsequent mutagenicity as a predisposition to MGMT promoter methylation, might potentially render the genome unstable in a manner sensitive to methylation/demethylation of the MGMT promoter region itself.

In this manner, perhaps, the state of methylation of the MGMT promoter region would constitute a measure of the degree of genomic instability relating specifically to gradations in difficulty in repair of C-G dinucleotides that would promote mutagenesis . Mutagenesis hence might actually be a function of stability or activation of DNA mismatch repair enzymes in a manner intrinsically incorporating a methylation/demethylation cycling of both silencing and nonsilencing events.

A prostatic tumor marker as a marker of carcinogenesis that parallels progressive tumor dedifferentiation: The conceptual significance of human Kallikrein 2 (HK-2) as an increased function of dedifferentiation, in a converse fashion to human Kallikrein 3 (Prostate specific Antigen, PSA) would constitute a system revolving around perhaps a mutual relationship between HK-2 and HK-3 that is pivoted on antiprotease binding[23]. In this sense, perhaps, the binding of HK-2 to Protease Inhibitor-6 in prostate cancer tissue would be determined by a release phenomenon from damaged and necrotic adenocarcinomatous cells that provoke the release of HK-2 and subsequent HK-2-PI-6 binding.

An increased tumor marker expression with progressive dedifferentiation of prostatic carcinomatous cells might constitute a marker of anaplasia fundamentally inherent to carcinogenesis as a primarily successive series of alternating transformation and progression events.

Perhaps it is in such terms that one might regard HK-2 as a marker of pathogenesis in prostatic carcinogenesis that identifies the neoplastic process of transformation as increased antibody staining.

The concept of a tumor marker that positively marks progressive dedifferentiation of the tumor would reflect directly the nature of the neoplastic tumor process not only in terms of progression but especially in terms of genesis and transformation towards increasing anaplasia pathobiologically.

Unchecked progressiveness of the s-phase in malignant transformation that is linked to apoptosis at random points of such a cell cycle?: Epithelial cell versus carcinomatous cell apoptosis of breast ductal origin would constitute a mechanism that distinguishes specific checkpoint failure of transition in the cell cycle of either the mammary epithelial cells or of the breast carcinomatous cells[24].

Cytodifferentiation response to estrogen becomes uncoupled from proliferative activity in response to estrogen as seen with sinus vaginal epithelium[25]. In this sense, perhaps, it might be more realistic to consider apoptosis of carcinoamtous cells as a phenomenon not specifically related to phases of the cell cycle whereas apoptosis of mammary epithelial cells would specifically relate to the cell cycle in a manner dependent especially on the specific inducing agent.

A concept of loss of specific cell cycle checkpoints as, for example, with carcinomatous keratinocytes, would perhaps implicate mechanisms of transformation of cell cycle dynamics affecting restriction points at G1-S and G2-M transitions promoting subsequent unrestricted progression in the S phase.

Is it possible to consider malignant cell proliferation as essentially one of unchecked S phase progression? Is it reasonable to consider malignant transformation as incorporating especially progressiveness of the S phase in a manner that would especially render that malignant cell susceptible to apoptosis?

Is in fact a fundamental disturbance in the unchecked progression of the S phase a pivotal point of reference in malignant phenotype characterization as reflected also in genotypic patterns of transformation that are inherently both progressive and unstable?

In a simple scheme of operative control of S phase progression in normal keratinocytes dependent on adhesion properties of such cells, it might perhaps be valid to link immortalization of cancerous kearatinocytes to their anchorage-independent proliferation.

Tumor cell infiltration and spread specifically evolving as carcinogenesis: Mismatch repair genes would appear to constitute a hereditary programmed predisposition to carcinogenesis more related to a sequence of events rather than as an actual system of carcinogenesis evolving through its initial steps of development[26].

Failure of effective mismatch repair of genes would possibly directly affect carcinogenesis as a strictly cyclical or acyclical process of progression that allows genetic instability to become manifested for example as microsatellite instability in aberrant colonic crypt foci.

It might be valid to consider an essential aspect of carcinogenesis as a process that incorporates a fully developed pathogenesis of subsequently determined systems of even transformed phenotype-genotype correlations.

Pathobiology of neoplasia would appear chiefly identifiable as a carcinogenesis coupled to progressiveness of such a neoplastic process that is inherent to tumor cell infiltration and spread.

Hence, perhaps, infiltrative tumor cell behavior and spread might actually constitute an integral aspect of the pathobiology of the carcinogenesis that specifically evolves and progresses in its own right.

Interactions with endothelial cells central to tumor cell infiltration, blood vessel invasion and spread: Endostatin as a suppressor not only of tumor angiogenesis but also towards the suppressed establishment of tumor metastatic deposits, would constitute an integration of processes affecting progression of tumor interactions with desmoplastic stroma on the one hand and progressive tumor cell interactions with blood vessel invasion, spread and metastases, on the other.

The fact that endostatin constitutes a fragment of the COOH-terminal domain of mouse collagen XVIII would appear suggestive of a single system of cause-effect whereby tumor angiogenesis promotes metastatic spread of tumor cells.

Tumor cell spread would constitute a simple mechanistic pathway centered on angiogenesis and on metastatic spread within a single operative system related to persistent endothelial proliferation.

Perhaps tumor cell infiltration with blood vessel invasion and metastatic spread might actually constitute different phases of interaction with proliferation and other biologic attributes of endothelial cell responsiveness. Indeed, tumor cell spread might largely function biologically, pathobiologically and pathologically as interactive potentiation between tumor cells and endothelial cells that arises and progresses largely in terms of amplified responsiveness to cellular proliferative events.

Does vegf potentiate endothelial cell angiogenesis and metastatic spread via blood and lymph: Tumor angiogenesis as induced by vascular endothelial growth factor and its receptors would constitute one overall complex of interactive effects contributing materially to the establishment of distant metastases[27].

VEGF might be directly implicated via mechanistic systems of tumor cell establishment in various organs.

For example, VEGFR-1 is expressed in osteoclasts and in VEGF-mediated blood vessel invasion it is coupled to cartilage resorption and bone formation.

Within various systems of dynamic interaction, VEGF would essentially integrate tumor cell infiltration with vascular invasion in terms of a single operative system allowing colonization and growth of metastatic deposits in organs such as brain, liver, and bone.

Endothelial cells with their VEGF receptors and VEGF induced effects would promote tumor angiogenesis that characterizes dynamism of the invasive process into blood vessels as reflected particularly in tumor cell deposition in various organs. VEGF might constitute an integral reactivity allowing a central unified role for endothelial cells not only in tumor angiogenesis but especially as promoters of tumor cell spread as specific metastatic systems of progression.

Desmoplastic stroma in tumor infiltration and angiogenesis and metastasis: Desmoplasia as a fundamental responsiveness would arise as a highly directed sequence of induced events subsequently promoting tumor cell proliferation consequent to stromal infiltration[28].

Stromal desmoplasia might condition the onset and progression of neoplastic cell infiltration as seen for example with pancreatic adenocarcinoma.

Biologic uncoupling of cellular growth from cellular proliferation would perhaps strictly characterize neoplastic cell infiltration as a stromal participation in induced potentiation of coupled neoplastic transformation and growth/proliferation events.

A full concert of growth factors including not only Transforming Growth Factor beta but also Connective Tissue Growth Factor and Platelet-derived Growth Factor might in some way also involve an interactive series of events to develop and progress specifically as infiltrative stromal desmoplasia.

It is this mutually effective relationship of progressive influences between proliferating and growing tumor cells and of the desmoplastic stroma that would account for an overall phenomenon of essential pre-requisites for infiltration also potentiating angiogenesis in terms of neoplastic metastatic spread.

REFERENCES.

1. Taille, A., M.W. Chen, M. Burchardt, D.K. Chopin and R. Buttyan, 1999. Apoptotic conversion: Evidence for exchange of genetic information between prostate cancer cells mediated by apoptosis. Cancer. Res., 59: 5461-5463.
2. Li, Z.R., R. Hromchak, A. Mudipalli and A. Block, 1998. Tumor suppressor proteins as regulators of cell differentiation. Cancer. Res., 58: 4282-7.
3. Isaksen DE, Baumann H, Zhou B, Novollet S *et al.*, 1995. Uncoupling of proliferation and Stat5 activation in thymic stromal lymphopoietin-mediated signal transduction. J. Immunol., 168: 3288-94.
4. Milde-Langosch, K., A.M. Bamberger, C. Golmann and E. Rossing, *et al.*, 2001. Expression of cell-cycle regulatory proteins in endometrial carcinomas: Correlations with hormone receptor status and clinicopathologic parameters. J. Cancer. Res. Clin. Oncol., 127: 537-44.
5. Hayashi, Y., Y. Honma, N. Niitsu and T. Taki, *et al.*, 2000. SN-1, a novel leukemic cell line with L(11;16) (Q_{23};P_{13}): Myeloid characteristics and resistance to retinoids and vitamin D3. Cancer. Res., 60: 1139-1145.
6. Yoder, J., C. Pham, Y.M. Iizuka and O. Kanagawa, *et al.*, 2001. Requirement for the SLP-76 adaptor GADS in T cell development Science., 291: 1987-91.
7. Sathya, G., C.Y. Chang, D. Kazmin, C.E. Cook, D.P. McDonnell, Pharmacological uncoupling of androgen receptor-mediated prostate cancer cell proliferation and prostate-specific antigen secretion. Cancer. Res., 63: 8029-36.
8. Lee, Y.T., L.D. Miller, A.N. Gubin and F. Makhlouf, *et al.*, 2001. Transcription patterning of uncoupled proliferation and differentiation in myelodysplastic bone marrow with erythroid-facused arrays. Blood, 98: 1914-21.
9. Smithgale, T.E., S.D. Briggs, S. Schreiner, E.C. Lerner, H. Cheng and M.B. Wilson, 2000. Control of myeloid differentiation and survival by Stats. Oncogene., 19: 2612-8.
10. Kuppers, R., 2003. Somatic hypermutation and B cell receptor selection in normal and transformed human B cells. Ann. NY. Acad. Sci., 987: 173-9.
11. White, S.M., M.H. Alarcon and D.J. Teardy, 2000. Inhibition of granulocyte colony stimulating factor-mediated myeloid maturation by low level expression of the differentiation-defective class IV granulocyte colony-stimulating factor receptor isoform. Blodo., 95: 3335-40.
12. Chang T.H. and E. Szabo, 2000. Induction of differentiation and apoptosis by ligands of peroxisome proliferator-activated receptor Y in non-small cell lung cancer. Cancer. Res., 60: 1129-1138.
13. Stern, L.E., R.A. Falcone Jr, C.J. Kemp, C.R. Erwin and B.W. Warner, 2000. (WAF1/CIP1) is required for the mitogenic response to intestinal resection J. Surg. Res., 90: 45-50.
14. Jakob, F., D. Homann and J. Adamski, 1995. Expression and regulation of aromatase and 17 beta-hydroxysteroid dehydrogenase type 4 in human type 4 in human THPI leukemia cells. J. Steroid. Biochem .Mol. Biol., 55: 555-63.
15. Liebermann, D.A., B. Hoffman and R.A. Steinman, 1995. Molecular controls of growth arrest and apoptosis: dependent and independent pathways. Oncogene., 11: 199-210.
16. Stohl, W., D. Xu, G.C. Sterling, P. Casali and P.A. Kiener, 2000. Promotion of activated human B cell apoptosis and inhibition of Ig production by soluble CD85 ligand: CD95-based downregulation of Ig production need not culminate in activated B cell death. Cell. Immunol., 203: 1-11.
17. Liu, K., Y. Guan, M.C. MacNicol, A.M. MacNicol, R.E. McGehee Jr, 2002. Early expression is associated with 3T3-L1 adipocyte differentiation. Mol. Cell Endocrinol., 194: 51-61.

18. Nicholls, S.E., C.M. Heyworth, T.M. Dexter, J.M. Lord, G.D. Johnson and A.D. Whetton, 1995. IL-4 promotes macrophage development by rapidly stimulating lineage restrictions of bipotent granulocyte-macrophage colony-forming cells. J. Immunol., 155: 845-853.
19. Lea, N.C., S.J. Orr, K. Stoeber, G.H. Williams, *et al.*, 2003. Commitment point during G0_G1 that controls entry into the cell cycle. Mol. Cell Biol., 23: 2351-2361.
20. Toyota, M., C. Ho, M. Ohe-Toyota, S.B. Baylin and J.P. Issa, 1999. Inactivation of CACNAIG, a T-type calcium channel gene, by aberrant methylation of its 5' CpG island in human tumors. Cancer. Res., 59 :4535-4541.
21. Enarsson, M., A. Erlandsson, H. Larsson, K. Forsberg-Nilsson, 2002. Extracellular signal-regulated protein kinase signaling is uncoupled from initial differentiation of central nervous system stem cells to neurons. Mol. Cancer Res., 1: 147-54.
22. Esteller, M., M. Toyota, M. Sanchez-Cespedes and G. Capella, *et al.*, 2000. Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is associated with G to A mutations in K-ras in colorectal tumorigenesis. Cancer Res., 60: 2368-2371.
23. Mikolagezyk, S.D., L.S. Millar, K.M. Marker, H.G. Rittenhous *et al.*, 1999. Identification of a novel complex between human kallikrein 2 and protease inhibitor-6 in prostate cancer tissue. Cancer. Res., 59: 3927-3930.
24. Zhang, Y., A.K. Rishi, M.I. Dawson and R. Tschang *et al.*, 2000. S-phase arrest and apoptosis induced in normal mammary epithelial cells by a novel retinoid Cancer. Res., 60: 2025-2032.
25. Boutin, E.L. and G.R. Cunha, 1997. Estrogen-induced epithelial proliferation and cornification are uncoupled in sinus vaginal epithelium associated with uterine stroma. Differentiation, 62: 171-8.
26. Pedroni, M., E. Sala, A. Scarselli and F. Borghi *et al.*, 2001. Microsatellite instability and mismatch-repair protein expression in hereditary and sporadic colorectal carcinogenesis. Cancer. Res., 61: 896-899.
27. Veikkola, T., M. Karkkainen, L. Claesson-Welsh, K. Alitalo, 2000. Regulation of angiogenesis via vascular endothelial growth factor receptors. Cancer. Res., 60: 203-212.
28. Lohr, M., C. Schmidt, J. Ringel and M. Kluth, *et al.*, 2001. Transforming growth factor beta 1 induces. desmoplasia in an experimental model of human pancreatic carcinoma. Cancer. Res., 61: 550-555.