Trends in Cell & Molecular Biology
Vol. 9, 2014

Review

Mouse models for breast cancer induced by radiation

Leena Rivina[1,#], Michael Davoren[1,*] and Robert H. Schiestl[1,2,$]

Departments of [1]Environmental Health Sciences, [2]Pathology and Laboratory Medicine, and Radiation Oncology, JCCC Healthy and At-Risk Populations Program Area, University of California, 650, Charles E. Young Dr. South, CHS 71-295, Los Angeles, CA 90095, USA.

ABSTRACT

Radiation therapy is a key weapon in the modern arsenal of cancer treatment. However, this effective treatment comes with risks of its own, and the sheer number of patients that undergo radiation as a part of their therapy regimen is only increasing. As this number increases, so does the incidence of secondary, radiation-induced neoplasias, creating a need for therapeutic agents targeted specifically towards reduction in the incidence of and treatment of these cancers. Development and efficacy testing of these agents requires not only extensive *in vitro* testing, but also a set of reliable animal models to accurately recreate the complex situations of radiation-induced carcinogenesis. The laboratory mouse *Mus musculus* remains the most relevant animal model in cancer research due to the molecular and physiological similarities it shares with man, its small size and high rate of breeding in captivity, and its fully sequenced genome. In this work, we review relevant *M. musculus* inbred and F_1 hybrid animal models, as well as methods of induction of radiation-induced breast cancers. Associated molecular pathologies are also included.

KEYWORDS: radiation carcinogenesis, breast cancer, animal models, secondary cancers

1. INTRODUCTION

As the population of the United States ages, cancer diagnosis rates continue to rise. At the same time, post-therapy survival rates are increasing due to advances in medical technology. Current predictions suggest that roughly half of all U.S. citizens will now be diagnosed with cancer at some point in their lifetimes, and of these a further half will receive radiation therapy as part of their treatment regimen [1, 2]. Radiation can be administered as the sole avenue of palliative care, or more commonly in combination with other treatments such as chemotherapeutic drugs, molecular targeted therapy, or immunotherapy. Radiation therapy is also routinely used to initiate immune suppression for bone marrow, stem cell and organ transplantation [3]. The power and utility of radiation as a therapeutic tool, however, brings with it the cost of unavoidable exposure of surrounding healthy tissue to its damaging effects. This collateral damage can result in a variety of acute toxicities or chronic secondary malignancies, and specifically radiation-induced cancer [4, 5].

Rapid technological advances in radiation oncology have provided a greater degree of targeted radiation delivery to tumor sites, reducing unnecessary exposure of healthy surrounding tissues. This more accurate delivery of radiation has the benefit of increasing maximum tolerated doses and increasing the therapeutic ratio [6, 7]. Unfortunately, the very nature of tumor growth and complex tumor/healthy tissue interaction makes it infeasible to completely avoid all collateral exposure, and therefore all potential subsequent malignancy. This fact calls for the development of alternative biological therapies to supplement technological solutions, in order to reduce secondary toxicity and malignancy risks to the absolute minimum.

*Corresponding author: mdavoren@ucla.edu
#yrivin@ucla.edu
$rschiestl@mednet.ucla.edu

Three potential classes of agents could be applied in order to modulate damage to normal tissue. The first class, radiation protectors, consists of agents given prior to radiation exposure. The second, radiation mitigators, would be given post-exposure (PE), but prior to the onset of symptoms; while the third, therapies, would be administered after the onset of symptoms [8]. Only one agent, amifostine [9], is currently approved by the Food and Drug Administration (FDA) for the protection of normal tissues during irradiation. Amifostine falls only under the first category, with intravenous administration generally occurring a few minutes prior to radiotherapy. The government and medical research community recognize that this single therapy is not sufficient. In order to meet this need, the National Cancer Institute (NCI), in collaboration with National Institute of Allergy and Infectious Diseases (NIAID) has proposed an algorithm to be used in the selection of agents for preclinical and clinical development aimed at decreasing the adverse effects of cancer therapy, including radiation [10]. The use of animal models to validate these agents is a key part of meeting the requirements of this algorithm. Therefore, a comprehensive description of animal models relevant to the adverse effects of radiotherapy of breast cancer is of great utility to researchers in the field of prospective treatment development. Williams and colleagues have already extensively covered the selection of animal models designed to mitigate and treat the more acute toxicities associated with radiation exposure [11]. The purpose of this work is to provide an updated review of select inbred mouse models that may be used in preclinical settings in order to test the efficacy of agents specifically intended to protect, mitigate or treat radiation-induced breast carcinogenesis.

2. METHODS

2.1. Research strategy

As a mammalian species with a short maturation time, the laboratory mouse, *Mus musculus*, is one of the best models available for the study of carcinogenesis and its corresponding pathologies. Over time the laboratory mouse has undergone a significant evolution in its complexity. As researchers continue to delve into its genome and develop precise techniques to manipulate it, it has gained the ability to mimic progressively more precise aspects of the multifaceted disease that is cancer. The modern researcher's arsenal contains murine models that range from specific carcinogen-inducible tumors, to xenograft models fully compatible with human neoplastic cells, to humanized mice expressing human genes. Genetically engineered mice (GEM) have now been imbued with the ability to accurately recapitulate the pathophysiological and underlining molecular features of many human cancers [12]. As a result, GEM have replaced many of the genetically homogenous inbred mice once used in environmentally induced cancer studies. With respect to their genetically engineered relatives, older models often developed tumors at low frequencies and with variable latencies. However, GEM specific to a particular question of carcinogenesis are often still difficult to come by, overly expensive, or have not yet been described to an adequate extent. In addition, as GEM are characteristically designed to follow an exact carcinogenesis progression path, their use precludes the study of alternative mechanisms. For these reasons, inbred strains remain a cornerstone of *in vivo* cancer research. Despite their flaws, inbred mice have been indispensable parts of the discovery processes of oncogenes and tumor suppressors, as well as preclinical assessment of the toxic or therapeutic effects of countless agents, [13] discoveries critical to the development of GEM.

In this review, we set out to identify inbred mouse models of radiation-induced (RI) cancers, intended for assessment of efficacy towards interventions aimed at protecting, mitigating or treating these malignancies. We have concentrated on models specific to breast cancers as this subtype has been identified as one of the most common secondary cancer, arising post radiation therapy [5].

2.2. Inclusion criteria

The scope of this review is limited to murine models of radiation-induced breast carcinogenesis. It is specifically focused on cancer induction following exposures to low-LET gamma- and X-ray radiations using both high total dose and high dose-rate. Carcinogenesis induced from high-LET radiation, genetically engineered mouse models, and xenograft models are outside of the scope of this work. For the most part, we have also excluded models requiring supplemental treatment in addition to radiation in order to induce carcinogenesis. Only inbred mice with cancer inducible by either a single

total body irradiation (TBI) or fractionated targeted exposures are described. In order to maximize clinical relevance, we have chosen to focus only on murine models that tightly mimic the underlying molecular pathologies of each type of cancer as observed in humans.

3. RESULTS AND DISCUSSION

3.1. Radiation-induced breast cancer

Japanese female survivors of the atomic bomb attacks, females subjected to diagnostic fluoroscopes in Massachusetts tuberculosis sanatoria, and women treated for postpartum mastitis in New York form three core groups providing compelling epidemiological data linking radiation exposure and breast cancer [5]. Data from the Japanese atomic bomb cohort in particular, demonstrates that breast carcinoma (BC) risk increases by a greater extent than all other solid tumor risks upon exposure to IR [4]. In the Massachusetts study, females exposed to over a hundred separate instances of diagnostic X-rays were shown to be 80% more likely to develop breast tumors [14]. Newer reports continue to emerge implicating radiation therapy as a causative agent in secondary breast cancers, and demonstrate dependency on age of exposure. Up to 35% of women treated for Hodgkin's disease with radiation therapy at an early age developed breast cancer by the age of forty. The studies of Bhatia and Sankila give an approximate IR-induced BC latency period of 10 years following radiation [15, 16]. Stovall and colleagues have reported that an absorbed radiotherapy dose of over 1 Gy to the contralateral breast is linked to a high risk of secondary *de novo* contralateral breast cancer (CBC) [17]. Reproductive history is also a factor in CBC risk. Women who did not have a child prior to their first diagnosis of cancer were more likely to develop CBC after radiotherapy than age-matched controls [18].

Ionizing radiation is a well-established etiological agent in both murine and human breast cancer [19-26]. Mammary cancer mouse models are invaluable to the study of chemotherapeutic interventions and modeling molecular pathologies, despite differences such as low hormonal dependence frequency of the tumor, and differences in precise site of carcinomas origination [20]. The BALB/c mouse is an extensively used model of mammary cancer, induced with either full body irradiation or the implantation of irradiated tissues into syngenic mice [27]. Table 1, summarizes the most commonly used BALB/c models.

3.2. BALB/c whole-body exposure model

Original studies in the BALB/c female whole-body irradiation model have shown an increase in mammary carcinogenesis, from a background frequency of around 8% to about 22% within the mouse's lifetime. The mammary adenocarcinoma induction method consists of irradiating 12 week old females with a total dose of 2.0 Gy, at the relatively high dose-rate ~0.35 Gy/min; irradiation with the same total dose at a much smaller dose-rate of 0.083 Gy/day resulted in roughly half the tumorigenesis

Table 1. Induction of breast cancer in mice with low-LET ionizing radiation.

Malignancy	Mouse strain	Age	Sex	Dosage	Fractionation	Latency	Spontaneous frequency	Induced frequency	Ref.
Breast cancer	BALB/c	12 weeks	Female	2.0 Gy TBI	Single	~24 months	8%	22%	[26]
Breast cancer	BALB/c orthograft	12 weeks	Female	1.0 Gy TBI of donor cells	Single	10 weeks	< 1%	Dysplasia ~75% Tumors ~25% (dependent upon donor cell passage)	[28]
Breast cancer	BALB/c chimera	12 weeks	Female	4.0 Gy TBI of host	Single	6 weeks	~19%	~81%	[29]

frequency, only ~13% [26]. The high dose rate seems to be key; even a dose of 0.25 Gy at 0.35 Gy/min induces mammary tumors in about 20% of mice [30]. Irradiation increases the incidence of breast adenocarcinomas, but does not seem to affect latency relative to spontaneously arising tumors. Hyperplastic lesions in the ductal dysplasia are detected 12-14 months after IR exposure, prior to appearance of the tumor proper [28]. Radiation-induced breast adenocarcinoma sensitivity in the BALB/c female has been attributed to polymorphisms of Prkdc, a DNA-dependent protein kinase, involved in DNA repair and post-IR cell signaling [31]. An unfortunate possible downside of this model, however, is its high rate of concurrent ovarian tumor development, detected in over 90% of autopsied mice [26].

3.3. BALB/c syngenic transplant model

In 1959, a great advance was made in the field of breast cancer biology when DeOme and colleagues introduced a murine orthograft breast cancer model. The model consists of clearing the mammary fat pad from a 3-week-old female virgin mouse, followed by a transplant of a 1 mm duct fragment from a donor mouse with hyperplastic lesions [32, 33]. Ethier and Ullrich successfully adopted this model from the original strain into BALB/c mice, using it extensively to demonstrate differences in sensitivity between strains and associated molecular mechanisms [31, 34-36]. Additionally, Dr. Barcellos-Hoff and colleagues employed this model, further revolutionizing the cancer research field by demonstrating the importance of tissue microenvironment in the breast carcinogenesis process [37-40].

Ethier and Ullrich also employed the 'cell dissociation assay', an *in vitro*/*in vivo* model in which 12 week old virgin donor BALB/c females are whole body irradiated with a total dose of 1.0 Gy, with mammary tissues removed at 24 hours, post-exposure. A single-cell suspension of 10^4 cells from these donor animals is then injected into 3-week-old virgin BALB/c females with cleared mammary fat pads. 10 weeks after the procedure, recipient mice are sacrificed and the outgrowths removed and analyzed for ductal architecture pathologies. Normal outgrowths contain 2 to 3 terminal ducts, are capped by end buds in the fat pad, and resemble anatomically correct ducts. Abnormal outgrowths, on the other hand, have up to 10 or more terminal ducts capped with hyperplastic end buds. These abnormal architectures are assigned an arbitrary classification between I and III, with Class III designated as the most severe [36, 41, 42].

In another series of elegant experiments, Ullrich and colleagues demonstrated that cells harvested from an irradiated donor, passaged *in vitro*, and finally transplanted into unirradiated recipient mice develop into either dysplasia or adenocarcinomas. The result depended upon time of harvesting and number of passages in culture prior to implantation. Cells harvested 52 weeks post-IR and injected into recipient host tended to regenerate dysplastic outgrowths at a high rate (3 in 4) and develop into tumors (1 in 4). Cells harvested at 1-16 weeks developed into normal outgrowths unless they underwent extensive *in vitro* passaging. The dysplasia and tumors observed resembled *in situ* tumorigenesis, with leukocyte infiltrations and angiogenesis [28].

Barcellos-Hoff and Ravani established a chimeric radiation model of their own [43] in which the fat pads of a BALB/c mouse host are cleared at 3 weeks of age, with the same mice whole body irradiated with 4.0 Gy at 10-12 weeks of age. Three days later these hosts receive a transplant of immortalized but non-malignant COMMA-D mouse epithelial cells derived from midpregnant BALB/c females [44] 6 weeks post-IR the cells injected into irradiated host had 81% tumor penetrance, compared to only 19% of cells injected into an unirradiated host. This syngenic model demonstrates that radiation causes changes in the stromal microenvironment which contribute to carcinogenicity. A tissue, rather than cell suspension-based alternative model can achieve a similar result, with a 1 mm^3 formed duct epithelial fragment acquired from a wildtype donor or a donor primed for neoplastic development transplanted into the irradiated host whose mammary fat pads have been cleared [29].

3.4. Breast cancer-associated molecular pathologies

Cell lines derived from female BALB/c mice and harvested at 4 weeks (EF42) or 16 weeks (EF137) after 1 Gy whole body irradiation have been used for some time to examine molecular pathologies leading to tumorigenesis *in vitro* or transplanted into recipient mice for *in vivo* studies. Cell culture studies point to a number of familiar players in the

oncogenic protein scene. Reduced or absent Rb can be detected in EF42 after 11 passages in EF42 cells, and after only 6 passages in the EF137 line. Mutant *p53* is present in 95% of these cells after 20 passages and can even be detected as early as passage 6 in 1-5% of cultures, suggesting *p53* mutation is an early transformation event in these preneoplastic cells. Angiogenesis is usually detected after about 20 passages [28]. In *in vivo* transplantation studies, Ethier and Ullrich reported that introducing ten times the amount of cells at ~10^5 actually decreased both the frequency and severity of observed dysplasia, compared to an injection of 10^4 cells [36, 41]. This suggests that replicative stress may be contributing to faster and more prominent progression into ductal dysplasia.

Barcellos-Hoff and colleagues have linked the rapid remodeling of the irradiated mammary gland microenvironment to changes in both the extracellular matrix and latent TGF-β expression [37, 45-47], later showing that this accelerates tumor progression. Transforming growth factor beta, TGF-β, is involved in the regulation of a variety of cell processes, including cell cycle control, apoptosis, and cell differentiation [47, 48]. Activation of TGF-β as a result of radiation has been implicated to influence cell fate decisions and DNA-repair kinetics in an ATM-dependent manner [49, 50].

Radiation chimera models are able to capture prominent features of breast cancers thought to arise following irradiation, even though the transplanted epithelium itself has not been irradiated. IR-associated human breast cancer arises from the duct cells and often infiltrates the rest of the breast tissue [5], a progression similar to that observed in transplantation models. Functionally p53 negative tumors induced in transplanted epithelium were estrogen receptor (ER) negative [29], akin to that observed in breast cancer of previously irradiated women [51]. The *Rb* deficiencies observed by Ullrich and Preston in neoplastic duct cells are also often reported in human breast cancer correlating with a highly invasive tumor phenotype [52].

4. CONCLUSION

The ideal radiation-induced carcinogenesis mouse model possesses a low spontaneous background frequency of the desired malignancy, has a short latency period, avoids co-developing cancers at alternative sites, and produces tumors nearly identical to the corresponding human cancer in onset, progression and underlying pathology. As a perfect model does not exist, researchers are inevitably forced to compromise on some of these features. It is generally more feasible to compromise on features such as cancer latency and induction frequency, as these can be compensated for by study design and sheer subject volume. However, one cannot compromise on the accurate emulation of molecular and pathophysiological features of human radiation-induced malignancies, as these are the features that make a model relevant in the first place. More advances must be made towards the development of more accurate recapitulations of human radiation-induced cancers. Radiation-induced secondary cancers can still be difficult to discern from primary tumors in humans due to unresolved questions about their respective molecular signatures. Identifying and investigating these signatures in mouse tumors following IR is a difficult challenge with great potential rewards.

The mouse models presented are often a compromise on the background frequencies and rates of induction, but all demonstrate strong molecular and phenotypic correlations to salient features of the human cancers they are meant to represent. These models provide a powerful tool for testing the therapeutic benefit of candidate drugs against radiation-induced breast carcinogenesis.

ACKNOWLEDGEMENTS

This work has been supported by grant no. 1 U19 A1 67769-01 from the National Institute of Allergy and Infectious Disease. The authors also wish to thank the NIEHS Training Grant in Molecular Toxicology for funding provided to Michael Davoren.

CONFLICT OF INTEREST STATEMENT

Robert H. Schiestl is affiliated with RadMit, Inc. The other authors declare no conflict of interest.

REFERENCES

1. Howlader, N., Noone, A. M., Krapcho, M., Neyman, N., Aminou, R., Altekruse, S. F., Kosary, C. L., Ruhl, J., Tatalovich, Z., Cho, H., Mariotto, A., Eisner, M. P., Lewis, D. R., Chen, H. S., Feuer, E. J. and Cronin, K. A. (Eds.), 2012, SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute.

2. Ringborg, U., Bergqvist, D., Brorsson, B., Cavallin-Stahl, E., Ceberg, J., Einhorn, N., Frodin, J. E., Jarhult, J., Lamnevik, G., Lindholm, C., Littbrand, B., Norlund, A., Nylen, U., Rosen, M., Svensson, H. and Moller, T. R. 2003, Acta Oncol., 42(5-6), 357-65.
3. Prasanna, P. G., Stone, H. B., Wong, R. S., Capala, J., Bernhard, E. J., Vikram, B. and Coleman, C. N. 2012, Transl. Cancer Res., 1(1), 35-48.
4. Fajardo, L. F., Berthrong, M. and Anderson, R. E. 2001, Radiation Pathology. New York: Oxford University Press, xv, 454.
5. Hall, E. J. and Giaccia, A. J. 2012, Radiobiology for the Radiologist. 7th Ed., Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.
6. de Arruda, F. F., Puri, D. R., Zhung, J., Narayana, A., Wolden, S., Hunt, M., Stambuk, H., Pfister, D., Kraus, D., Shaha, A., Shah, J. and Lee, N. Y. 2006, Int. J. Radiat. Oncol. Biol. Phys., 64(2), 363-73.
7. Zelefsky, M. J., Fuks, Z. and Leibel, S. A. 2002, Semin. Radiat. Oncol., 12(3), 229-37.
8. Kim, K., Damoiseaux, R. Norris, A. J., Rivina, L., Bradley, K., Jung, M. E., Gatti, R. A., Schiestl, R. H. and McBride, W. H. 2011, Int. J. Radiat. Biol., 87(8), 839-45.
9. Rubin, P. 2008, Late effects of cancer treatment on normal tissues: CURED I, LENT, Medical Radiology, Berlin, New York, Springer, xxii, 140.
10. Ryan, J. L., Krishnan, S., Movsas, B., Coleman, C. N., Vikram, B. and Yoo, S. S. 2011, Radiat. Res., 176(5), 688-91.
11. Williams, J. P., Brown, S. L., Georges, G. E., Hauer-Jensen, M., Hill, R. P., Huser, A. K., Kirsch, D. G., Macvittie, T. J., Mason, K. A., Medhora, M. M., Moulder, J. E., Okunieff, P., Otterson, M. F., Robbins, M. E., Smathers, J. B. and McBride, W. H. 2010, Radiat. Res., 173(4), 557-78.
12. Jackson, E. L., Willis, N., Mercer, K., Bronson, R. T., Crowley, D., Montoya, R., Jacks, T. and Tuveson, D. A. 2001, Genes Dev., 15(24), 3243-8.
13. Frese, K. K. and Tuveson, D. A. 2007, Nat. Rev. Cancer, 7(9), 645-58.
14. Boice Jr. J. D., Engholm, G., Kleinerman, R. A., Blettner, M., Stovall, M., Lisco, H. Moloney, W. C., Austin, D. F., Bosch, A., Cookfair, D. L., Krementz, E. T., Latourette, H. B., Merrill, J. A., Peters, L. J., Schulz, M. D., Storm, H. H., Bjorkholm, E., Pettersson, F., Bell, C. M. J., Coleman, M. P., Fraser, P., Neal, F. E., Prior, P., Won Choi, N., Hislop, T. G., Koch, M., Krieger, N., Robb, D., Robson, D., Thomson, D. H., Lochmuller, H., von Fournier, D., Frischkorn, R., Kjorstad, K. E., Rimpela, A., Pejovic, M.-H., Kirn, V. P., Stankusova, H., Berrino, F., Sigurdsson, K., Hutchison, G. B. and MacMahon, B. 1988, Radiat. Res., 116(1), 3-55.
15. Bhatia, S., Robison, L. L., Oberlin, O., Greenberg, M., Bunin, G., Fossati-Bellani, F. and Meadows, A. T. 1996, New England Journal of Medicine, 334(12), 745-751.
16. Sankila, R., Garwicz, S., Olsen, J., Döllner, H., Hertz, H., Kreuger, A., Langmark, F., Lanning, M., Möller, T. and Tulinius, H. 1996, Journal of Clinical Oncology, 14(5), 1442-1446.
17. Stovall, M., Smith, S. A., Langholz, B. M., Boice Jr. J. D., Shore, R. E., Andersson, M., Buchholz, T. A., Capanu, M., Bernstein, L. and Lynch, C. F. 2008, Int. J. Radiat. Oncol. Biol. Phys., 72(4), 1021-1030.
18. Brooks, J. D., Boice Jr. J. D., Stovall, M., Reiner, A. S., Bernstein, L., John, E. M., Lynch, C. F., Mellemkjaer, L., Knight, J. A., Thomas, D. C., Haile, R. W., Smith, S. A., Capanu, M., Bernstein, J. L. and Shore, R. E. 2012, Int. J. Radiat. Oncol. Biol. Phys., 84(4), 917-924
19. Finerty, J. C., Binhammer, R. T., Schneider, M. and Cunningham, A. W. 1953, J. Natl. Cancer Inst., 14(1), 149-57.
20. Imaoka, T., Nishimura, M., Iizuka, D., Daino, K., Takabatake, T., Okamoto, M., Kakinuma, S. and Shimada, Y. 2009, Journal of Radiation Research, 50(4), 281-293.
21. Medina, D. 2000, Journal of Mammary Gland Biology and Neoplasia, 5(4), 393-407.
22. Preston, D., Ron, E., Tokuoka, S., Funamoto, S., Nishi, N., Soda, M., Mabuchi, K. and Kodama, K. 2007, Radiat. Res., 168(1), 1-64.

23. Ronckers, C. M., Erdmann, C. A. and Land, C. E. 2005, Breast Cancer Res., 7(1), 21-32.
24. Shellabarger, C. J., Cronkite, E. P., Bond, V., Lippincott, S., Scott, W., Pavelec, M. and Canner, M. 1957, Radiat. Res., 6(4), 501-512.
25. Thomas, D. B., Rosenblatt, K., Jimenez, L. M., McTiernan, A., Stalsberg, H., Stemhagen, A., Thompson, W. D., Curnen, M. G. M., Satariano, W. and Austin, D. F. 1994, Cancer Causes & Control, 5(1), 9-14.
26. Ullrich, R. L. 1983, Radiat. Res., 93(3), 506-15.
27. Medina, D. 2010, Cold Spring Harbor Perspectives in Biology, 2(10), a004523.
28. Ullrich, R. L. and Preston, R. J. 1991, J. Radiat. Res., 32(Suppl. 2), 104-9.
29. Nguyen, D. H., Oketch-Rabah, H. A. Illa-Bochaca, I., Geyer, F. C., Reis-Filho, J. S., Mao, J. H., Ravani, S. A., Zavadil, J., Borowsky, A. D., Jerry, D. J., Dunphy, K. A., Seo, J. H., Haslam, S., Medina, D. and Barcellos-Hoff, M. H. 2011, Cancer Cell, 19(5), 640-51.
30. Ullrich, R. L., Jernigan, M. C., Satterfield, L. C. and Bowles, N. D. 1987, Radiat. Res., 111(1), 179-84.
31. Yu, Y., Okayasu, R., Weil, M. M., Silver, A., McCarthy, M., Zabriskie, R., Long, S., Cox, R. and Ullrich, R. L. 2001, Cancer Res., 61(5), 1820-4.
32. DeOme, K. B., Faulkin, L. J. Jr., Bern, H. A. and Blair, P. B. 1959, Cancer Res., 19(5), 515-20.
33. DeOme, K. B., Miyamoto, M. J., Osborn, R. C., Guzman, R .C. and Lum, K. 1978, Cancer Res., 38(7), 2103-11.
34. Ethier, S. P., Adams, L. M. and Ullrich, R. L. 1984, Cancer Res., 44(10), 4517-22.
35. Ethier, S. P. and Ullrich, R. L. 1984, Cancer Res., 44(10), 4523-7.
36. Ethier, S. P. and Ullrich, R. L. 1982, Cancer Res., 42(5), 1753-60.
37. Barcellos-Hoff, M. H. 1993, Cancer Res., 53(17), 3880-6.
38. Barcellos-Hoff, M. H. 1998, J. Mammary Gland Biol. Neoplasia, 3(2), 165-75.
39. Barcellos-Hoff, M. H. 2005, BJR Suppl., 27, 123-7.
40. Barcellos-Hoff, M. H. 2005, Semin. Cancer Biol., 15(2), 138-48.
41. Ethier, S. P. and Ullrich, R. L. 1982, J. Natl. Cancer Inst., 69(5), 1199-203.
42. Ullrich, R. L., Bowles, N. D., Satterfield, L. C. and Davis, C. M. 1996, Radiat. Res., 146(3), 353-5.
43. Barcellos-Hoff, M. H. and Ravani, S. A. 2000, Cancer Res., 60(5), 1254-60.
44. Danielson, M. 1984, Acta Pharmacol. Toxicol. (Copenh), 54(Suppl. 1), 33-6.
45. Barcellos-Hoff, M. H. and Brooks, A. L. 2001, Radiat. Res., 156(5 Pt 2), 618-27.
46. Barcellos-Hoff, M. H. and Medina, D. 2005, Breast Cancer Res., 7(1), 33-6.
47. Barcellos-Hoff, M. H., Park, C. and Wright, E. G. 2005, Nat. Rev. Cancer, 5(11), 867-75.
48. Alberts, B. 2008, Molecular Biology of the Cell, 5th Ed., Garland Science, New York.
49. Andarawewa, K. L., Erickson, A. C., Chou, W. S., Costes, S. V., Gascard, P., Mott, J. D., Bissell, M. J. and Barcellos-Hoff, M. H. 2007, Cancer Res., 67(18), 8662-70.
50. Andarawewa, K. L., Paupert, J., Pal, A. and Barcellos-Hoff, M. H. 2007, Int. J. Radiat. Biol., 83(11-12), 803-11.
51. Castiglioni, F., Terenziani, M., Carcangiu, M. L., Miliano, R., Aiello, P., Bertola, L., Triulzi, T., Gasparini, P., Camerini, T., Sozzi, G., Fossati-Bellani, F., Menard, S. and Tagliabue, E. 2007, Clin. Cancer Res., 13(1), 46-51.
52. Arima, Y., Hayashi, H., Sasaki, M., Hosonaga, M., Goto, T. M., Chiyoda, T., Kuninaka, S., Shibata, T., Ohata, H., Nakagama, H., Taya, Y. and Saya, H. 2012, J. Biol. Chem., 287(11), 7896-906.