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RESEARCH ARTICLE

GENE SIGNATURES AND GENE FUNCTION PROFILES IN CANCER MANIFESTATION – A REVIEW

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ABSTRACT

Two categories of genes namely, proto-oncogenes and tumor suppressor genes in the normal cells undergo mutations prior to malignant Transformation. Proto-oncogenes become oncogenic, whereas tumor suppressor genes are silenced to allow the mutational events in genome to accumulate. The malignant transformation involves initiation, promotion, dis-differentiation, differentiation, proliferation, progression and invasion. At every level of the transformation cascade, gene signatures are found. The cumulative increases of abnormal gene segments manifest in complete cancer phenotypic expression involving both gains and losses of metabolic functions and enables the disease progression to the fatal end in the continuum. Therapeutic intervention may be required at every level of these cascades. Such interventions may prevent initiation and promotion of malignant transformation and oncogenic differentiation at all levels. Studying the gene signatures at every level of malignant transformation is critical for personalized therapy for controlling lymph node and/or organ metastasis, as well as to improve both overall and disease-free survival of the cancer patients.

INTRODUCTION

As for the tumorigenesis process, research works over the past few decades have identified several genes whose functional gain or anergy leads to confer the cancer cell properties such as the autonomous proliferative activity, resistance to cell death cues, angiogenesis, altered cell adhesion, motility and evasion to host cells immune surveillance. After the growth and multiplication, the malignant cells acquire some new genic determinants prior to metastasis. Thus the success of malignant cell population depends upon the functional dynamics of a series of genic determinants. After metastasis post metastatic proliferation in the distant organs represent another area of interest in cancer pathogenesis and cancer mortality. In the case of naive tissue cell population the differentiated normal cells are endowed with two sets of genes viz., the proto oncogenes and tumour suppressor genes. Their frequencies in the cell population may be constant as long as the disturbing factors come into play in vivo and/or from the without. However, they may be like the cryptic genes, subject to alterations such as function gain or loss by the environmental cues. The inherent/imminent mutations in both sets of genes confer them the above functional gain or loss. Studies on tumour development have also analyzed their mutation frequencies and revealed that their sequential acquired abnormalities indicate the transition of normal state to tumourigenic state. Thus within the normal cell populations the two sets of genes viz proto oncogenes and tumour suppressor genes remain in differential

states of functionality viz,
Silent Proto oncogene – a (normal)
Active oncogene – A (Mutated)
Active Suppressor gene – b (normal)
Silent suppressor gene – B (Mutated)

When both sets have transformed into mutated state completely to fulfillment of the tumourgenic functions viz., unlimited proliferation, evasion of cell intrinsic and extrinsic constraints, attraction of a blood supply (Angiogenesis) the capacity to detach and move away from the original location, occur. Malignancy qualifying functions continue to remain throughout malignant progression. However the characteristic and diagnostic cancer attribute viz., the aggressive behavior of malignant cells to undergo metastasis needs besides the already altered gene mutations other genetic alterations remained also.

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For instance in most of the cancers the mutations/variations in such genes as the tumour suppressors have been unequivocally proved as the established cases of gene signatures (eg., BRCA1, BRCA2, TP53, MSH, Etc). In addition to these core genes, alterations or variations due to mutations in certain enzymes remain as markers for the manifestation of cancers. For example, E-cadherin a Ca^{++} dependent cell to cell adhesion molecule and mutation of the gene has been reported in various human non-cohesive cancers particularly in the familial gastric cancers (Guidford *et al*., 1998). Gastro-intestinal cancers due to gene expression signatures have been reported in the haplogroups of Japan, New Zealand, Maori, other europian populations and also in chinese, Caucasians and pacific Islander populations. Ramalingam and Indra (2013) have reported misense mutations in the E-cadherin gene segment in familial gastric cancers and not in healthy subjects. Moreover they have reported the substitution of isoleucine due to mis-sense mutation in all the ten patients. Such gene signatures expression and isoleucine substitution have been deduced to both familial and non-familial gastro-intestinal cancers by several investigators recently (Yin Wang *et al*., 2003; Guilford *et al*., 1998; Shinnurrial *et al*., 1999; Salahsor *et al*., 2001).

Yet another example to cite is the gene signature (mutation) in the 5,10 methylene tetrahydrofolate reductase gene (Ch 1) which hydrolyses the reduction of the substrate to 5-methylene tetra-hydrofolate. Ramalingam and Rajeswari (2011) (personal observation) who analysed the base sequences (220 base sequence forward and reverse) in cervical cancer patients revealed the four out of eleven showed conspicuous mutations in the gene segment which has a total base pairs of about 19322. It may not also be unexpected that similar changes throughout the base sequences elsewhere could have happened to add to the complexity of the cell profile changes.

Gene signatures in cancers

Studies have also revealed recently that additional genetic variations in the down line genes of core genes have occurred in several cancers. Despite such findings, it is still unclear, whether these variations should reach a threshold to make the aggressive cells to initiate metastasis and their dissemination. In case, the threshold reach is stochastic we can formulate and/or hypothesize that N be the total threshold and n1, n2, n3,…nx the cumulative occurrence of variations in the various segments of the genome and the time to reach the threshold is stochastic/random. Recent works have delineated that early stage tumour metastasis from the primary tumour mass as well as recurrence of metastasis both involve gene expression signatures as well as their suppression. For instance, Van de vijver (2002) V'ant veer *et al*.,(2002), Ramasamy *et al*.,(2003) have revealed 70 gene and 76 gene poor prognosticator or prognosis gene-signatures in the breast tumors respectively. Paik *et al*.,(2004) have obtained a 21 gene recurrence score for recurrence of metastasis in the breast cancer patients whose lymph nodes were metastasis free and who were treated with tamoxifen. A 186 gene invasion signature was derived by comparing normal breast epithelial cells with breast cancer samples that were enriched for tumorigenic cells (Liu *et al*., 2007). Further 18 gene lung metastasis signature was derived from breast cancer cells that selectively metastasized to the lungs.

Though all the above studies and their observations of gene signatures for both malignancy development and malignant cells metastasis indicate poor prognosis, they also obviate the operation of multiple oncogenic stimuli, deregulation of normal differentiation pathways and activation of oncogenic pathways. The above examples give a cue to the present hypothesis that the number of genic mutations that go on cumulatively increasing, are not finite but infinite and they are also stochastic or random.

Cancer clonal stem cells

The delineation of literature on cancer pronunciation and cancer metastasis thus reveals that the mutational potencies in the core gene faculties as well as in the down line gene segments contribute to the total gene prognosis signatures which in turn correlate to the various profiles of cancer phenotype expressions such as initiation stage, differentiation stage, sub-types classifications, malignant cells potential to aggressiveness, and their consequent metastasis and invasion, etc. Besides the above cancer cells proliferative and differentiational profiles, latest contributions brought to light the evolution of clonal stem cells (CSCs) populations in the case of solid tumours. They provide evidences that the CSCs represent an offshoot in the phylogenetic evolution of cancer cells within normal cell population of various tissues.

Cell surface marker studies on mammary tumorigenesis mouse models have revealed the presence of 1 -4 % of cancer population to have a highly enriched tumourigenic activity. These studies also suggest a clonal evolution or stochastic model of tumorigenesis. Their studies revealed the homogenous nature of these CSCs, both in solid as well as in haematologic malignancies. (Cho *et al.*, 2008). These studies also opined that mouse models may not be representative of human malignancies and thus cannot be extrapolated both in terms of diagnostic and therapeutic indices. Moreover, in human malignancies, invariably metastasis is the predominant cause of mortality in cancer patients. But its potential depends on multifarious factors. For epithelial malignancies, the epithelial mesenchymal transition (EMT) is crucial and the critical event in this transition is the disruption of epithelial cell homeostasis and the acquisition of a migratory mesenchymal phenotype. EMT or loss of differentiation has been linked to both metastasis and CSC properties. (Kaplan *et al.*, 2005; Mani *et al.*, 2007; Yang *et al.*, 2008). These studies adumbrate that cells undergoing the EMT could conceivably the precursors to metastatic CSCs. Since metastasis is effected with a tissue specific tropism in cancer cells in general and cancer stem cells in particular, they may acquire metastatic potential priori and migrate to the specific organ/tissue niches. Studies have also revealed that primary tumour cells generate a premetastatic niche through gene signatures and recruit progenitor cells to the tumour specific areas (Kaplan *et al.*, 2005). Probably, the tissue specific tropisms by the metastatic cells suggest that the recruited progenitor cells may acquire the metastatic potential at the primary site and transform to CSCs like the normal differentiation process of T-cells at the thymus tissue niche. Hence it may be inferred that the variable forms of gene – signatures in the cancer cells only promote the premetastastic properties and the CSC potential/metastatic potential. Only CSCs with specific expression of CD34+ receptor could induce

tumours in syngenic skin transplantation experiments and CD34- cells could not do, thus strengthens the above contention (Malanchi *et al.,* 2008) of the present review. Thus genes that mediate tumour formation initially and later the progression might not specifically mediate the steps of metastasis. On the other hand, specific metastasis genes after the functional gain or loss enable tumour cells to circulate, home to, penetrate and/or colonize distant organs, on the basis of their level of participation in the metastasis process.

Metastasis genes

Three classes of metastasis genes have been distinguished viz., i. metastasis initiation genes, ii. metastasis progression genes and iii. Metastasis virulence genes. After the completion of the function of tumorigenesis by internal/external cues to produce locally and provisionally aggressive tumour cell population, the new lease of metastasis genes may take up the next stage of disease progression/manifestation in the cancer continuum. Genes that are expressed conspicuously in the metastasizing cells reveal such new gene signatures.

Metastasis initiation genes provide an advantage in a primary tumour and pave the way for the tumour cells to escape into the circulation. Most genes that underline tumour cell motility, invasion or angiogenesis fell into this category. One documented examples is the caspase-8 genes, the loss of function of which favors dissemination by protecting tumour cells from apoptosis. Angiogenesis promoting genes make the dense malignant cells to be vascularized and to intravasate into circulation.

Secondly metastastic progression genes (MPGs) are another class of genes but found to be within gene-expression signatures that promote organ specific dissemination. It is a fact that distant organs maintain selective pressures and immunological competence/responsiveness against the invasion of any foreign cell types. For the cancer cells metastasizing to such target organs they have to overcome the above pressures in the later, similar to host tissues graft interaction in transplantations. The MPGs confer additional functions to the primary tumour cells reaching the target organs and in colonizing the same. Here the role of MHC genes in the metastasizing cancer cells and CSCs need to be understood. This area may give more insights about the polymorphic significance of HLA complex genes which confer adaptability to normal individuals, but promote immune unresponsiveness in the new target organs of diseased persons metastasized by the aggressive malignant cells seem to be a pertiment area in cancer metastasis.

MHC antigens and cancer cell metastasis

The immunological privileges enjoyed by the primary tumour cells metastasizing in the target organs which draw parallelism to the human placenta and the fetal tissue is to be understood. Invariably the low expression or no expression of HLA class Ia alleles (HLA-A, HLA-B and HLA-Cw) with concomitant increase in HLA class Ib alleles such as HLA-E, HLA-G, on cancer cells in several types of cancers. Such anergic gene function of MHC genes enable the tumour cells formation and proliferation under a protective atmosphere, free from the host immunological surveillance. Natali *et al.*,(1983), Hui *et al.*,(1984), Rosenthal *et al.*,(1984), Doyle *et al.*,(1985), Wallich *et al.*,(1985), Tanaka *et al.*,(1985), have demonstrated that early embryonic stem cells derived from murine embryonal carcinoma (EC) cells do not transcribe H-2 Class I genes. Moreover murine model studies have also revealed that oncogenic adenoviruses alter the transcriptional activity of class I genes which in turn cause the transition of normal cells to a malignant phenotype (Brickell *et al.,* 1983; Burgret and Kvist 1985). The neoplastic transformation by adeno viruses through loss of surface class I expression has also been documented. The above studies imply the role of MHC genes not only in the initiation and transformation of normal cells into cancer cells but also their further phenotypic transformation into clonal stem cells (CSCS) and their subsequent metastatic behavior.

Metastatic cells versus target tissue interaction

In the process of metastasizing cells reaching the target organs, the role of HLA/MHC genes in making the receiver cells/tissues may draw parallelism to that of placental tissue expressing public antigenic determinants such as “Pa” instead of private antigenic determinants, the former then do not elicit a destructive immune response but induce suppressor cells or factors. The tissue unresponse of placenta against embryological tissues has also been proved experimentally and unequivocally using anti MHC antibodies raised against the trophoblasts of rats, mice and human. The anti MHC antibodies reacted against public antigenic determinants. On the contrary, antisera raised against private MHC determinants did not bind to the placental/trophoblast tissues. The incompatible reactions between placenta and foetal tissues leading to spontaneous abortions have been traced to genetic mechanisms in both mice and humans. (Sunderland *et al.*,1981; Gatter *et al.*,1983; Misra *et al.*,1983; Tanaka *et al.*,1983; Ghani *et al.*,1984 a,b; Kawata *et al.*,1984; Redman *et al.*,1984). Similar mechanisms may be construed to happen in metastatic cells vergues target tissue interaction in view of the embroyonic characters being recapitulated in the cancer cells.

The metastatic cells reaching new target organs/tissues and their combined presence may evoke some host immune reactions. However both metastatic cells and the target tissue cells remaining free from the host immunosurveillance could be attributed to a successful and selective invasion mechanism of aggressive tumour cells and/or CSCs. In the interaction, the tumour cells or the target cells may release immunosuppressive factors through genic activation (gene signature – gain). Studies have already proved that trophoblast cells secreting immunosuppressive factors and the same released by the tumour cells counterpart exhibit certain biochemical and functional similarities (Hamaoka *et al.*,1983). Thus the interaction between metastastic cells and the target tissues cells shows similarity to the placental foetal tissue interactions. In this context, the genetic mechanisms and the proteomic factors that cause premature and perinatal death or foetal wastage may give a cue to employ such mechanisms to disrupt the target tissue – metastastic cancer cells/CSCs interactions. Studies conducted on women with recurrent spontaneous abortions revealed that their IgG isotype antibodies specific to the negatively charged phospholipid viz., cardiolipin caused

platelet membrane damage, endothelial wall injury, inhibition of prostacyclin and failure of protein C activity (Harris, *et al*., 1986; Canreas *et al*., 1982; Lyden *et al*., 1992). Another study implicated antiphosphoserine the most common phospholipid epitope and its antibody predominantly of the IgM isotype as an inhibitor of placental formation and a cause of spontaneuous abortions (RSA). Thus collateral usage of such antiphospholipid antibodies (APL) / aticardiolipin antibodies (ACL) which have been well documented to cause tissue damage alongside tumour specific antigen antibodies (TSA) may help in the induction of metastatic/cancer destruction. Such synergistic antibodies may prove to be suitable clinical agents for the therapeutic intervention in metastatic cancer patients in whom the cancer cells make a clandestine operation against their survival. In cancer continuum several prognostic factors play crucial roles in eliciting the gene signatures and their functional profiles. Fig 1 illustrates such factors which culminate cervical cancer manifestations (personal observation-Rajeswari 2011).

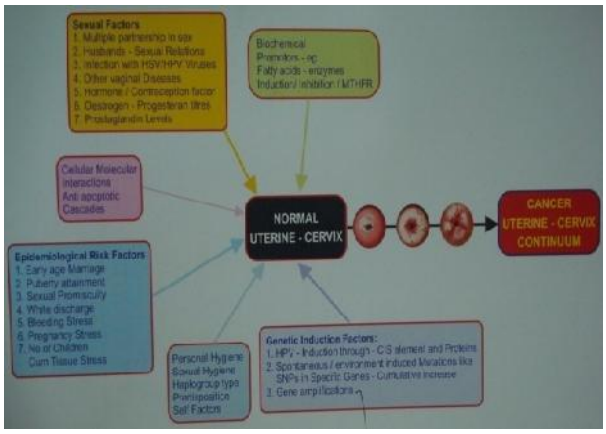

Fig 1 Prognostic factors and gene signatures in cancer continuum

CONCLUSION

Currently cancer chemotherapy has brought only partial success in reducing the tumour burden but with side effects to the patient. Though chemotherapy could eradicate primary tumour, cancer cells population evolve novel strategies like clonal stem cells which become radiation resistant and chemo resistant and have the capacity to undergo metastasis, remain quiescent with in a niche (target tissue) for a prolonged period and become activated once again in that growth permissive micro environment to continue their onslaught. Current chemo therapeutics have so far targeted the major pathways such as Hedgehog, Notch, Wnt, Ras-Raf and PTEN etc to reduce the tumour burden. Alongside chemotherapy, immunotherapy through antibodies against stem cell antigens may arrest the multipotent cancer stem cells and their recapitulation of the original tumour phenotype. In this context **t**he monoclonal antibodies prepared against clonal cancer stem cells antigens would be a promising strategy to contain such metastatic cells. Concurrently the monoclonal antibodies against the immuo suppressive factors also could enhance the natural immune cells activity against the metastatic cancer cells. The former strategy is in operation as of now. However the latter strategy is to be contemplated by the immuno tech laboratories. The experimental trials of such monoclonal antibodies raised against trophoblasts immune suppressive factors as well as, of the metastasized cancer stem cells would be a worthy therapeutic strategy in its own right.

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