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Defining Stem Cell Attributes of Origin in Breast Neoplasms

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Abstract: Carcinogenesis would appear distinct from a conceptual framework implicating progression from a series of truly hyperplastic ductal lesions of the breast. An a priori concept of established predetermined evolution of the single large duct papilloma as a benign lesion would contrast with a concept of possible malignant transformation of atypical hyperplasia of breast ducts. Characteristics of a process of transformation in the added given context of attributes of a specific cell type of origin would further define systems of change in terms of stem cells that are biologically distinct from cell of origin of specific organs or tissues. It is only in terms of such stem-like cells that one would better explain proliferative and metastatic potential for various malignant lesions. These may either arise denovo or else evolve in a context of previous insitu proliferation of cells that become progressively more atypical morphologically and more biologically active with increase of the lesion. Transitory and straddling cell forms would alternatively adopt attributes of a stem-like type in the origin and subsequent course of development of desuppressed progression of a malignant neoplasm.

Key Words: Stem cell, breast, neoplasms

INTRODUCTION

The term papillary would obscure the sharp biologic differences between a single subareolar duct papilloma of the breast and papillary carcinoma. Any semblance between these two types of lesion is accentuated in cases of papillary carcinoma with stromal core elements. Papillary carcinoma of the breast may consist of one or more layers of single-type neoplastic cells surrounded by groups of blood vessels. The epithelial cell proliferation is asynchronous with the deposition of the scanty fibrous stroma and may help define biology of the lesion. Breast fibroblasts appear to support the normal growth and differentiation of human breast epithelium equally[1].

Multiple papillomas in the same breast appear distinct from the single duct papilloma with corresponding sharp distinguishing features affecting patient treatment or management.

The papillary cystadenocarcinoma that occurs especially in elderly women appears primarily an in situ lesion that lines the inner wall of a duct-derived cyst.

The carcinogenic effect would determine at an early stage whether the induced lesion that develops is a duct papilloma or a duct papillary carcinoma. The matrix metalloproteinase 3 is a key player for carcinogenesis and tumor growth. This concept would apply to many major categories of lesion, with the possible recognition of frank malignant transformation of essentially previously recognizable normal cells. Telomerase reactivation is associated with acquisition of invasive malignancy[2]. Different breast cancer pathways emerge early in the process of carcinogenesis, alternatively leading to clinically different tumor types[3].

On the other hand, the single duct papilloma and the multiple duct papillomas would constitute a separate distinct group of tumors that fail to undergo malignant transformation.

The single duct papilloma generally carries little risk of subsequent malignant transformation. The multiple duct papillomas carry a significant risk for malignant neoplastic change, on the other hand.

This quantitative aspect in operative malignant transformation in multiple duct papillomas would perhaps indicate constitutional genetic factors affecting ductal epithelial cells in terms reflecting qualitative carcinogenic influence.

The metastatic phenotype of a tumor would be affected by the germline genetic configuration of the host[4]. Transforming growth factor switches from tumor suppressor to prometastatic factor in breast cancer progression[5].

The frankly malignant papillary carcinoma is essentially a single lesion. Focal dynamics of the individual carcinogenic process that affect the rest of the duct system would operate as constitutional factors that are primarily focal. A superimposed series of changes would result in the focal malignant transformation event in such a case.

There is decreased estrogen receptor beta expression in carcinoma compared with benign tumors and normal

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tissues, whereas estrogen receptor alpha expression is unaffected. This decrease in estrogen receptor beta expression would reflect dedifferentiation.

Essential unresponsiveness as phenotypic of malignant neoplastic cells: In the first instance, there would operate a set of constitutional factors that allow the development of that malignant neoplasm in a specific organ that arises as a modification of a specific cell type in that organ or tissue.

In this manner, for example, heavy smoking is followed by bronchial carcinogenesis in only some of the patients and not in others. Also, the histologic subtype of any developing carcinoma may vary considerably.

The precise interplay of constitutional and extrinsic operative factors would evolve as a qualitative phenomenon that induces a true transformational event. Phosphatidyl 3-kinases subunit p110 alpha is the most common mutated oncogene in breast cancer[6]. Cytochrome P450 may be involved in local activation of estrogen in initiating and promoting the carcinogenic process[7]. The individual involvement of cells beyond controlling influence of cell division and of cyto-architecture would assume distinct biologic attributes affecting migratory infiltration and would characterize also metastatic dynamics of tumor spread. The transcription factor NF-kappaB is activated to promote carcinogenesis, especially due to its ability to protect transformed cells from apoptosis[8].

A homing series of mechanisms would determine the spread of tumor cells in the body that are analogous to the lymphocytic migration in development and maturation of the individual. Genetic instability might be a molecular mechanism favored by Bcl-xL evolved in the selection process of breast cancer progression that favors organ-selective chemoresistance[9] .

A recapitulation of normal homing mechanisms of cells would result in aberrant attempts of metastatic spread of tumor cells reflected in lymphatic and blood vessel spread.

Deregulated and desuppressed mechanisms would constitute mechanistic upsets resulting from an essential unresponsiveness of tumor cells in biologic evolution. In addition, steroidal estrogens may stimulate cellular proliferation with accumulated genetic damage, a cytochrome P450-mediated metabolic activation with increasing mutation rates and induction of aneuploidy[10] .

Unresponsive microenvironmental influence would account for the exerted replicative pathways that affect the entry to a resting stage in the mitotic cell cycle, and focal localization of the cells leading to subsequent migratory infiltration and spread. Several parallel and stepwise progression pathways would operate in breast carcinogenesis[11].

Cell membrane unresponsiveness would give rise to an incorporated series of events that phenotypically characterize the malignant cells and lead to a distortion of biologic mechanisms affecting cell development and maturation.

Unresponsiveness to chemotherapy and radiotherapy may reflect biologic unresponsiveness in terms of extrinsically exerted influence controlling even response to systemic therapy.

Malignant cells as individually insular cells: The conversion of a fully mature cell to a malignant cell constitutes a problematic concept that would require the re-acquisition of attributes of rapid proliferation, infiltration and widespread dissemination in the body.

It may very well prove valid to consider cells of origin of a given neoplasm as distinct from naturally established cell elements that histologically characterize the organ or tissues involved. A possibly staged series of events would implicate a stem cell in terms that are distinct from stereotyped responsiveness of histologically mature cells. Using modern molecular genetic techniques, evidence suggests that atypical hyperplasia and insitu carcinoma are nonobligate precursors of invasive breast lesions[12].

In fact, undifferentiated or uncommitted cells of origin of a given neoplasm would themselves differ in biologic attribute from the normal stem cells that populate developing and maturing tissues and organs.

Carcinogenesis might prove a fundamental process of replacement that goes beyond stem cell biology and implicates the existence of factors of susceptibility to malignant transformation[13].

The cell undergoing malignant transformation is one that rapidly proliferates and even infiltrates with subsequent replacement of damaged or effete mature cells. A situation may develop that involves a window period of susceptibility in cell injury implicating migration and replacement by stem-like cells capable of subsequent malignant progression.

Fundamental cell-cell interactions would be involved in aberrant stem-cell biologic development and progression.

Intercellular restrictive influence would become de-regulated in malignant transformation and result from mechanisms such as chalones or primary loss of intercellular adhesion.

Cell replication and migration appear to arise and to become established as intercellular influence with possible participation of a whole host of microenvironmental factors operating also as induced cell-

cell interaction in a multistep fashion[14].

The implicated abnormal stem cell in malignant transformation appears implicated in the process of deregulation or desuppression of controlled mechanisms in differentiation. A whole series of gradations would implicate specific biologic traits of the stem cell in terms of actual stage of differentiation and of exerted carcinogenic influence. The regulation of protein stability by the ubiquitin-proteasome pathway is critical to a molecular basis of carcinogenesis[15]. Chromosomal instability and cancer predisposition provoked by BRCA2 inactivation are due to failure to restart stalled DNA replication, and to repair DNA double-strand breaks[16].

Any stem cell pool would constitute a heterogeneous population of cells affecting the intrinsic ability to specify differentiation attributes and as genetically stable maturation of cell morphology and function.

The recruitment or activation of a significantly large population of stem cells would render the development of a malignant neoplasm more likely in a given patient. Persistent activating stimulation that is abnormal would possibly account for development of carcinogenic influence affecting stem cells[17].

The malignant cell appears randomly oriented and differentiated and would render the individual cells of the tumor an insular form of progression in malignant transformation.

Cell membrane biology that simplifies or otherwise modifies intercellular reactivity would participate with stem-cell attributes in the evolution of malignant transformation. Stimuli in the infiltration of tissues by malignant cells appear a primary source of subsequent evolution in carcinogenesis. Macrophages may induce Tumor Necrosis Factor-alpha -dependent metalloproteases[18]. Cyclooxygenase-2 promotes cellular proliferation and angiogenesis, makes cells resistant to apoptosis, enhances invasiveness and modulates immunosuppression[19].

In-situ carcinoma of the breast and atypical hyperplasia of ducts as detected morphologically: Hyperplasia at time of inception of the lesion would distinctly evolve as focal insitu lesions. Subsequent biologic and clinical evolution is sharply distinct from the insitu carcinoma of breast ducts. Tumor-derived and host-derived nitric oxide regulates breast carcinomatous spread to the lungs[20]. Architectural and cytologic characterization of carcinoma in situ[21] would derive from a correct approach in recognizing it as distinct from a basic process of hyperplasia.

An essentially composite group of proliferative lesions would account for the possible presence of hyperplasia that can be positively identified histologically.

Identifying morphologic features of a carcinoma in situ of the ducts includes cribriform to comedo forms as recognizable distension of ducts, tumor necrosis and abnormal mitotic figures. Nuclear atypia of a progressive nature underlies such insitu carcinomatous development. Major Compatibility Complex Class I and II antigen expression are early events in breast carcinogenesis and are important in metastatic progression[22].

The risk for subsequent malignant transformation of an insitu carcinoma is one that demarcates and further defines attributes of a lesion progressively undergoing malignant transformation, evolution and subsequent spread in the body. Monocyte chemoattractant protein-1 influences breast carcinogenesis by facilitating tumor growth and metastatic spread[23].

Sharp distinction of a given proliferative lesion in the body as either hyperplastic or carcinoma-in situ would implicate a degree of distinction mainly based on the established primary attributes of the cells of origin of the lesion.

Aberrant activation of the Wingless-type/beta-catenin signaling pathway occurs with a variety of cancers[24]. Human telomerase reverse transcriptase mRNA is downregulated in ductal carcinoma in situ[25].

Ductal and lobular pseudo-hyperplasia of the breast: The term hyperplasia appears not to fully account for attributes of lesions that may atypically evolve to form malignant tumors of the breast. A full spectrum of biologic and transformational events would exist with regard to the proliferation of such hyperplastic lesions that subsequently undergo malignant change.

Hyperplasia as applied to ductal lesions of the breast would constitute transitory lesions that involve potential transformation as proliferating and invasive spreading tumors. Several cooperatively acting factors would implicate a pseudo-hyperplasia that evolves as a carcinoma-in sit or as an infiltrative lesion in its own right. Transforming growth factor is a negative growth regulator that locally enhances cellular responsiveness[26].

Proliferative lesions may not be either frankly benign or malignant but would reflect a tendency for potential change in a continuum affecting malignant cellular atypia.

Failed acquisition of a malignant phenotype would be intrinsic to several apparently benign solid proliferative lesions rendering malignant transformation unlikely in that given patient. This would apply particularly to the single ductal papilloma with a definite fibrovascular core in a major duct of the breast. Limited hormonal stimulation of the breast during a critical window in postpubertal women

imparts a long-lasting protective effect against breast carcinoma[27].

Increased mitotic rate and genetic instability might help account for a possible or probable development of carcinogenic influence in a given particular lesion in the breast ducts. A comparison of insitu lesions with fully invasive tumors identified altered transcripts encoding for proteins involved in extracellular matrix remodeling, invasion and cell mobility functions[28]. Malignant transformation would help indicate how proliferative lesions are primarily either benign or malignant only insofar as subsequent progression can or cannot develop biologically. Interactions particularly of p53 with steroid receptors would underlie DNA damage, hypoxia and transcriptional defects in breast cancer[29] .

A permissive role for the malignant transformation process in ducts or lobules of the breast: At times features of both ductal and lobular type may be detected in a given breast lesion.

The basic cell type of origin in such cases would straddle both the duct system and the glandular lobules. Also, once such a cell type of origin undergoes malignant change, there would develop transformation of both ductal and lobular patterns of growth and biologic behavior of the carcinoma. Alternatively, one component may predominate and determine systems of evolution in a given carcinoma. In addition, chromosomal rearrangements resulting in gene fusions are frequently involved in carcinogenesis[30].

The cell of origin would predetermine subsequent malignant course in terms of attributes that are akin more to the ducts or more towards lobular differentiation.

The malignant transformation process itself would underlie systems of influence that differentially distinguish ductal and lobular carcinoma only in terms of a predominant subsequent course of the neoplasm. Also, progression from preinvasive lesions to palpable disease of the breast requires angiogenesis via a vascular endothelial growth factor-dependent mechanism[31].

Transitional or straddling cells of origin in paget's disease of the nipple or breast duct/lobular carcinoma: The focus of Paget's disease of the nipple is generally separate from an underlying focus of breast carcinoma. Both foci of tumor development represent a common dual set of foci to the same carcinogenic process. The clinical behavior of the Paget's lesion would arise as attributes of the cell of origin.

Such cell of origin would lie at the junction between the galactophore with the nipple epidermis. Ductal carcinoma often appears to arise at the junction between the terminal ductule and the lobule in terms also of subsequent course. Malignant transformation may also be possibly ascribed to dynamics of proliferation and of genetic instability of such junctional cell types in general. Telomerase length abnormalities are an early and prevalent genetic alteration in a multistep process of malignant transformation inducing genetic instability[32].

Such a fundamental form of susceptibility to malignant change would give rise to neoplasms that straddle morphologic and biologic characteristics of more than one cell-type.

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