PERGAMON

European Journal of Cancer 38 Supplement 6 (2002) S31–S32

European Journal of Cancer

www.ejconline.com

Pathways of carcinogenesis and prevention in the human breast

J. Russo*, H. Lareef, Q. Tahin, I.H. Russo

Breast Cancer Research Laboratory, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

1. Introduction

Breast cancer is the most frequent neoplasm affecting the female population in the Western world and is the second cause of death after lung cancer. There are epidemiological, clinical and basic research data that points to oestrogens as being one of the most important aetiological factors and an early full-term pregnancy as a protective factor in the development of breast cancer [1–4].

2. Mechanism of breast carcinogonesis

Oestradiol (E2) exerts its effect in the mammary gland in specific glandular structures, the lobules type 1 (Lob 1). Lob 1 emerges at the time of menarche and if pregnancy does not occur, the breast remain undifferentiated. Only after a full-term pregnancy does the breast differentiate [1,2]. At menopause, breasts from both nulliparous and parous women look structurally similar, but they have a different genomic signature that makes the gland of the latter refractory to carcinogenesis. The target cells in the process of breast carcinogenesis are located in the Lob 1 and are characterised by a high proliferation rate, high affinity for polar metabolites, a low DNA reparative activity and a genomic signature that makes them highly susceptible to carcinogenesis [1]. The proliferating cells are different from those containing oestrogen (ER) and progesterone receptors (PgR) [1]. The questions that emerge from these data are if the oestrogen-positive cells are not the proliferating ones, how does the mutation event take place and if the ER-negative cells are the proliferating cells and the target of a mutation event, what is the role of oestrogen in carcinogenesis? Using human breast epithelial cells that are negative for ER and PgR, we have found that oestradiol, at doses of 0.007 or 70 nM or 1 μmol, produced in a dose-dependent manner the same transformation phenotypes as a chemical carcinogen benzo (a) pyrene (BP) [3]. 4 Hydroxy-oestradiol (4-OH-E2), an oestrogen metabolite has a transformation effect at a very low dose (0.007 nM). Pure anti-oestrogens like ICI-182–780 or tamoxifen do not abrogate the effect induced by the E2 or 4-OH-E2. E2 and its metabolites produce loss of heterozygosity in different loci of chromosomes 1lq and 13q12 as well as changes in the mitotic spindle resulting in altered mitosis with consequent aneuploidy. This last event is associated with the upregulation of the kinetochoral protein CENP-F. cDNA array has allowed us to identify a cluster of genes that is the same for cells transformed either by BP, E2 or 4-OH-E2. This data indicate a common genotoxic pathway in the transformation of human breast epithelial cells.

3. Role of gland differentiation

During hormonally-induced differentiation or in response to the physiological milieu of an early first full term pregnancy, the Lob I differentiates to Lob 2, Lob 3 and Lob 4 [4]. This differentiation process is associated with a lower cell proliferation, lower amounts of ER and PgR and a more efficient DNA repair capacity creating a stem cell in the differentiated breast that is more refractory to carcinogenesis [4]. This has been clearly demonstrated in the rat experimental system in which hormonal manipulation that induces the same pattern of differentiation in the mammary gland as a

* Corresponding author. Tel.: +1-215-728-4782; fax: +1-215-728-2180.

E-mail address: j_russo@fccc.edu (J. Russo).

PII: S0959-8049(02)00276-9

full-term pregnancy creates a genomic signature that renders the mammary gland refractory to carcinogenesis. This specific genomic signature is the one responsible for the preventive effect of differentiation.

4. Conclusions

Our studies have discovered a biological law: 'Differentiation of the mammary gland determines the susceptibility to carcinogenesis'. This law allows us to establish three basic norms for breast cancer prevention: (i) the breast at puberty is a developing organ with numerous undifferentiated structures (Lob 1) containing stem cells that are more susceptible to carcinogens, (ii) differentiation of the breast can be manipulated by physiological or physiologically-like conditions, and (iii) breast cancer can be prevented by changing the differentiation status of the susceptible organ.

Acknowledgements

This research was supported by grant DAMDI7-99-l-9182 from the department of Defense of the USA and a donation of the HealthEd Foundation, Philadelphia, PA, USA.

References

1. Russo J, Hu YF, Yang X, Russo IH. Developmental, cellular and molecular basis of human breast cancer. *J Natl Cancer Inst Monogr* 2000, **27**, 17–38.
2. Russo J, Hu YF, Silva JDCG, Russo H. Cancer risk related to mammary gland structure and development. *Microsc Res Tech* 2001, **52**, 204–223.
3. Russo J, Hu YF, Tahin Q, *et al*. Carcinogenicity of estrogens in human breast epithelial cells. *APMIS* 2001, **109**, 39 52.
4. Russo IH, Russo J. Hormonal approach to breast cancer prevention. *J Cell Biochem* 2000, **34**, 1–6.