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HYPOTHESIS

Pathophysiology of Breast Carcinogenesis as Stromal-Epithelial Cell Interactivity

Lawrence M. Agius*

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

Abstract. Evolving consequences of a series of genotoxic events reproducibly enhance the interactivity between stromal cells and the epithelial cells of the terminal ductule-lobular units of the breast. Realized involvement of angiogenic and apoptotic responses would characterize activation of the damaged DNA microenvironment as related particularly to stromal cell elements. Involvement of variability of response of epithelial cells and the ongoing development of the genotoxic pathways as evidenced by oxidative stress and apoptosis/necrosis of epithelial cells implicate a successive series of events that further compromise recoverability of normal processing pathways within damaged cells. One might speak of a complex interplay of apoptosis and anti-apoptosis pathways in the reconstruction of a patch architecture reflected secondarily in models of clonality and polyclonality that go beyond simple characterization of monoclonal derivation from a single common cell of origin of the breast neoplasm.

* *Correspondence:* Dr. Lawrence M. Agius, Department Of Pathology, St Luke's Hospital, Gwardamangia, University Of Malta Medical School, Msida Malta, Europe. Tel: 356-21451752. Fax: 356-2595-6317. E-mail: Lawrence.Agius@um.edu.mt

Abbreviations used: HIF-1-alpha, hypoxia-inducible factor 1-alpha; VEGF, Vascular endothelial growth factor.

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MULTISTAGE RESPONSE

Breast cancer pathophysiology constitutes a multistage response to genotoxic events [1]. The further reflection of events as ongoing consequences of such genotoxicity is best defined in terms of ongoing responsiveness that alters mitotic reproducibility of phenotypic traits [17]. Indeed, in further reconstructive attempts of an ongoing remodeling of the cardinal set points in such definition of combined proliferative and apoptotic pathways one might recognize the importance of a combined reproductive construct in malignant phenotype determination. The realization of events borne out by modeling representations of the infiltrative and metastasizing events reflect in variable manner the combined angiogenesis- and apoptosis- inducing activities of both the epithelial cells and the stromal elements in breast carcinogenesis [40].

In the realization of pathways of reconstructive remodeling of genotoxic pathways there develops a less than faithful reproduction of dynamic events as interactive between epithelial cells and stromal cell elements. Indeed, there arises a full schematic representation of pathways that involves primarily stromal cells, as further reflected in the angiogenesis and production of hypoxia-inducible factor 1-alpha (HIF-1-alpha) [2]

ATM reduced expression is associated with neoangiogenesis and breast cancer progression [29].

TRANSFORMING POTENTIALITY

Multistage progression constitutes a dynamic model in such reproducible events in breast carcinogenesis induced by principal pathways of transforming potentiality and as indicated by both morphologic and tumor marker studies [3]. It might be significant that viral oncogenesis as represented by suggestive pathways of inducible progression following Epstein-Barr virus infection is a constitutive pathway that progresses largely as sporadic tumor occurrence [15].

Sporadic and familial forms of a breast carcinogenesis phenomenon represent ongoing events transforming phenotypic characterization beyond simple genotypic predetermination (4). Interactive events involving stromal cells constitute paracrine and autocrine pathways that eventually determine the progressiveness beyond onset dynamics in carcinogenesis [24].

Estrogens are tumor promoters that definitively reclassify the mitogenic stimulus as uncontrolled proliferation in breast carcinogenesis [22]. Immediate early response protein IEX-1, small stress protein 1 (HSPB8), and tumor necrosis factor-associated factor-interacting protein mRNAs are hyperexpressed in invasive carcinoma of the breast. They induce anchorage-independence, cell hyperproliferation and antiapoptosis singly or in collaboration with erbB2 [25].

The outlined dimensions of reproduction of the genotoxicity pathways especially define parameters borne out by both angiogenesis and density vascularization of the stroma in breast carcinomas.

STROMAL INTERACTIVITY

Further details of characterized events in breast carcinogenesis appear paradoxically reproducible largely in terms of onset and progression pathways that are interactively linked particularly as stromal cell attributes [15]. The documentation of epithelial transformation events in breast carcinogenesis is further reclassified in terms of the pathways that span both increased apoptotic events and a tendency for progressive anti-apoptosis in carcinogenesis. In terms beyond representation of the interactivity of stromal elements as parametric determination of carcinogenesis, one might further recognize the development of pathways as borne out by the balanced or unbalanced interactions between oncogenes and suppressor genes in breast tissues.

MICROENVIRONMENTAL ACTIVATION

A highly activated microenvironment for breast carcinogenesis reproducibly represents a consequence of further transforming potentiality as indicated by the variability of precursor le-

sions in the development of neoplasia of the breast [20].

The HER family of receptor tyrosine kinase couples binding of extracellular growth factor ligands to intracellular signal transduction pathways and is implicated in breast carcinogenesis [31].

The highly variegated precursor lesions leading to the evolving infiltration of stroma by histological categories of neoplastic cells are best defined as ongoing dynamics of excessive proliferation of stromal and especially epithelially transformed cells.

In terms indicative of pathways of reproduction beyond definition of simple proliferative events, the nature of the transformation as a malignant characterization of the neoplastic phenotype is further represented by the angiogenesis of stroma. Vascular endothelial growth factor (VEGF) effects prove particularly significant especially in terms of onset reproduction of pathways as indicated by the prognostic significance of high vascular density of the adjacent stroma in breast transformation events.

Breast carcinogenesis is particularly significant in terms of variability in focus predetermination that spans a systemic involvement due to malignant transformation of tissues and as interactive progressiveness between stromal cells and epithelial cell elements.

Epigenetic changes such as hypermethylation of the p16 (INK4a) promoter sequences may create preclonal tumorigenesis that subsequently progresses to malignancy [33].

Usual ductal hyperplasia reproducibly represents an ongoing eventual composite construct as possible emergence of atypia and carcinoma-in-situ events. Pathways of constructive representation are further characterized by the various histologic variants of breast carcinoma.

A dichotomy in the reproducible representation of breast ducts or lobules constitutes a simplified construct in the further progression of a lesion that both infiltrates and spreads in terms particularly of interactive dynamics between stroma and epithelial cells. N-myc downstream regulated gene-1(Ndrg-1) is involved in epithelial cell differentiation and is significantly downregulated in breast carcinogenesis [27].

DYNAMIC TURNOVER

Alternative splicing that inactivates the wild type tumor suppressor genes would constitute a baseline parameter in the interactive dynamic turnover between stroma and epithelial cells as represented particularly by estrogen receptor beta protein [12, 18]. Estrogen receptor beta constitutes a tumor suppressor that inhibits estrogen mitogenic activity [37].

Nuclear receptor comodulators control transcription and splicing as selectively constitutive events in differential dysregulation of estrogen receptor β1 and estrogen receptor βcx in in-situ breast carcinoma [14].

A combinatory reproduction of increased estrogen receptivity and VEGF effects represents a constitutive pathway in sporadic tumor occurrence as induced by pathways of stromal and epithelial cell interactivity. Cyclin D1 and D3 appear selectively overexpressed in estrogen-induced experimental breast carcinogenesis [30]. HIF-1-alpha constitutes the final emergence of pathways as inter-related with vascularization and angiogenesis of the stroma in progressive breast carcinogenesis [16]. Hypoxia and nutrient deprivation induce genetic and epigenetic adaptation of clones and increase tumor infiltration and spread [26].

Estrogen possibly modulates HIF-1-alpha levels. Increased cell proliferation via receptor mediated activity, activated cytochrome P450 and induced aneuploidy by estrogen are possible molecular mechanisms in breast carcinogenesis [35].

BIOLOGICAL ANTAGONISM

Biological antagonism appears a referable set point in terms of ongoing dynamics in reproduction of carcinogenesis of the breast epithelium of ducts and lobules. Accelerating cell turnover along the continuum of breast carcinogenesis develops as an imbalance in favor of apoptosis that evolves in the transition of hyperplasia to preinvasive lesions [38]. An asymmetric cell division series of events constitutes not only a possible embryonic pathway in progression, but also variable reproduction as further portrayed

by oncosuppressors and oncogene action [21]. Nuclear proto-oncogenes c-myc, c-jun, and c-fos indicate early response events during cell proliferation [34].

Extracellular remodeling is an interactively reproducible series of pathways that reciprocally recasts events as modulating and transforming potentiality.

Oxidative stress constitutes a disruption of base stacking in the determination of cellular redox status of the DNA of the breast epithelial cells. An obligatory representation of pathways of genotoxicity might be an order-disorder transition in DNA structure [19]. A constitutive chaos theory represents events that unify theories of carcinogenesis in terms of the creation of order or disorder pivotal in tumor development.

Stimulated hedgehog signaling promotes carcinogenesis and cell survival during development [28].

AUTONOMOUS INTERACTIONS

Aberrant methylation appears an insufficiency of mechanisms of DNA repair pathways and of replicative reproducibility. Genetic instability as an overall scheme of progression involves cytogenetic disruption as further evidenced by genetic or epigenetic states of variable deletion of transcriptional events.

Non-cell autonomous interactions constitute a marker of genotoxic injury as constitutive characterization and as represented by TP53 wild type and mutated forms [13]. Polyclonality of cell proliferative events is transformed into multifocal monoclonal pathways of reproduction as further evidenced by subpopulations of selective growth and spread. Proviral insertion sites in the DNA constitute a working framework in such progression to a predominant clonal constitution of pathways as represented by infiltrating and metastasizing tumor cells of breast origin.

CLONALITY

Clonality studies reconstitute mutational analysis in terms of ongoing events as prototypically represented by chromosome X-inactivation that is present as patch reconstructs about tumor subfields.

Terminal ductule-lobular units are an attempted characterization of events that morphologically span regions of patch configuration and as represented by both polyclonal and monoclonal cellular proliferative pathways.

Allele imbalance and stem cell hierarchy in the adult breast would constitute variable schemes of production of a carcinogenesis pathway that progresses beyond paracrine and autocrine events. One might in particular represent the variability in constitutive pathways as further evidence of the marked genetic instability induced by aberrant methylation and cytogenetic abnormalities in particular, and also by the telomere shortening. Critically short telomeres together with abrogated DNA damage checkpoints induce genomic instability due to end-to-end chromsomal fusions with breakage and rearrangements [32].

TRANSCRIPTION

Aneuploidy and centrosomal amplification and chromosomal aberrations affecting the regulation of transcription might be reflected particularly in the caretaker function of BRCA1 and in the steroid hormone responsiveness of tumors [11]. Master regulators and homeobox genes and G_2 cell cycle checkpoint progression might be differential expressions of a DNA-damaged microenvironment.

Inactivating TP53 mutations in stromal cells would constitute an apoptotic response to genotoxic stress under normal circumstances but would indeed be reflected in a latency of the tumorigenesis and in the morphology of the resulting tumors (6).

The bypassing of cell cycle arrest might be represented by the ongoing reproduction of pathways that remodify both progression and onset dynamics of subsequent events [10].

"SEED-AND-SOIL" HYPOTHESIS

The growth promoting activities of reactive stroma and the heparan sulfate attachment sites would correlate with a "seed-and-soil" hypothesis within subsequent frameworks of multifac-

eted communication systems.

Cell adhesion, cell migration and growth factor activity and also "invasion-specific" genes might constitute signal exchange pathways in the ongoing transformation potentiality of breast carcinogenesis events. Ionizing radiation initiates and promotes neoplastic progression due to induced genetic damage, cell death and new gene expression patterns with global alterations of mammary gland microenvironment [39].

The progeny of a single embryonic stem cell would reflect patterns of distribution of chromosome X-inactivated cells in tissues as constitutive patches of relatively large size.

Such patch patterns are central to clonal and mutational analyses and might further complicate the determination of strict clonality in tumorigenesis [9].

Concurrent and independent pathways of reproduction of events simply constitute events as borne out by the further defining attributes of biological antagonism models in breast carcinogenesis.

PROLIFERATIVE/DIFFERENTIATING IMBALANCE

A proliferative/differentiating imbalance would perhaps constitute events that are hardly reproducible in terms of secondary remodeling of the extracellular matrix in particular.

Development and homeostasis events implicate overall characterization of aberrantly constitutive pathways of carcinogenesis and as reflected in the development of tumor neoplasia [23].

Numb as an oncosuppressor and Notch as a plasma membrane receptor reflect cell fate determination and proteasome-mediated degradation in the further reproduction of pathways of consequence in breast carcinogenesis and as reflected in loss of Numb-mediated control of Notch signaling.

Intragenic mutation and regional amplification constitute derivation of pathways of progression in a presumed common cell origin of a given breast carcinoma [7].

Microenvironmental disruption would activate various mechanistic pathways in the ongoing reproduction of events as further evidenced by biological antagonism systems.

UNIFIED SCHEME

A unified scheme of carcinogenesis in breast further accounts for the development of variable morphologic/histologic parameters of the inducible pathways of transformation of cells of the terminal ductule/lobular unit. The representation of the microenvironment in further characterizing such dynamics is significant in the constitutive pathway formulation of such events as potentiality of transforming models of paracrine and autocrine biology that interactively modify both epithelial cells and stromal elements.

Obligatory remodeling schemes in carcinogenesis reflect creative pathways with the attainment of order in DNA reconstructive events. Multifaceted communications would constitute a mechanistic system of inter-relative pathways that further co-modifies and modulates pathways of transforming potentiality in determined breast carcinogenesis [8].

Heterotypic interactions progress as heterodimerization of molecular forms such as estrogenic splice variants. Furthermore, epigenetic alterations of critical growth-regulating genes would lead to attempts at reconstruction of breast tissue events that transform as carcinogenesis.

Direct cell-cell contact and elevated levels of mitogenesis rather than decreased apoptosis might better allow for the proposed reconstruction of pathways of inducible progressiveness in malignant transformation.

Balanced persistence and inducible reproduction of activation pathways implicate a reactivation of stromal elements as a primary source of the transforming potentiality in breast carcinogenesis.

It seems plausible that angiogenesis would remodulate an uncontrolled status of cell proliferation in the face of ongoing development of other systems of progression such as a paradoxical combined system of increased apoptosis and evolving anti-apoptotic series of effects in constitutive tumor cells of breast origin. Loss of Trans-

forming Growth Factor beta inhibitory proliferative effect might act in conjunction with permissive effects on stroma angiogenesis and the immune system (36).

CONCLUDING REMARKS

Activated pathways of interaction arising as stromal-epithelial cell reactivity implicate a selective response pattern in ongoing relative production of cytokines and chemokines.

Apoptosis and anti-apoptosis responses progress largely within a context of relative abundance of such cytokines and chemokines in the further activation of the tumor microenvironment. It is in the overall reproduction of events of cell and DNA injury that one might recognize ongoing potential transformation of pathways of progression as states of stromal-epithelial cell inter-relationships.

One might include a whole array of phenomena in the reproduction of pathways of induced response that transform to autonomous cell interactivity. Genotoxic injury constitutes a further progressive step in transformation of the DNA constitutive response towards such autonomous cell proliferation and spread. Stromal reactivity implicates angiogenic response and anti-apoptosis arising within a context of further progression of the injury to cellular DNA. Cytokine action complicates a series of responses as microenvironmental activation and as patterns of inducible change. Breast carcinogenesis involves a clonal and multiclonal derivation of cellular traits that responsively convert the nature of the microenvironmental activation pathways as primary and subsequent further patterns of transforming potentiality.

Breast carcinogenesis might entail a self-replication of pathways of response within systems of genotoxic injury to both stromal and epithelial cells.

It is in the further detailed reconstruction of a patch architecture of breast tissue elements that there evolves a representation of the injury as activated response of an autonomous nature. Paracrine and autocrine reactivity responses determine a full representation of the injury that is specific for the microenvironmental activation patterns of response and for autonomous interactivity between stromal cells and epithelial cells of breast origin.

REFERENCES

1. **Bos R, Zhong H, Hanrahn CF, Mommers ECM, Semenza GL, Pinedo HM, et al.** [2001] Levels of hypoxia-inducible factor-1alpha during breast carcinogenesis. J Natl Cancer Inst 93: 309-314.
2. **Zhong H, De Maizo AM, Langhner E, Lim M, Hilton DA, Zagzag D, et al.** [1999] Overexpression of hypoxia-inducible factor 1 alpha in common human cancers and their metastases. Cancer Res 59: 5830-5835.
3. **Kurose K, Hoshaw-Woodard S, Adeyinke A, Lemeshow S, Watson PH, Eng C** [2001] Genetic model of multi-step breast carcinogenesis involving the epithelium and stroma: clues to tumor-microenvironment interactions" Hum Mol Genet Sep 10: 1907-1913.
4. **Kerangueveu F, Noguchi T, Coulier F , Allione F, Wargniez V, Simony-Lafontaine J, Lougy M, et al.** [1997] Genome-wide search for loss of heterozygosity shows extensive genetic diversity of human breast carcinomas. Cancer Res 57: 5469-5474.
5. **Moinfar F, Mau YG, Arnauld L, Bialthauer GL., Ratsclek M, Tavassoli FA** [2000] Concurrent and independent genetic alterations in the stromal and epithelial cells of mammary carcinoma: Implications for tumorigenesis" Cancer Res 60: 2562-2566.
6. **Done SJ, Arneson NC, Ozcelik H, Redston M, Andrulis IL** [1998] p53 mutations in mammary ductal carcinoma in situ but not in epithelial hyperplasias. Cancer Res 58: 785-789.
7. **Pece S, Serresi M, Santolini E, Capra M, Hulleman E, Galimberti V, et al.** [2004] Loss of negative regualtion by Numb over Notch is relevant to human breast carcinogenesis. J Cell Biol 167: 215-221.
8. **Malinis DC, Polissar NL, Shaefer S, Su Y, Vinson M** [1998] A unified theory of carcinogenesis based on order-disorder transitions in DNA structure as studied in the human ovary and breast. Proc Natl Acad Sci USA 95: 7637-7642.
9. **Tsai YC. Lu Y, Nichols PW, Zlotuckov G, Jones PA, Smith HS** [1996] Contiguous patches of normal human mammary epithelium derived from a single stem cell: implications for breast carcinogenesis. Cancer Res 56: 402-404.
10. **Ford HL, Kabingu EN, Bump EA, Mutter GL, Pardee AB** [1998] Abrogation of the G2 cell cycle checkpoint associated with overexpression of HSIX1: A possible mechanism of breast carcinogenesis. Proc Natl Acad Sci USA 95: 12608-12613.
11. **Rosen EM, Fan S, Isaacs C** [2005] BRCA1 in hormonal carcinogenesis: basic and clinical research. Endocr Relat Cancer 12: 533-548.
12. **Henderson BE, Fergelson HS** [2000] Hormonal Carcinogenesis. Carcinogenesis 21: 427-433.
13. **Kiaris H, Chalzistamori I, Trimis G, Frangou-Plemmenou M, Pafiti-Kondi A, Kalofoutis A** [2005] Evidence for nonautonomous effect of p53 tumor sup-

pressor in carcinogenesis. Cancer Res 65: 1627-1630.
14. **Esslimani-Sahla M, Kramar A, Simony-Lafontaine J, Warner M, Gustafsson J-A, Rochefort H** [2005] Increased estrogen receptor Bcx expression during mammary carcinogenesis. Clin Cancer Res 11: 3170-3174.
15. **Glaser SL, Hsu JL, Gulley ML** [2004] Epstein-Barr virus and Breast Cancer: State of the evidence for viral carcinogenesis. Cancer Epidemiol Biomarkers Prev 13: 688-697.
16. **Costa A, Coralini D, Carrassi A, Erdas R, Sardelle A, Dardone MG** [2001] Re: Levels of hypoxia-inducible factor 1-alpha during breast carcinogenesis. J Natl Cancer Inst 93: 1175-1177.
17. **Bartow SA** [1993] Toward a model for early stages of human breast carcinogenesis. J Natl Cancer Inst 85: 1710-1711.
18. [2006] Mechanisms of Disease: Estrogen Carcinogenesis in Breast Cancer. N Engl J Med 354: 228.
19. **Smith TR, Miller MS, Lohman KK, Case LD, Hu JJ** [2003] DNA damage and breast cancer risk. Cancerogenesis 24: 883-889.
20. **Euhus DM, Cler L, Shwapurkar N, Milchgrub S, Peters GN, Leitch AM, et al.** [2002] Loss of heterozygosity in Benign breast epithelium in relation to breast cancer risk. J Natl Cancer Inst 94: 858-860.
21. **Osborne C, Wilson P, Tripathy D** [2004] Oncogenes and tumor suppressor genes in breast cancer: Potential diagnostic and therapeutic applications. Oncologist 9: 361-377.
22. **Shaabau AM, Sloane JP, West CR, Foster CS** [2002] Breast cancer risk in usual ductal hyperplasia is defined by estrogen receptor-alpha and Ki-67 expression. Am J Pathol 160: 597-604.
23. **Kuperwasser C, Chavarria T, Wu M, Magrane G, Gray JW, Carey L, et al.** [2004] From the Cover: reconstruction of functionally normal and malignant human breast tissues in mice. Proc Natl Acad Sci USA 101: 4966-4971.
24. **Arpino G, Laucirica R, Elledge RM** [2005] Premalignant and in situ breast disease: Biology and clinical implications. Ann Intern Med 143: 446-457.
25. **Yang C, Trent S, Ionescu-Tibra V, Lau L, Shioda T, Sgroi D, et al.** [2006] Identification of cyclin D1- and estrogen-regulated genes contributing to breast carcinogenesis and progression. Cancer Res 66: 11649-11658.
26. **Kimbro KS, Simons JW** [2006] Hypoxia-inducible factor-1 in human breast and prostate cancer" Endocr Relat Cancer 13: 739-749.
27. **Kovacevic Z, Richardson DR** [2006] The metastasis suppressor , Ndrg-1: a new ally in the fight against cancer" Carcinogenesis 27: 2355-2366.
28. **Mukherjee S, Frolova N, Sadlonova A, Novak Z, Steg A, Page GP, Welch DR, et al.** [2006] Hedgehog signaling and response to cyclopamine differ in epithelial and stromal cells in benign breast and breast cancer. Cancer Biol Ther 5: 674-683.
29. **Cuatrecasas M, Sautamarea G, Velasco M, Camacho E, Hermandez L, Sanchez M, et al.** [2006] ATM gene expression is associated with differentiation and angiogenesis in infiltrating breast carcinomas. Histol Histopathol 21: 149-156.
30. **Weroha SJ, Li SA, Tawfik O, Li JJ** [2006] Overexpression of cyclins D1 and D3 during estrogen-induced breast oncogenesis in female ACI rats. Carcinogenesis 27: 491-498.
31. **Zaczck A, Brandt B, Bielawski KP** [2005] The diverse signaling network of EGFR, HER2, HER3 and HER4 tyrosine kinase receptors and the consequences for therapeutic approaches. Histol Histopathol 20: 1005-1015.
32. **Meeker AK, Argani P** [2004] Telomere shortening occurs early during breast tumorigenesis: a cause of chromosome destabilization underlying malignant transformation?" J Mammary Gland Biol Neoplasia 9: 285-296.
33. **Tlsty TD, Crawford YG, Holst CR, Fordyce CA, Zhang J, McDermott K, et al.** [2004] Genetic and epigenetic changes in mammary epithelial cells may mimic early events in carcinogenesis. J Mammary Gland Biol Neoplasia 9: 263-274.
34. **Calaf GM, Hei TK** [2004] Ionizing radiation induces alterations in cellular proliferation and c-myc, c-jun and c-fos protein expression in breast epithelial cells. Int J Oncol 25: 1859-1866.
35. **Russo J, Russo IH** [2004] Genotoxicity of steroidal estrogens. Trends Endocrinol Metab 15: 211-214.
36. **Benson JR** [2004] Role of transforming growth factor beta in breast carcinogenesis. Lancet Oncol 5: 229-239.
37. **Lazennec G, Bresson D, Lucas A, Chauveau C, Vignon F** [2001] ER beta inhibits proliferation and invasion of breast cancer cells. Endocrinology 142: 4120-4130.
38. **Bai M, Agnantis NJ, Kamina S, Demou A, Zagorianakou P, Katsaraki A, et al.** [2001] In vivo cell kinetics in breast carcinogenesis. Breast Cancer Res 3: 276-283.
39. **Barcellos-Hoff MH** [1998] The potential influence of radiaton-induced microenvironments in neoplastic progression. J Mammary Gland Biol Neoplasia 3: 165-75.
40. **Werb Z, Ashkenas J, MacAuley A, Wiesen JF** [1996] Extracellular matrix remodeling as a regulator of stromal-epithelial interactions during mammary gland development, involution and carcinogenesis. Braz J Med Biol Res 29: 1087-1097.