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Diverse Multigenic Effect as Integral Genomic Pre-determinants of Disease Expression

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Abstract: Mutual alternative pathways of influence central to neoplastic disease development and progression appear based on a multiplicity of associated genetic lesions that are generated and expressed via common pathways of effective influence. Indeed, an integral participation of the organism would paradoxically account for central attributes of a selective vulnerability of cells to such environmental factors as hypoxia or carcinogenesis in a manner that reflects an integral genomic participation in such multiplicity of genetic lesion creation and expression in disease. Indeed, a strictly non-Mendelian series of susceptibility traits of an integral genome might help account for development of a neoplastic lesion in a given individual that integrally evolves both in terms of creation of further multiple genetic lesions in the involved genome and also in terms of subsequent expression of such created multiple genetic lesions in this given integral genome. In simple terms, a given neoplastic lesion that is generated and that progresses in a focal region of a given organ or tissue would paradoxically belie a multiplicity in predisposition to a combined creation and expression of genetic lesions within an integral genome of that individual patient. Such paradoxical aspects of neogenesis might help account for a participation of various genetic systems of influence that would associate in terms of pathways that allow the development of a neoplasm that proliferates and spreads only with reference to a contextual involvement of multiple genetic lesions and multiple gene expression of mutations, deletions, or translocations. In such terms, diseases ranging from neoplasms, atherosclerosis, diabetes mellitus, Alzheimer's disease, even schizophrenia and myocardial infarction, would perhaps evolve strictly as developmental systems of participation of essentially multiple genetic influences that are generated specifically within the integral context of one given genome of an individual.

Key words: Multigenic effect, integral, disease, gentic leison

INTRODUCTION

A central issue is the whole question of maintenance of various integral cellular processes that determine biologic vitaliity and viability of that cell. For example, the multigenic control of susceptibility to infection with certain human pathogens is beginning to be characterized by quantitative trait locus mapping in genome wide scans[1,2]. Also, the major histocompatibility complex contains a large number of genes relevant to the immune response belonging to different multi-genic families[3]. Certainly, strict consideration of the individual cell in terms of its viability, particularly the mechanisms responsible for maintenance of such viability would implicate also conceptually tissue and organ differentiation in terms of an integral organism and in terms of increased efficiency as for example in terms of circulatory dynamics or of oxygen delivery to tissues.

Also, for example, S100 protein, a multigene family of non-ubiquitous Ca(2+)-modulated proteins appears implicated in intracellular and extracellular regulatory activities involving enzyme activities, cytoskeletal dynamics, cell growth and differentiation and Ca(2+) homeostasis[4].

Indeed, viability of a given individual cell might constitute a primarily fallacious point of contention but would strictly necessitate considerations of organs such as the brain or heart as fundamental contributors towards even aspects of characterized viability of the individual neuron or individual cardiomyocyte. For example, familial hypertrophic cardiomyopathy has a complex multigenic background[5]. In this regard, considerable interest has developed in terms of modifier genes and protective alleles in modulating the phenotype of individuals with monogenic and multigenic traits and diseases[6].

For several reasons, it is particularly in terms of a whole supporting array of biologic systems of various tissue types, vasculature and nerve supply that make up such an organ as the heart or brain that one better understands concepts of viability and of increased

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vulnerability of cells as seen also in autoimmune disorders such as systemic sclerosis[7]. Also, for example, development of systemic lupus erythrematosus as a multigenic disorder of autoimmunity would appear to implicate Interleukin-4, -6 and beta 2-microglobulin as influenced by interferon gamma[8].

Systems of integral organ physiology, biology and also of organ pathology, might secondarily indirectly influence the individual parenchymal cell in terms of both viability and vulnerability pathways of progression.

In fact, it would appear that physiologic and pathologic aspects of involvement might in an important sense not be restricted simply to just cellular pathology. It would indeed appear fundamentally erroneous to regard the full scope of physiologic and of pathologic processes in terms of just cellular events of determined or predetermined character. There might exist a propensity for the development ultimately of incorporated systems of essential integrity of an organ or organism in terms of maintenance mechanisms ensuring viability of that organ or organism that specifically evolve or de-evolve. For example, multigenic aging would appear to possibly develop in association with increased concentrations of deleterious mutation on the mitochondrial and Y chromosomes[9].

In such terms, for example, various polymorphisms affecting activated protein C/factor V Leiden, prothrombin, protein C or S and antithrombin, as risk factors for thrombosis, would depend for their clinical expression on the coexistence of additional thrombophilic mutations or environmental conditions in inducing venous thromboembolism[10,11].

It is simply not enough to interpret pathologic lesions simply as events but that paradoxically essential elements of organ and organism would contribute in strictly characterized fashion towards determinations of state of biologic viability. Also, for example, different allelivariatons in the interleukin-12/interferon-gamma receptor 1 gene would appear to elevate or decrease the risk to tuberculosis in certain ethnic groups[12]. In other words, there are aspects of the very nature of physiology and pathology of organs and individuals that go far beyond cellular concepts of involved participation of various pathologic pathways. It is because of this reason that strict considerations of systems of selective vulnerability of the neuron, of neuronal viability and of specific viral neurotropism are simply different dynamic aspects of a core series of events that maintain or do not maintain biologic status or of recoverability. It would appear that the selective vulnerability of a neuron might incorporate simultaneously both a selectivity of effects implicating regional groups of neurons and also a specificity of cell types within contexts of regional distribution of such regions in brain or spinal cord as an organ. Only in this way might one realize a comprehensive scheme of selective vulnerability in terms applicable to systems such as selective vulnerability of the CA1 region of the hippocampal cortex.

In a sense, perhaps, the selective vulnerability of a particular neuron to a specific form of injury such as hypoxia would constitute only a visible or recognizable endresult of a whole series of integral mechanisms that manifest themselves simply with reference to susceptibility or progressiveness to neuronal death.

Such considerations might assume crucial significance in terms of mechanisms of maintained viability of cells as exemplified pathologically in various forms of neurodegeneration. Indeed, neurodegeneration might constitute active pathways of failed maintenance of mechanisms implicating specifically incorporated participation at various levels of cellular, tissue, organ and organism within one essential integration of biologic resolution or promotion of biologic events.

It is for such reasons that malignant transformation of a particular cell and of a particular cell type can be a fallacious concept of pathologic events. In a sense, malignant transformation is a disease of the whole body, not simply in terms of essential metastatic tumor spread and death of the organism, but particularly in terms of origin and progression of a lesion understood but as a transformation of biologic events and even as transformation of subsequent pathobiologic events.

In this sense, for example, Parkinson's disease would appear to constitute a multigenic disorder of the ubiquitin proteasome system involving both pathogenic mutations and polymorphisms of the 3 genes alpha synuclein, parkin and ubiquitin carboxy-terminal hydroxlase L_1[13].

It would appear fallacious to consider a neoplasm in terms of cell type of origin, or of specific organ of derivation, or even in terms of strict microscopic morphology or mitotic proliferative rate, or even in terms of an apparent strict carcinogenesis that specifically operates in terms of endogenous or of exogenous derivation. In this sense, indeed, for example, breast cancer is a very heterogenous and multigenic disease; molecular marks such as estrogen receptors, HER2-Neu and cathepsin D would help predict required targeted therapy in these patients[14].

Even concepts of hereditary predisposition to the subsequent possible development of a malignant neoplasm would essentially fail to account for occurrence of a malignant transformation process that evolves both as an event as a characterized generation and progressiveness of pathways such as Aurora A as a member of a multi-gene family of mitotic kinases[15].

Beyond all such considerations it would appear that an essential event develops in terms of the integrity of maintenance of homeostasis possibly reflected in dynamics of initial fertilization of the ovum. In this regard, for example, a small group of special genes are imprinted and result in only one of the parenteral alleles actually expressed in target cells—such epigenetic process would regulate different stages of development[16].

In some way, the fertilized ovum is itself so integral a unit that it would embody not only the source of the whole organism that especially include development of sources of influence affecting mechanisms with possible subsequent pathologic consequence, as malignant transformation of cells and tissues of an integral organism. In this connection, for example, genotypic polymorphism of nonhomologous end-joining genes would appear significantly associated with breast cancer risk susceptibility implicating multiple defects in DNA double strand break repair mechanisms[17].

Of course, what complicates so profoundly such a concept of the important determining role in terms of the nature and attributes incorporated within the fertilized ovum are possible forms of pathologic consequence arising from environmental processes influencing cells and the organism involved.

Indeed, even responses and compensatory mechanisms might be activated or de-activated in terms of consequences of environmental exposure that originate via systems of exogenous or endogenous systems of evolving consequence.

In this connection, for example, the next generation of human immunodeficiency virus type 1 vaccines would necessarily have to stimulate broad and durable cellular immune responses to multiple HIV antigens[18].

Also to be considered is a real phenomenon of increased susceptibility of the neuron in terms of for example hypoxia as contrasted with say the fibroblast. Hence, there would exist an integrative resolution of a vast range of factors determining selective vulnerability of the neuron to say hypoxia in a manner that would strictly characterize the hypoxic event itself and especially the environmental exposure to such hypoxia in a full setting of strict cell type. Indeed, cellular forms of life in general might incorporate components of vast integral dimensions towards resolution of biologic as well as pathobiologic events and pathways in terms applicable ultimately of the integral organism or individual patient.

In such terms, genomic instructions for development are encoded in arrays of regulatory DNA and specify large interactive gene networks in producing transcription factors and signaling components. Multigenic feedback loops and repressive regulatory interactions would operate within such networks[19].

Such considerations might further help delineate attributes recognizable as dynamics of participation of a single genome for a particular organism within a full setting of that particular individual or individual species. In this regard, for example, a complex differential transcriptional activation, repression and antirepression of the interferon-A multigenic family would appear implicated following viral infection of eukaryotic cells and early activation of the interferon regulatory factor[20].

It might simply be in terms of an approach of primarily natural events of biologic rather than pathologic nature that one would better understand neuronal systems of selective vulnerability. Indeed, neurodegeneration, progressive till death of that neuron, or else malignant transformation proves an effective integral counterpart of cellular biologic events as reflected in increased mitotic activity and in enhanced metabolism.

In a final analysis, perhaps, a central question of selective suppression would help delineate pathologic forms of injury that are inflicted on the cell and the organism as a whole, in a context of evolving, transforming and self-progressive pathways of increased susceptibility of cells as applicable only as an integral individual patient.

Certainly, for example, common cardiovascular diseases such as hypertension, atherosclerosis, hypercholesterolemia, appear united by association with distinct subsets of genes[21].

Multiple genetic interactions of combinatory and associative nature: A central form of associated occurrence of distinct phenotypes along non-Mendelian lines would particularly tend to progress in terms of multiple different phenotypes associated with multiple mutations of the same gene. Indeed, in a particular sense, it might be useful to consider a possible inheritance of certain diseases as unusual patterns of incidence not accounted for by Mendelian laws as for example with diabetes mellitus or schizophrenia. For example, neural cell adhesion molecules of the immunoglobulin superfamily are multidomain proteins that regulate axon growth, guidance and synaptic plasticity and would appear implicated in cognitive dysfunction in schizophrenia and mental retardation[22].

Type 2 diabetes, on the other hand, is a heterogeneous disorder involving variable components of both impaired insulin secretion and insulin resistance[23]. These particular disorders would evolve as truly non-Mendelian in terms of an inheritance pattern that is related to variability in disease phenotype expression in spite of identical genetic lesions present. Different mutations of the same gene might possibly follow different inheritance

patterns particularly if these patterns of incidence are evaluated purely in terms of phenotype occurrence. Also, for example, multigene complexes such as that of the uncoupling protein family involved in uncoupling oxygen consumption by the respiratory chain from ATP synthesis would appear involved in controlling not only ATP synthesis, but also fatty acid metabolism and reactive oxygen species production. Indeed, uncoupling protein 2 is associated with especially type 2 diabetes[24] .

For example, a particular mutation in the concerned gene might be silent clinically but would be prone to express itself in terms of a lesion affecting another part of the genome. A phenomenon of variability in penetrance itself would appear to be inconsistent with a full conceptual relevance of a universal biologic validity of the Mendelian inheritance patterns.

Schizophrenia would perhaps constitute characterizations of inherited disease traits that somehow implicate a variability of expression in terms of interactive multiple compounding influence.

One mechanism of a multigene causation for disease might involve the production of clinical states of the disorder in a manner that might be suggestive of a nonMendelian inheritance of multigenic defects that are distinct from single gene inheritance patterns that are generally or specifically of Mendelian inheritance type.

Certain patients would appear susceptible to a multiplicity of genetic mutations and deletions in terms of multiple different genes that somehow evolve in terms of a conceptual Fragility of chromosomes or as seen in Bloom's syndrome and Xeroderma pigmentosum, even beyond systems of apparent facilitated association.

Significant constitutive pathways of predisposing influence might in different ways operative in such conditions as Schizophrenia[25] that would be comparable to the evolving processes of malignant transformation in carcinogenesis. In this connection, for example, prostate carcinoma would appear a multigenic system involving common polymorphic variants of genes such as the androgen and vitamin D receptor in contributing to tumorigenesis[26].

It might be valid to consider predisposing influence a prerequisite for lesion creation in a manner specifically determined by that lesion that would itself produce a full series of genetic mutations and deletions, as seen so characteristically in many forms of neoplasia such as leukemias of different lineage.

Indeed, for example, susceptibility to N-methyl-N-nitrosourea-induced lymphomas would appear to constitute a multigenic trait in its own right[27].

Atherosclerosis, arterial hypertension and particularly neoplasia would appear to effectively evolve both in terms of a multigenic predisposition and of subsequently determined genetic lesions created as distinct systems of expression of such predisposing multigenic pathways that would influence directly pathologic expression of the systemic or somatic lesions in question.

In this regard, for example, interacting genetic loci on chromosome 20 and 10 would influence extreme obesity[28] in a manner subsequently influencing the expressed evolution of atherosclerosis and arterial hypertension.

In terms of a variability of degree of predisposition both in multigenic participation and also in terms of how expression of the induced pathology both evolve as interactive systems of transformation, it is perhaps significant that multiple genetic lesions would also associate with frequent polymorphisms in pleiotropic genes to form different formulae of genotype distribution in different multigenic disease according to their contribution to the onset and/or progression of the disease in question[29].

Basic mechanisms of production of lesions of neoplastic nature would in various ways have to account for the creation of delineated pathways of expression somehow also determining subsequent predisposition to further steps in a carcinogenetic system of progression that is autonomaous and somehow also prototypic. It is in terms indeed of a pathobiology of multiplicity of factors that interact in predictable patterns of interactive effect, that one might perhaps recognized pathologic lesion or neoplastic expression as simply a form of how multigenic associative pathways ultimately do interact finally to a predetermined system of cause and effect.

Even if one were to recognize strict patterns of predetermined pathologic outcome as purely expressed systems of cause and effect, one would in addition perhaps view the neoplastic lesion as itself an outcome of how predetermined effect is itself a form of predisposing influence towards how susceptibility to neoplasia does indeed evolve as such.

Indeed, disease generation and progression would constitute an effective expression of how a lesion does in fact evolve as a form of expressed predisposition somehow converted in effective generation and progression of that pathologic lesion.

Systems of strict pathobiologic progression as constituted by neoplastic proliferation and spread and of atherosclerotic deposition in vessel wall, or of myocardial infarction development or of neurodegenerative progression might effectively constitute a true form of progressiveness applicable to a wide range of disease states. Elucidation of the nature of etiologic events generating predisposition to such diverse disease states

would perhaps help render identifiable systems of determined nature somehow paradoxically predetermining the development of lesional states such as neoplasia or Alzheimer's disease or even coronary artery disease that apparently defy a conventional cause and effect evolution.

Even if one considers how a lesion does develop into a neoplasm in the first place in terms of a full series of carcinogenetic pathway effects, one might in real terms perhaps recognize how promotion and induction of such a neoplasm do actually have to interact both in determined and predetermined modes in order for prototypic expression of that neoplasm.

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