International Journal of Molecular Medicine and Advance Sciences 6 (2): 14-18, 2010
ISSN: 1813-176X

Stromal Infiltration and Microvascular Density Pathogenically Promote Integral Breast Carcinogenesis

Lawrence M. Agius
Department of Pathology, University of Malta Medical School,
Mater Dei Hospital, Tal-Qroqq, Msida, Malta, Europe

Abstract: Active acquisition of the established malignant phenotypic traits of primary breast carcinoma is primarily directed by an infiltration of the stroma that concurrently and in turn also acquires an increased vascular density. In such a setting of biologic instability and progressiveness, the mechanics of pathogenesis of the malignant transformation process are primarily dictated by a series of overlapping regions of influence in multiple foci of breast involvement such process evolves in a manner that specifically and deterministically outlines integral lesion pathogenesis as carcinogenesis. Stromal infiltration and increased stromal vascular density, hence are active promoters of the malignancy in terms that do not solely or phenomenally outline such carcinomatous transformation. The stromal phenomena integrally enveloping proliferative foci of ductal and lobular epithelium are the source of the incremental progressiveness in carcinogenesis in a manner that also contributes to potential diversity of the specific morphologic attributes of the primary malignant lesion. Such processes are operatively determined irrespective of subsequent dynamics of spread of the lesion, locally and systemically. In this manner, an integral complexity of evolution of the acquired malignant process primarily originates within potential sites of an apparently initial reactive or proliferative focus that initiates stromal change; this is dominantly characterized by involved infiltrative change as reflected and classically denoted at times by infiltrating epitheliosis or papillomatosis in the first instance. It is in the analysis of such regionally dynamic and overlapping phenomena that the carcinogenesis phenomena are determined biologically beyond simple consideration of the subsequent sequential consequences of local spread and metastasis of the proliferative focus. Such considerations implicate attributed novel phenomena as a redefined malignant transformation series of events through the initiation and maintenance of progression and as further amplified infiltrativeness and spread, locally and systemically. It is in terms of such redefinition of the mechanics of malignant characterization that the proliferative neoplasm is both an original focus for infiltration and spread and also a real consequence of such phenomena in the enhancement of neoplastic malignancy both biologically and pathogenically.

Key words: Breast carcinoma, proliferation, stroma, carcinogenesis, microvascular density, malignancy

INTRODUCTION

Evolutionary development of systems of interactive lesions of a carcinomatous nature are inherently ones of proliferative activity as related primarily to the native structure of the ducts and lobules maintaining integral constitutive identity within a context of hormonal influences acting on the Terminal Ductule-Lobular Unit (TDLU).

The transition from slow to fast proliferation involves dramatic worsening of prognosis (Schmidt *et al*., 2009). The marked predominance of involvement of the female breast by primary carcinoma is synonymous with a strong tendency for hormonal responsiveness and also with the inherent susceptibilities of the breast to replicative maintenance of such TDLU. A concept relative to a basic structural and morphologic system that constantly entails cellular replacement is indicative of the various replicative systems that maintain a quantitatively stable population of epithelial cells.

Also, crosstalk between innate and adaptive immune response evolves during progression of breast carcinoma (De Nardo and Coussens, 2007). It is significant that the protease-centered hypothesis inadequately accounts for the molecular mechanisms of infiltration by breast carcinoma cells (Man and Sang, 2004).

Corresponding Author: Lawrence M. Agius, 27 Ballarat, Guzeppe Caruana Str., Tal-virtu, Rabat RBT 09, Tal-Qroqq, Msida, Malta, Europe

THE TERMINAL DUCTULE-LOBULAR UNIT

The contrasting attributes of the TDLU as reference systems that induce a replicative response of constituent cells is clearly a series of mechanistic pathways that correlate with a much higher susceptibility to malignant change as contrasted with the epithelial cells lining the larger breast ducts. Loss of cell-adhesion molecules with concurrent loss in tissue architecture, correlates with matrix remodelling in inducing a migratory advantage to breast cancer cells (McSherry *et al*., 2007). The various attributes that significantly help identify the active participation of proliferative events are particularly of note in terms of such maintenance systems that complement the biology of the terminal ductule-lobular unit. Fibroblasts can inhibit the growth of normal and hyperplastic epithelium but are less able to regulate transformed epithelial cells during carcinogenesis (Sadlonova *et al*., 2007).

The referential context with which the malignant potential for change is directly correlated, implicates various pathogenic pathways that contribute to a relative frequency in carcinoma cases as contrasted with the larger duct lesions. It is also in terms of the decreased susceptibility of the male breast (Petrocca *et al*., 2005) that the multiplicity of replicative events of the terminal ductule-lobular unit so significantly contributes to susceptibility for malignant change in the female breast. The functional unit of the breast includes the epithelial cell plus its microenvironment. The mammary stroma would remodel to a microenvironment inhibitory to tumor cell progression in response to tamoxifen administration (Hatter *et al*., 2009).

MENOPAUSAL STATUS

The premenopausal status and the postmenopausal consequences of such premenopausal susceptibility to both hormonal action and malignant change correlate with component pathways that differentially distinguish particularly, the much-decreased susceptibility of the male breast to neoplasia. Estrogen receptor negativity in many cases of axillary node-negative breast carcinoma constitutes a major prognostic marker in these patients.

The rarity of the lobular carcinoma subtype in male breast carcinogenesis is particularly striking in terms of the morphologically poor definition of the integral lobular unit in males. The overall dimensions of the field of operative effect in carcinogenesis are further exemplified by the wide susceptibility to pathways of increasing dynamic influence with advancing age of the woman. Lobulitis is often presenting breasts prophylactically removed from women with a high hereditary risk for breast cancer (Hermsen *et al*., 2005). It is significant that a peak age incidence of the woman as also a postmenopausal patient with primary breast carcinoma is further contributory evidence for systems of injury to the TDLU within contexts of premenopausal hormonal influence as well. The initial invasive mechanisms in carcinogenesis are largely unknown.

Stromelysin-3/matrix metalloproteinase 11 correlates with tumor cell infiltration (Andarawewa *et al*., 2005). The diversity of morphologic expression of carcinomatous lesions arising primarily in the female breast is indicative of a plethora of inflammatory and reactive changes with proliferative involvement of the breast that generally develop as benign lesions in the younger woman. The loss of E-cadherin expression and the translocation of β-catenin to the nucleus often correlate with metastatic spread (Mestdagt *et al*., 2006).

PRE-MALIGNANT POTENTIAL

The difficulties in recognizing the pre-malignant potential of many types of proliferative or atypical hyperplastic lesions is indicative of a whole range of potential outcomes of systems of involvement also affecting at times the more proximal portions of the breast ductal system. Some ductal in situ carcinomas show focally disrupted myoepithelial cell layers and basement membrane; these tend to correlate with white blood cell infiltrates that appear implicated in tumor cell infiltration. One might consider sites of involvement of ducts as relative determinants of morphologic attributes of lesions that variably and consequentially contribute to persistent proliferative stimulation as also in terms of the wide diversity of morphologic variants of the malignant lesions. One might consider the forms of development of breast carcinoma as stem cell attributes of a pre-evolutionary nature especially as far as hormonal influences are concerned.

It is possibly, the full developmental stage in morphogenesis of the female breast that correlates with certain morphologic attributes of a given primary breast carcinoma later in life. It is the consequential dynamics of subsequent development that converts the TDLU to an operative field influence in carcinogenesis. It is in this context that hormonal carcinogenesis in the female breast only explains a specific susceptibility pattern in terms of malignant definition of the lesion.

Tumor angiogenesis and chemotaxis may account for a functionally worse prognosis of breast carcinoma in African American patients compared to European Americans (Martin *et al*., 2009).

STROMAL INTERACTIONS

The interactivity between the epithelial cells of the TDLU and the surrounding stroma might significantly modify the susceptibility to malignant change in terms especially constituting the selectivity of involvement of a given site within the breast. Tumor microvessel density independently correlates with poorer cancer-specific survival (Al Murri *et al*., 2008). There might indeed evolve a patterned involvement that modulates such susceptibility to malignant change such process initially revolves as direct and indirect consequences of the pathologic involvement of the ducts and lobules as inflammatory and reactive lesions. The various benign proliferative lesions of the breast as reflected particularly within the spectrum of fibrocystic disease and also of ductal hyperplasias would specify attributes of potential transformation to malignant change. Matrix metalloproteinase-13 produced by breast carcinoma cells correlates with a poor prognosis (Zhang *et al*., 2008).

The spectral range of possible outcomes of reactive conditions of the breast primarily contribute not only to the variability in morphologic attributes of many types of primary carcinomatous lesions affecting the breast but also to a vast range of modulating influence implicating either direct pathways to carcinogenesis or various intermediate steps in carcinogenesis as exemplified by hyperplasia, atypical hyperplasia and *in situ* forms of carcinoma. Angiogenesis modulates leukocyte infiltration possibly via suppression of endothelial intercellular adhesion molecule-1 expression (Bouma-ter Steige *et al*., 2004).

Particularly significant is the aggressive or alternatively indolent nature of given recognized morphologic forms of primary carcinoma of the breast within contexts of lesion size at presentation of the woman. Inflammatory breast carcinoma constitutes a highly malignant tumor type with characteristic extensive infiltration of lymphatics and blood vessels (Renz *et al*., 2008).

Of note is the differential biologic behavior of lesions detected on mammography of the breast as compared with palpable lesions that clinically are detected at patient presentation. It would appear that modulatory influence of biologic attributes of lesion malignancy are an acquired attribute that may be significantly contributed to by subsequent interaction of the proliferative epithelial lesion with the stroma as especially modulated by stromal infiltration and vascular density. Increased stromal hyaluronan is related to breast cancer and promotes stromal cell recruitment and tumor angiogenesis (Koyama *et al*., 2007).

The later evolutionary steps in acquisition of the developed malignant phenotype of the breast lesion are significantly responsible for the morphologic correlates that histopathologically characterize the carcinoma primary in the breast. Monocytes in the breast cancer microenvironment modulate matrix metalloproteinases (Szabo and Singh, 2005; Lin *et al*., 2006).

COMPLEX HETEROGENEITY

A complex heterogeneity of influences that range from potential pre-malignancy to proactive systems of progression characterize the potentiality for carcinogenesis as specific modes of acquisition within fields of operative modulation of a morphologic and dynamic nature. The pathogenesis of various possible etiologic factors that operate within a given breast region contrast with a uniform series of possible potentialities that either abort such carcinogenetic process or else ensure progression to established malignant change. Conversion of circulating monocytes to tissue macrophages is associated with reprogramming of hypoxia-responsive genes promoting angiogenesis within a complex microenvironment (Knowles *et al*., 2004).

The pathogenic roles of influence as progression of potential consequences of a whole range of proliferative epithelial lesions are set within a matrix of dynamically variable potentiality for malignant change that is partly reflected in specific incidence rates of malignant lesion occurrence. The morphology of pathway effects only imperfectly reflects potentiality for development of lesion malignancy and it is highly significant that hormonal carcinogenesis insufficiently accounts for the whole spectrum of developing lesions that undergo malignant change within the breast. Inflammatory host response correlates closely with poor tumor differentiation, proliferation and cancer progression (Al Murri *et al*., 2008).

SPECTRUM OF POTENTIAL MALIGNANCY

The spectrum of potential malignant lesions that primarily involve the breast is a relative indicator of the pathogenic role of variability potential as predetermined susceptibility to malignant change in a given individual patient. The infiltrating carcinoma of not otherwise specific nature is a serial consequence of pathogenic pathways that primarily evolve as an infiltrating focus with often no detectable previous morphologic precursor or *in situ* lesion.

The whole array of potential consequences of a given reactive, proliferative lesion arising in the breast is extensively modulated in terms of the subsequent

susceptibility to evolution to a specifically infiltrating lesion in most cases of malignant transformation. Chemokines modulate proliferation, apoptosis, infiltration, leukocyte recruitment and angiogenesis in cases of breast cancer (Ali and Lazennec, 2007). The pathogenesis of primary breast carcinoma is largely concerned with the acquisition of pathways determining infiltrative capability and also of secondary consequences of the interactivities of both stroma and blood vessels by such infiltrating lesions. The vascular density of the stroma surrounding neoplasm as well as the carcinomatous cells are implicated in angiogenesis affecting tumor growth and metastasis (Tsutsui *et al*., 2005).

PROLIFERATIVE ACTIVITY

Proliferative activity of epithelial foci as TDLUs and as further foci of transformation would indicate a preparatory step in sequential predetermination in inducing increased vascular density of the adjacent stroma. The effects of biologic involvement of stroma appear to occur primarily as an antecedent event to the full acquisition of the established malignant phenotype of the lesion. The vascular stromal density is a primary modulator in the acquisition of the malignant phenotype in a manner that is progressive and self-amplifying. Infiltration of the stroma would appear also a modulatory influence both in development of the stromal vascular density and also as a biologic source for the subsequent reactivity transforming to an integral focus of infiltrating primary carcinoma.

A wide array of potential proliferative lesions may constitute fields of possible operative influence in the development of a powerful determining influence exerted by stromal infiltration within the added context of increased vascular density of such stroma. The temporal and sequential series of such events constitutes overlapping modulatory influences that demarcate progressiveness in pathogenesis of the lesion both as a further proliferative focus and particularly as an actively acquired infiltrative and metastasizing lesion.

MORPHOLOGIC ATTRIBUTES

The specific characterizations of the morphologic features of a given carcinoma primary in the breast would contribute to the evolutionary acquisition of malignant traits that further evolve as infiltrative capability of the lesion and as vascularity of the involved lesion focus.

In this manner, there would evolve systems of adjacent focal involvement that contribute both directly and indirectly to the eventual definition of a given focus of malignant change within the breast based on primarily overlapping and incremental influence specifically constituting the malignant lesion.

INFILTRATION

The realization of a focus of infiltration of the stroma is particularly illustrative of the infiltrating attributes of epitheliosis or papillomatosis as seen in radial scar lesions and also sometimes with sclerosing adenosis. It is not solely the active acquisition of infiltrative capability that demarcates the final emergence of a malignant primary lesion of the breast. It is however, the contributing role of such stromal infiltration that secondarily leads to a vast array of molecular events in the acquisition of a malignant cellular phenotype both systemically and locally. This combinatorial series of systems would further define the increased stromal vascular density as a mechanistic pathway determining and predetermining evolution, leading to the acquired malignant phenotype as projected systemically.

CONCLUSION

It is the acquisition of infiltrative capabilities to involve stroma and the invasion of lymphatics and blood vessels that morphologically distinguishes the primary neoplastic lesion in malignant transformation. However, the active biologic consequences of the infiltrative and metastasizing potential are also the mechanism of active acquisition of the malignant potential for carcinogenesis beyond simple phenotypic characterization of the events of spread of the lesion, locally and systemically.

It is the progressive proliferative activity of the terminal ductule-lobular unit with the development of infiltrating cells and increased stromal vascular density that would implicate pathogenic mechanisms of carcinogenesis beyond simple dynamics of spread of a predetermined or transformed original lesion. *In situ* carcinomatous characterization of the primary lesion constitutes a system that potentially requires subsequent acquisition of infiltrative capabilities and a stromal vascular density for the integral malignant phenotypic transformation to develop pathogenically.

REFERENCES

Al Murri, A.M., M. Hilmy, J. Bell, C. Wilson and A.M. McNicol *et al*., 2008. The relationship between the systemic inflammatory response, tumor proliferative activity, T-lymphocytic and macrophage infiltration, microvessel density and survival in patients with primary operable breast cancer. Br. J. Cancer, 99: 1013-1019.

Ali, S. and G. Lazennec, 2007. Chemokines: Novel targets for breast cancer metastasis. Cancer Metastasis Rev., 26: 401-420.

Andarawewa, K.L., E.R. Motrescu, M.P. Chenard, A. Gansmuller, I. Stoel, C. Tomasetto and M.C. Rio, 2005. Stromelysin-3 is a potent negative regulator of adipogenesis participating to cancer cell-adiopocyte interaction/crosstalk at the tumor invasive front. Cancer Res., 65: 10862-10871.

Bouma-ter Steige, J.C., C.I. Baeten, V.L. Thyssen, S.A. Satijn and I.C. Verhoeven *et al*., 2004. Angiogenic profile of breast carcinoma determines leukocyte infiltration. Clin. Cancer Res., 10: 7171-7178.

De Nardo, D.G. and L.M. Coussens, 2007. Inflammation and breast cancer. Balancing immune response: Crosstalk between adaptive and innate immune cells during breast cancer progression. Breast Cancer Res., 9: 212-212.

Hatter, R., O. Maller, S. McDaniel, K.C. Hansen and K.J. Hedman *et al*., 2009. Tamoxifen induces pleiotrophic changes in mammary stroma resultingin extracellular matrix that suppresses transformed phenotypes. Breast Cancer Res., 11: R5-R5.

Hermsen, B.B., S. von Mensdorff-Pouilly, H.F. Fabry, H.A. Winters, P. Kenemans, R.H. Verheijen and P.J. van Diest, 2005. Lobulitis is a frequent finding in prophylactically removed breast tissue from women at hereditary high risk of breast cancer. J. Pathol., 206: 220-223.

Knowles, H., R. Leek and A.L. Harris, 2004. Macrophage infiltration and angiogenesis in human malignancy. Novartis Found Symp., 256: 189-200.

Koyama, H., T. Hibi, Z. Isogai, M. Yoneda, M. Fujimori and J. Amano *et al*., 2007. Hyperproduction of hyaluronan in neu-induced mammary tumor accelerates angiogenesis through stromal cell recruitment: Possible involvement of versican/PG-M. Am. J. Pathol., 170: 1086-1099.

Lin, E.Y., J.F. Li, L. Gnatovskiy, Y. Deng, L. Zhu and D.A. Grzesik *et al*., 2006. Macrophages regulate the angiogenic switch in a mouse model of breast cancer. Cancer Res., 66: 11238-11246.

Man, Y.G. and Q.X. Sang, 2004. The significance of focal myoepithelial cell layer disruptionsin human breast tumor invasion: A paradigm shift from the protease-centered hypothesis. Exp. Cell Res., 301: 103-118.

Martin, D.N., B.J. Boersma, M. Yi, M. Reimers and T.M. Howe *et al*., 2009. Differences in the tumor microenvironment between African-American and European-American breast cancer patients. PLoS ONE, 4: e4531-e4531.

McSherry, E.A., S. Donatello, A.M. Hopkins and S. McDonnell, 2007. Molecular basis of invasion in breast cancer. Cell. Mol. Life Sci., 64: 3201-3218.

Mestdagt, M., M. Polette, G. Buttice, A. Noel, A. Ueda, J.M. Foidart and C. Gilles, 2006. Transactivation of MCP-1/CCL2 by beta-catenin/TCF-4 in human breast cancer cells. Int. J. Cancer, 118: 35-42.

Petrocca, S., M. La Torre, G. Cosenza, T. Bocchetti and M. Cavallini *et al*., 2005. Male breast cancer: A case report and review of the literature. Chir Ital., 57: 365-371.

Renz, D.M., P.A.T. Baltzer, J. Bottcher, F. Thaker and M. Gajda *et al*., 2008. Inflammatory breast carcinoma in magnetic resonance imaging: A comparison with locally advanced breast cancer. Acad. Radiol., 15: 209-221.

Sadlonova, A., S. Mukherjee, D.B. Bowe, S.R. Gault and N.A. Dumas *et al*., 2007. Human breast fibroblasts inhibit growth of the MCF10AT xenograft model of proliferative breast disease. Am. J. Pathol., 170: 1064-1076.

Schmidt, M., J.G. Hengstler, C. Von Torne, H. Koelbl and M.C. Gehrmann, 2009. Coordinates in the universe of node-negative breast cancer revisited. Cancer Res., 69: 2695-2698.

Szabo, K.A. and G. Singh, 2005. Modulation of monocyte matrix metalloproteinase-2 by breast adenocarcinoma cells. Breast Cancer Res., 7: R661-R668.

Tsutsui, S., K. Yasuda, K. Suzuki, K. Tahara, H. Higashi and S. Era, 2005. Macrophage infiltration and its prognostic implications in breast cancer: The relationship with VEGF expression and microvessel density. Oncol. Rep., 14: 425-431.

Zhang, B., X. Cao, Y. Liu, W. Cao and F. Zhang *et al*., 2008. Tumor-derived matrix metalloproteinase-13 (MMP-13) correlates with poor prognoses of invasive breast cancer. BMC Cancer, 8: 83-83.