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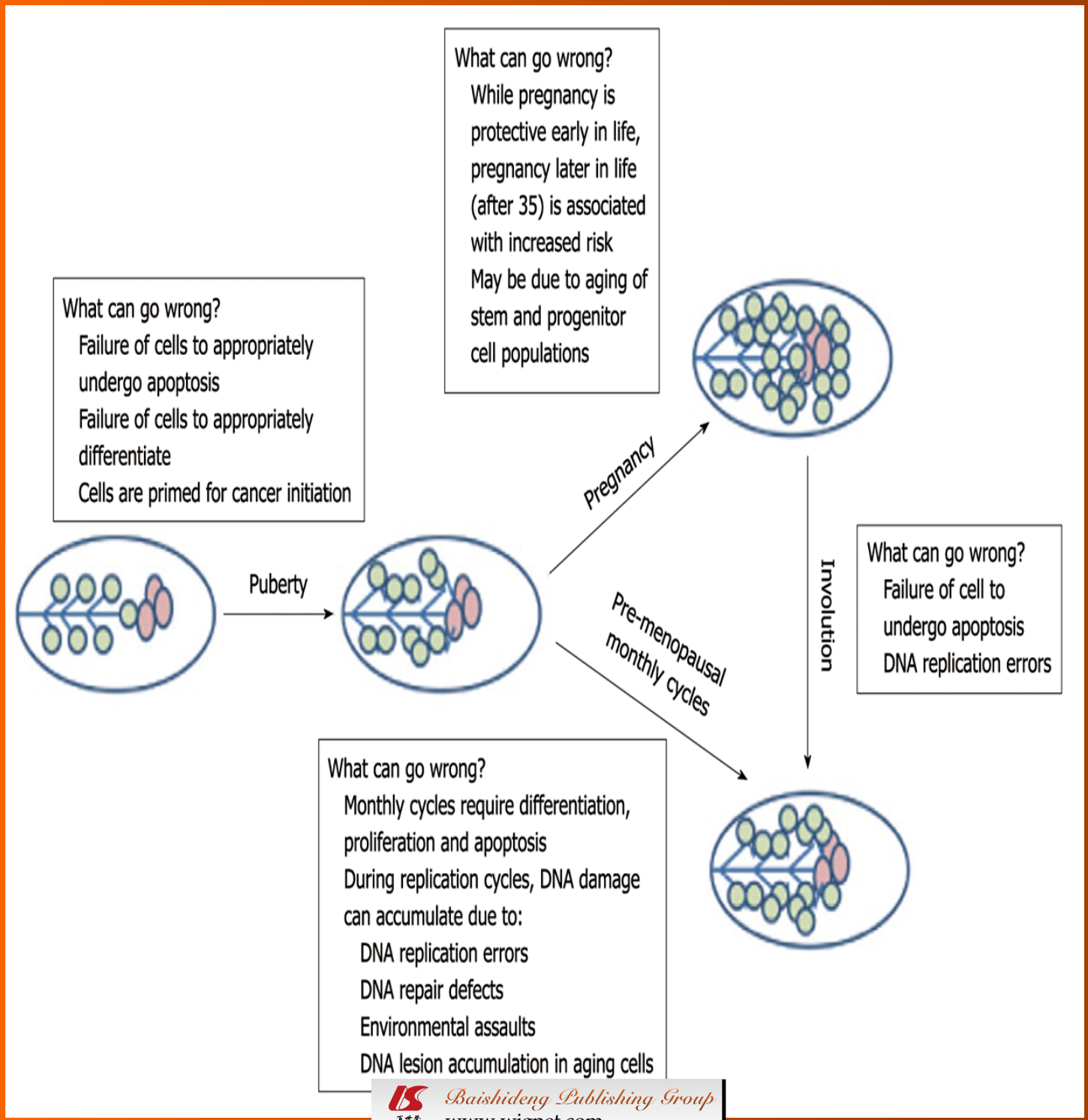

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Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
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Telephone: +86-10-5908-0036
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Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
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Room 903, Building D, Ocean International Center,
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Beijing 100025, China
Telephone: +86-10-8538-1892
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EDITORIAL

DNA damage and breast cancer

Jennifer D Davis, Shiaw-Yih Lin

Jennifer D Davis, Shiaw-Yih Lin, Department of Systems Biology, Unit 950, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States
Author contributions: Davis JD made substantial contribution to the conception, writing and revision of the editorial for important intellectual content; Lin SY provided critical evaluation, writing and revision for important intellectual content; All authors approved the version to be published.
Supported by (in part) Grants from the National Institutes of Health (to Lin SY)
Correspondence to: Shiaw-Yih Lin, Dr, Associate Professor, Department of Systems Biology, Unit 950, The University of Texas MD Anderson Cancer Center, South Campus Research Building II, 7435 Fannin Street, Houston, TX 77054, United States. sylin@mdanderson.org
Telephone: +1-713-5634217 Fax: +1-713-5634235
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Abstract

Cancer is intimately related to the accumulation of DNA damage, and repair failures (including mutation prone repair and hyperactive repair systems). This article relates current clinical categories for breast cancer and their common DNA damage repair defects. Information is included on the potential for accumulation of DNA damage in the breast tissue of a woman during her lifetime and the role of DNA damage in breast cancer development. We then cover endogenous and exogenous sources of DNA damage, types of DNA damage repair and basic signal transduction pathways for three gene products involved in the DNA damage response system; namely BRCA1, BRIT1 and PARP-1. These genes are often considered tumor suppressors because of their roles in DNA damage response and some are under clinical investigation as likely sources for effective new drugs to treat breast cancers. Finally we discuss some of the problems of DNA damage repair systems in cancer and the conundrum of hyper-active repair systems which can introduce mutations and confer a survival advantage to certain types of cancer cells.

INTRODUCTION

In the first section we will first discuss the overlap between classification schemes of breast cancers and the relationship between DNA damage and breast cancer. Next we will discuss endogenous and exogenous sources of DNA damage, and how DNA damage might accumulate in a woman's breast tissue over her lifetime. In the latter half of the review we discuss the role of and briefly touch on the molecular biology of three important DNA damage response genes, *BRCA1*, *BRIT1* and *PARP-1*. This information is vitally important to the development of personalized medicine regimens and to the development of new drugs focused upon removing cancer cells resistant to normal chemotherapeutic and radiation treatment regimens.

CLASSIFICATION OF BREAST CANCERS AND TYPES OF DNA DAMAGE

Breast cancer develops from a heterozygous population of diseases of the breast occurring as tumors in the

breast. Most often (except for fibroids) these tumors can progress to become invasive and deadly in nature if left untreated. Currently, breast cancer classification is utilized by clinicians to form a "plan of attack" for individual patients whose tumors are considered pre-cancerous. Ductal carcinoma *in situ* phenotypes are considered non-cancerous neoplasms compared to invasive breast cancer phenotypes which have spread outside the duct or lobule[1,2]. Although in the near future personalized medicines based on genomics or proteomics might become the preferred approach to determining individualized treatment plans[3], the broad classifications utilized today clinically are described in this review. Breast cancers and neoplasms are intimately related to DNA damage repair defects or defects in cell-cycle checkpoints which allow damaged DNA to go unrepaired. We will present a detailed discussion of the role of two DNA damage response genes, *BRCA1* and *BRIT-1* as well as briefly discussing *PARP-1*. Aberrant DNA damage response gene expression is common in nearly all breast cancer phenotypes[4].

In the last decade, genetic and clinical studies have described several sub-types of breast cancers based upon hormone and growth factor receptor status[5]; genomic descriptions of cancer cell sub-types (Luminal A, Luminal B, Basal-like, HER2+) which have been the basis of modified models of breast cancer development[1]; or protein expression descriptions such as *HER2*-overexpressed or Claudin-low. With the diversity of these classification schemes it is still true that a commonality among breast cancers is a defect in DNA damage repair and BRCA1 inactivation through mutation or epigenetic modification is very common[4,6,7]. We may start our dissection of breast cancer phenotypes with two broad classifications, i.e. inherited *vs* sporadic.

The simplest denomination of breast cancer is based upon inherited susceptibility to breast cancer *vs* sporadic occurrences of breast cancer. Heightened breast cancer risk may be due to a genetic alteration that increases susceptibility based upon an inherited heterozygous gene defect in for example *BRCA1*, *TP53*, *PTEN* or other tumor suppressors[6,8]. Most often these tumor suppressor genes are involved with maintenance of DNA fidelity as is the case for *BRCA1* (DNA damage repair), *TP53* (cell cycle checkpoint) and *PTEN* (blockage of cell-cycle progression in G1 and participation in DNA repair). The genes involved in heritable susceptibility to cancer often function as DNA damage response effectors or cell cycle control effectors[4,9]. Inherited breast cancers occur early and in pre-menopausal years because of the increased risk of loss of heterozygosity, and thus loss of gene expression of a DNA damage response or cell cycle control effector gene product[6,10].

Only 5%-10% of breast cancer cases are thought to be caused by germ-line mutation[5,8,11]. Yet many of the same genetic aberrations present in heritable cancers are present in individuals without genetic pre-dispositions. These breast cancers are often called "sporadic" breast cancers. In sporadic breast cancer-the majority of breast cancers-an acquired mutation or epigenetic inactivation occurs due to mechanisms other than inheritance of defective genetic material. Again many of these mutations or epigenetic inactivations occur within genes involved in DNA damage repair[4,6].

A second method of breast cancer classification is based upon hormone receptor (in particular estrogen and progesterone receptors) and epidermal growth factor receptor (HER-2 specifically) positivity. In this particular classification scheme, estrogen receptor (ER), progesterone receptor and ErbB2/HER2 classification is divided into: (1) hormone receptor positive; (2) hormone receptor negative with HER2 over-expression; and (3) "triple negative" (breast cancer which does not express any of the three receptors)[5,12]. Triple-negative breast cancers often contain inactivation of the DNA repair gene *BRCA1*[4-7,9,12]. In fact, as much as 30% of breast cancers are thought to have some degree of *BRCA1* inactivation[9]. Typically, hormone receptor positive cancer-which is not considered refractory to anti-estrogens-will be treated with ER modulators (SERMs) such as Tamoxifen, Raloxifene or selective ER down-regulators (SERDs) like Fulvestrant in an attempt to slow cancer cell growth[13,14]. Radiation therapy is often utilized to instigate DNA damage in these cancers and thus a combination of surgery, radiation (causing DNA damage) and hormonal therapies can be quite successful. One problem, however, with treatment regimens such as this one is that it is assumed that cells will respond to the DNA damage caused by radiation treatment by apoptosis. If DNA damage responses are not intact in a tumor cell-it may be able to evade the normative mechanisms of cell death instigated by DNA damage. An unfortunate fact is that hormone-sensitive breast cancer, upon recurrence, can evolve into hormone insensitive forms and thus acquire resistance to SERMs and SERDs[15]. If a breast cancer is hormone receptor negative but *HER-2* over-expressing, treatment courses normally include Trastuzumab or other *HER-2* antagonists[14]. Again the focus of these treatments has been to slow cellular growth with the assumption that DNA damage pathways in these breast cancers are functioning appropriately and thus they will respond to radiation therapy by committing cellular suicide. The situation may not be this simple. "Triple-negative" breast cancers (TNBC), i.e. those which are both hormone receptor negative (hormone insensitive) and *HER-2* negative, often have inactivation of *BRCA1*, and thus defects in DNA damage repair mechanisms[5,6,12]. TNBC breast cancers tend to be sensitive to traditional chemotherapeutic agents and treatments, but often reoccur and metastasize aggressively, thus the treatment outcome is poor[11,16]. New research which profiles gene expression early in the etiology of breast cancer development might indicate those cancers which have already acquired resistance to mechanisms that initiate cell death in response to DNA damage. This type of test may be vital to the survival of the patient. The breast cancers with aberrant DNA dam-

Table 1 Categories of breast cancer and associated DNA lesions; breast cancer classification schemes, common DNA damage detected, and current clinical treatments[1]

Breast cancer classification	Screening tests on biopsy sample	Current treatments	Expected outcomes
Hormone receptor positive	Immunohistochemistry, confirmed by CGH	Mostly SERM or SERD which may slow tumor growth. Drugs include: tamoxifen, raloxifene and fulvestrant	High survival rate if responsive to chemotherapy
TNBC	Immunohistochemistry	Surgery, radiation and chemotherapies which inhibit mitosis such as cisplatin	Initially sensitive to traditional chemotherapies and radiation therapy, but high recurrence rate thus poor survival rate[6,71,72]
HER-2 Over-expression	Immunohistochemistry, confirmed by CGH or FISH	HER-2 agonists such as trastuzamab or lapatinib and sometimes doxorubicin	Although this is a fast growing cancer if responsive to therapy *HER2* agonists can half the rate of recurrence[5,73]
Luminal type A or B	Immunohistochemistry and micro-array or tissue array	As described above depending upon hormone receptor and growth factor receptor expression	5-year recurrence rate is lower and survival rate higher than for basal-like breast cancers[71,72]
BLBC	Immunohistochemistry and micro-array or tissue array	Similar to TNBC	5-year recurrence rate higher and survival rate lower than for luminal breast cancer types[71,72]

[1]Categories based upon claudin-over-expressing, microRNA expression patterns or comparative genomic hybridization expression patterns are currently not widely utilized, thus standardized clinical protocols have been omitted from this table. TNBC: Triple negative breast cancer; BLBC: Basal-like breast cancer; SERM: Selective estrogen receptor modulators; SERD: Selective estrogen receptor down-regulators; CGH: Comparative genomic hybridization.

age responses may be particularly responsive to drugs which are poly (ADP) ribose-1 (PARP-1) inhibitors. PARP-1 inhibitors may work by generating massive spontaneous DNA damage and causing catastrophic chromosomal abnormalities in cancer cells which lack proper DNA repair mechanisms due to defective repair genes such as *BRCA1*. The outcome in the cancer cell is then to initiate cell death. This may be highly effective in TNBC cancer cells with abnormally high tolerance to replication stress[16,17].

A third classification method for pre-malignant and malignant breast lesions and tumors is based upon micro-array data and associated cell-type of origin. In this classification scheme, cancers are termed as Luminal A type, Luminal B type, Basal type or ErbB2-over-expressing. This classification scheme, created by Allred *et al*[1], bases itself upon micro-array and immunohistochemical data tied to traditional models of breast cancer development and evolution. Because the mammary epithelium consists of multiple cell-types, this classification scheme attempts to predict the outcome of treatments based upon the predicted behavior of the cancer cell-type of origin in relation to breast cancer development. Basal-like breast cancers (BLBC) often share similar gene profiles with TNBC and often tumors with BRCA1 inactivation can also be classified as TNBC or BLBC[11,16,18]. Because the stem cell compartment of the breast epithelium is hypothesized to be basal in origin, the fact that in this model basal breast cancers tend to be the most aggressive would agree with theories of breast tumor-initiating cells as the "resistant" population of cells which re-initiate tumors during breast cancer relapse[11,18]. A refinement of this classification scheme includes a "claudin-low" breast cancer sub-type, described as the cancer phenotype enriched for tumor-initiating cells[11,18]. Large epidemiological studies determining whether these breast cancer stratifications are effective predictive models for treatment outcomes have yet to be performed. However, standard classification models such as hormone receptor positive, *HER-2* over-expressing or TNBC have been utilized clinically for over a decade to determine breast cancer treatment courses.

Comparative genomic hybridization (CGH) has been utilized to determine *HER-2* status when immunohistochemical analysis is equivocal[2]. This can further inform physicians of the need for a particular clinical approach which may or may not include targeting *HER-2* utilizing Trastuzumab. As the genetic underpinnings of breast cancers and gene signatures become more refined, it is likely that CGH will become an important validation test for initial screening of breast cancer samples. In addition, researchers have recently suggested that microRNA screening may be an effective means of detecting down regulation of gene products[19]. Some microRNA is also suggested by initial studies to confer resistance to commonly used chemotherapy drugs such as Fulvestrant[15]. This complements studies suggesting that microRNAs can regulate *BRCA1* cascades and thus DNA damage programs in cancer cells during cancer development[20]. For a brief review of breast cancer classification, screening tests, current treatment and expected outcomes (Table 1).

ETIOLOGY AND RISK OF DNA DAMAGE DURING DEVELOPMENT AND ADULTHOOD

One important factor to keep in mind is that breast (mammary) tissue has increased opportunity for DNA damage occurrence because of the extensive remodeling that occurs throughout a woman's life. Breasts are one of the few organs in the body that undergo precisely defined cell death and cellular proliferation on a moderate to large scale during *in utero* development, puberty, monthly pre-menopausal 28-d cycles, during pregnancy, lactation and involution (weaning-induced process of massive

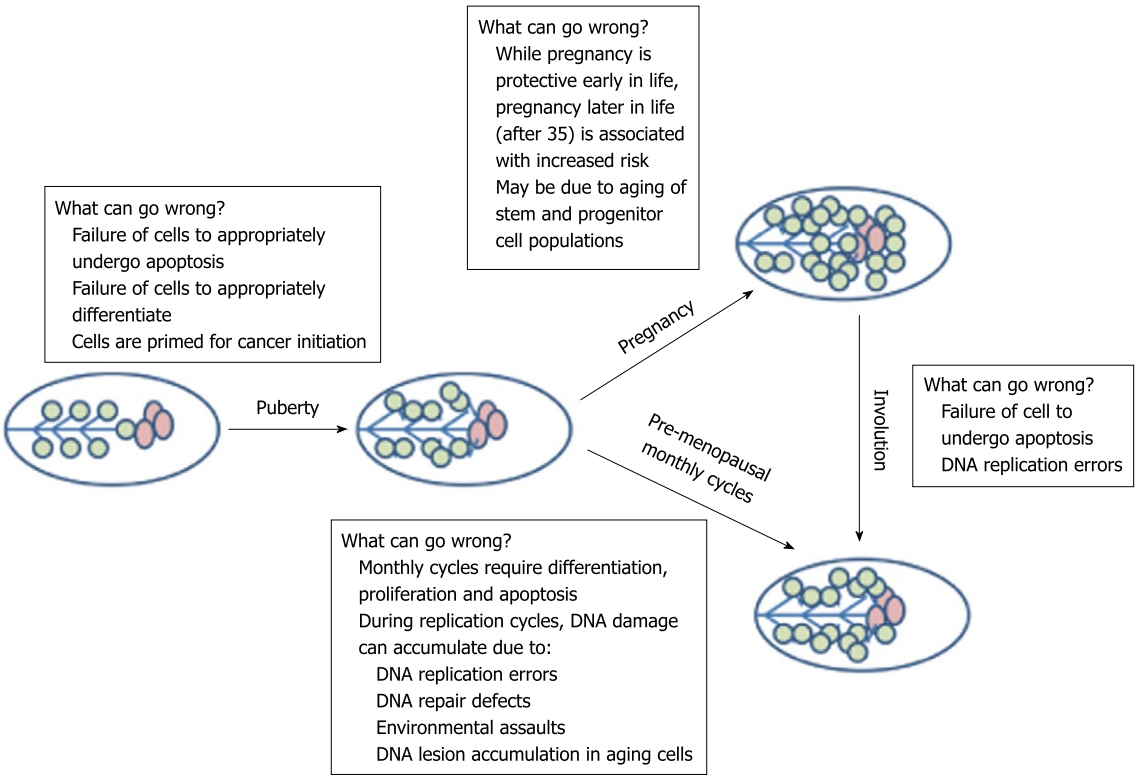

Figure 1 Mammary biology and cycles of remodeling requiring carefully controlled cell cycle regulation in which dysfunctional DNA repair mechanisms may instigate carcinogenesis. At any point during development and mammary remodeling, defects in repair of DNA damage can occur and become the basis for later oncogenesis. In this illustration, the relative numbers of remodeled structures (ducts and lobules) are illustrated by the mammary epithelial tree with green dots representing end buds and lobules and red dots representing lymph nodes.

mammary remodeling)[21-23]. Thus, throughout a woman's lifetime her mammary tissue is undergoing proliferation, apoptosis and differentiation at a rate higher than most other tissues. Problems in DNA structure and function might accumulate in puberty due to a failure of cells to mature (differentiate). DNA damage can be detected even post-pubertal in animal models when female animals are exposed to certain foods either pre-pubertal or *in utero*[24,25]. Other common problems in the developing mammary gland might be a failure of fidelity in DNA replication or a failure of cells to die where appropriate during the rapid bodily growth and development that occurs during puberty. During pregnancy, the mammary environment changes at a very rapid pace[22,23,26] and because of extensive proliferation, DNA replication is likely to produce mutations during this process. In adulthood, the mammary gland undergoes monthly hormonal fluctuations inducing cycles of proliferation, senescence and apoptosis. With the busy environment of the mammary gland it is no wonder that breast cancer is the most common female malignancy and many women (up to 1 in 5) will develop breast cancer some time in their life[22]. A summary of key time-points of mammary proliferation, differentiation and apoptosis, and "what can go wrong" to contribute to DNA damage accumulation is shown (Figure 1). However, it remains to be determined which dietary and environmental exposures may present the most DNA damage in early life or adulthood, and whether this accumulation of DNA damage is directly related to breast cancer risk.

DNA assaults during these times of mammary remodeling may be endogenous (replication stress, oxidative species, replication errors), environmental (chemical exposures, food contaminants, naturally occurring endocrine disruptors in foods) or simply due to the process of aging which in itself can produce increased susceptibility to chromosomal abnormalities because of reduced expression of enzymes which protect the ends of chromosomes (telomerase). Because of the enormous activity of the mammary tissue, it is easy to understand that-of all the bodily tissues-it may be one of the most susceptible to DNA damage and one with the most need for intact, sensitive DNA damage response systems. Below we will discuss in further detail three categories of DNA assaults which can cause DNA lesions and damage, namely (1) endogenous assaults on DNA; (2) environmental assaults on DNA; and (3) aging and senescence.

Endogenous assaults

Endogenous assaults on DNA are common, and three basic assaults are DNA copying errors, replication stress due to a requirement for high levels of proliferation and endogenously created reactive oxygen species. Replication of DNA is error prone, however, there are several endogenous mechanisms of DNA repair (which will be discussed later in this review). Some DNA damage occurs under the normal fluctuations of physiological

conditions such as removal of purines by acidic or high temperature conditions (occurs at about 1×10^4 purines per day per cell in the mammalian genome), removal of altered bases by DNA glycosylases, incorrect base-pairing which can occur because of defects in 3'→5' exonuclease proofreading and incorporation of bases[27]. However, the process of DNA repair itself can create mutations, insertions, deletions and base replacements. For example, mutations can occur due to inappropriately high levels of a repair mechanism which normally suppresses tumorigenesis-mitotic recombination and hyper-recombination-which has recently been linked to mutations in BRCA1 but is also likely to occur due to other defects in DNA damage repair genes[28-30].

Gross DNA lesions and chromosomal abnormalities can be induced by DNA replication stress. Replication stress is a hall-mark of pre-cancerous cells and may occur when accelerated replication is required such as with tissue regeneration or response to hormones or growth factors which stimulate replication. During this time chromosomal abnormalities can accumulate in the DNA synthesis phase of the cell cycle (S phase) and carry over to mitosis (M phase). The result can trigger tetraploidy, aneuploidy or chromosomal breakage at fragile sites on chromosomes[31]. The DNA replication stress model suggests that genomic instability is activated by hyper-proliferation induced by "oncogenes" or genes which when over-expressed induce high levels of proliferation[32]. However, it must also be remembered that at times of tissue regeneration or remodeling, high levels of DNA replication and cellular proliferation are required and so replication stress could be an endogenous mechanism of DNA damage-especially in tissues like mammary glands which must go through frequent cycles of remodeling. However, if cells acquire resistance to apoptosis or senescence, genomic instability can ensue[32,33].

Reactive oxygen species (ROS), mainly produced by metabolic by-products of energy production in mitochondria can also promote DNA damage. This type of DNA damage is often called oxidative damage. Much of the endogenous source of reactive oxygen species in the mitochondrion is the created by-products of cellular respiration. These include, but are not limited to, superoxide anions, hydroxyl radicals, hydrogen peroxide, nitric oxide and peroxynitrite. Some of these potent oxidants react with hydroxyl groups of DNA and can induce the breakage of DNA strands. Normally *PARP-1* is activated in a situation of oxidative stress as a mechanism to protect DNA from further damage and initiate either DNA repair mechanisms or cell death[34]. Recently, a more sophisticated understanding of *PARP-1* has evolved, and it has therefore become a current target of breast cancer drug strategies under intense investigation for the initiation of apoptosis in cancer cells. In particular, cancer cells deficient in *BRCA1*, another DNA repair protein, can be especially sensitive to *PARP-1* inhibition. In this treatment strategy, significant accumulation of chromosomal abnormalities is proposed to lead to cell death in cancer cells sensitive to this mechanism of triggering apoptosis[34,35].

Environmental assaults

Environmental assaults occur almost daily in adult tissue and can be due to exposure to radiation such as gamma irradiation or various chemicals known as carcinogens. Gamma irradiation can cause DNA lesions such as single and double-strand breaks by inducing breakage of phosphodiester bonds which form the back-bone of the DNA double-helical structure. This type of damage is normally repaired by homologous recombination. Chemical DNA damaging agents are present in the environment, water, air, and pollution. Individual job occupations can also increase the risk of exposure to these agents. Several categories of carcinogens exist, but we will only cover a few broad categories. DNA base-pair analogs that have a chemical structure almost identical to that of a DNA base can therefore change DNA base-pairing rules thus "tricking" DNA polymerase into substituting an incorrect base during replication. One common example is an analog of thymidine (5-bromouracil for example) causing a T:A base pairing to become a C:G substitution. Hydroxylating agents add a hydroxyl group, and for example hydroxylated cytosine pairs with adenosine instead of guanine causing a T:A substitution. Alkylating agents add an ethyl or methyl group to DNA and can cause either base-pair substitutions or epigenetic silencing of gene expression. Deaminating agents remove amine groups from base-pairs thereby causing instability in the DNA backbone by interfering with normal formation of hydrogen bonds. A final broad category is insertion agents, often called intercalating agents, which cause DNA bulges that can be repaired to insert or delete a random base-pairing where the bulge was present. One example of a common intercalating agent is proflavin[36].

Reversal of aging and senescence can result in accumulation of DNA damage

Cancer has been described as a "disease of aging" but might more appropriately be called a disease of "aging gone wrong". Aging is a normal process of life and of the life-cycles of cells. One sign of aging is shortening of telomeres. Telomeres consist of repetitive DNA sequences located at the ends of chromosomes and function to protect the ends of chromosomes from deterioration or fusion with other chromosomes during mitosis. Telomerase is an enzyme that maintains telomere length by adding long repeats of TTTAGGG during replication cycles, normally of gametes, stem cells and abnormally in cancer cells. Shortening of telomeres occurs as a natural process of aging and as a consequence of DNA replication. In humans, DNA replication has an "end replication" problem caused because DNA polymerases are unidirectional and thus cannot continue DNA synthesis to the ends of the chromosome. Telomeres are the structures that have evolved to solve this problem. In normal human somatic cells, senescence occurs after a predictable time and is

triggered by the activation of interdependent mechanisms including telomere shortening. Telomeres naturally shorten due to the problem of replicating the ends of chromosomes in the linear DNA synthesis process utilized by mammals[37]. In order to prevent premature telomere shortening, the cell utilizes telomerase complexes which contain a telomerase reverse transcriptase (hTERT in humans) and a telomerase RNA. Together this complex can renew the repetitive end-repeats of chromosomes and thus extend the proliferative potential of the cell. In somatic cells, telomerase expression is normally very low, however, in highly proliferating cells and cancer cells, telomerase expression and function is exceptionally high[37-39].

Telomerase can be activated in tumor cells and is likely a mechanism by which cancer cells acquire an ability to continue replicating beyond the normal life-cycle of a cell, failing to go into senescence. Recent *in vitro* studies suggest that breast cancers might contain tumor-initiating cells which have become resistant to the normal induction of senescence[38,40]. One of the tumor suppressing mechanisms of the gene BRCT repeat inhibitor of hTERT (*BRIT-1*), which was discovered through a genetic screen of telomerase inhibitors is directly linked to stopping the inappropriate maintenance of telomeres[41-43]. This cellular immortalization then can allow for accumulation of mutations which confer to the cancer cell an even further survival advantage or metastatic potential. However, *BRIT1* which was first cloned by Dr. Lin and has been characterized by our laboratory has many other, more complex roles with regards to DNA damage repair. These roles will be discussed in detail in a later section.

DNA repair mechanisms

Thus far, we have discussed the classification of breast cancers, the developmental time points of DNA damage accumulation and the ways in which DNA damage may accumulate in breast tissue over time. We will now discuss basic types of DNA lesions and the DNA repair mechanisms utilized by the somatic and cancer cell. By manipulating these repair mechanisms, cancer cells often gain a survival advantage. However, by understanding key players in DNA damage response, better targets may be developed for the treatment of breast cancers. Two key players we will thus discuss are *BRCA1* and *BRIT-1* which control *BRCA1* signal transduction as one mechanism among other methods of tumor suppression. *PARP-1* also plays a role in DNA repair and will be discussed briefly as a current target for clinical therapies.

Types of DNA lesions and their repair mechanisms

There are several types of physical DNA lesions acquired throughout life by mechanisms described earlier. The broad categories include DNA mutations (insertions, deletions, inappropriate repetitions), and DNA chromosomal abnormalities including single strand breaks (SSB), double strand breaks (DSB) and chromosome fusion. There are also anomalies such as hyper-methylation of promoter regions, but these epigenetic modifications of DNA will not be discussed in this review. For now we will focus on DNA lesions which are repairable by proteins either under investigation or clinical trial for current drug targets, namely *BRCA1, BRIT1 and PARP-1*.

Single nucleotide substitutions, base-pair insertions and base-pair deletions and inappropriate base-pair repeats can occur as a consequence of DNA damage due to environmental factors or simply as a mistake in the proof-reading ability of DNA polymerases. These types of DNA damage are repaired through (1) nucleotide excision repair (NER); (2) base excision repair (BER) or (3) mismatch repair (MMR).

NER is a rapid and efficient mechanism used by cells to repair distortions in the DNA double helix which may be recognized as bulky adducts. These are often caused by thymidine dimers induced by ultraviolet light overexposures. Specific protein machineries will recognize and remove the distorted bases from the replicated strand and a few adjunct nucleotides. Next, a DNA polymerase delta or epsilon will fill in the gaps while ligase activity rejoins the bases to the strand. This mechanism of DNA repair is particularly important in maintenance of the skin, and loss of NER activity is related to heritable skin diseases such as Xeroderma pigmentosum or Cockayne' s syndrome. NER mechanisms differ from BER in that BER requires specific glycosylases which will recognize only certain types of DNA damage. NER consists of two subpathways, one functioning as a global genomic nuclear excision repair (GG-NER repair) in which the entire genome is surveyed for helix-distorting DNA damage and another nuclear excision repair that is coupled to transcription (T-NER)[44,45]. These processes, similar to other DNA repair processes, are modified by ubiquintination of several DNA repair proteins involved in the machinery which recognizes or repairs double helix distortions[45].

The BER DNA repair mechanism repairs small, non-helix-distorting, nucleotide base lesions or single strand breaks within the genome. This type of repair is initiated by DNA glycosylase which recognizes the damaged bases. The chemical bonds between damaged bases are then cleaved by endonucleases causing a single-strand break. The repair can involve replacement of single nucleotides (thus a short-patch repair) or several nucleotides (a long-patch repair in which two or more nucleotides are replaced)[45,46]. An important protein involved in BER and single strand break repair is PARP-1, and this particular target is under intense clinical investigation as a fruitful treatment for TNBC patients[35,47,48].

MMR is a DNA repair system that recognizes errors such as incorrectly paired nucleotides, insertions and deletion loops[45]. The errors can occur during DNA replication and recombination as well as, some forms of DNA damage. One unique characteristic of mismatch repair is that it is strand specific, focusing on correcting mistakes in the daughter strand and in this type of DNA repair, the parental strand is utilized as a template for DNA repair.

Table 2 Summary of DNA lesion type, repair mechanism and gene products

Repair mechanism	DNA lesion type	Genes or gene families involved in repair
NER	Distortions of DNA double helix or bulky adducts	Xeroderma pigmentosum related genes (*XPA*, *XPC* and others) and Cockayne's syndrome related genes (*ERCC6* and others)
BER	Small, non-helix-distorting nucleotide base lesions or single strand breaks	AP endonucleases, DNA glycosylases
MMR	Incorrectly paired nucleotides, insertions and deletion loops	*MSH2*, *MLH1*
HR	SSB and DSB	*BRCA1/2*, *BRIT1*, *BLM*
NHEJ	Chromosomal breaks, also to create genetic diversity for immune cells	*Ku70*, *Ku80*, *DNA-PKcs*, *XRCC4*

NER: Nucleotide excision repair; BER: Base-pair excision repair; HR: Homologous recombination; MMR: Mismatch repair; NHEJ: Non-homologous end joining; SSB: Single strand breaks; DSB: Double strand breaks.

Mismatch repair requires not just the mis-matched nucleotide to be excised, but also several flanking base-pairs by the exonucleases involved in correcting the replication problem. DNA polymerase activity can then place the correctly matched nucleotides on the daughter strand and ligases will re-join phosphor-diester bonds. MMR is often a function of their proof-reading abilities of enzymes involved in DNA replication and requires complex protein machineries consisting of mutationally activated proteins, polymerases, exonucleases, helicases as well as others. MMR defects are common in colon cancer[49], while enhanced mismatch repair in breast and ovarian cancer cells can confer resistance to chemotherapeutic drugs based on platinum structure such as cisplatin[50]. The goal of platinum-based drugs is to confer DNA damage which is severe enough to trigger apoptosis in rapidly dividing cells (those which may already be encountering replication stress).

Single strand breaks (SSB) can occur as a consequence of exposure to carcinogens, reactive oxygen species or as a consequence of mistakes in DNA repair. SSB are repaired through (1) mitotic recombination (MR) or (2) base excision repair (BER as described above). The proteins discussed in this review and involved in HR and mitotic recombination include *BRCA1, BRIT1* and *PARP-1*.

HR is vital to genetic diversity during meiosis in gametes and for repair of single strand DNA breaks. HR can most simply be explained as the exchange of genetic material between homologous chromosomes. HR works *via* a mechanism of single-stranded DNA molecule invasion of a homologous sister strand and formation of a heteroduplex which is then stabilized by base-pairing between each transferred strand and the intact polynucleotides of the invaded or recipient strand. Branch migration then occurs by unknown mechanisms and subsequently a Holliday structure is formed when DNA ligase seals the two strands together forming a cross-shaped junction or Holliday junction. Holliday junctions which eventually make D-loop formations are then cleaved and DNA ligases reseal the DNA strands of the recombined double-helices. These junctions form between two homologous double-stranded stretches of DNA which can be between homologous chromatids during mitotic DNA replication or homologous chromosomes during meiosis. The most important feature of this model is the heteroduplex which is stabilized by base-pairing between each transferred strand and an intact polynucleotide of the recipient or invaded strand. HR is a very flexible mechanism for repairing SSB, DSB, interstrand crosslinks, stalled or collapsed replication forks or simply for creating genetic diversity[28,29,51-53]. HR is a common DNA repair mechanism employed by cells undergoing replication stress, and over-use of these repair mechanisms in themselves can lead to mutations[28,29,52]. Spontaneous recombination in response to DNA damage occurs due to lesions that do not block the replication fork, but instead leave potential recombinogenic substrates such as single-stranded gaps in DNA sequences[28,29,51,52].

Double strand breaks are caused by environmental carcinogen exposure (such as exposure to certain benzene-derived products)[54-56] and replication stress[31,32]. This type of DNA damage is repaired through (1) HR recombination (as described above) or (2) non-homologous end-joining (NHEJ). NHEJ is utilized when sister chromatin is unavailable and normally occurs when cells are in G1 of interphase of the cell cycle. It consists of ligation of broken DNA double strand breaks without further replication of homologous DNA sequence. It has been shown that only less than 50% of DSBs were repaired by HR in mammalian cells. NHEJ is also a mechanism utilized by immune cells in V(D)J recombination to create genetic diversity which in turn aids in the probability of certain types of immune cell recognition of diverse antigens to which humans are exposed[57]. Initial studies suggest that breast cancer cells deficient in BRCA1/2 may utilize NHEJ in order to obtain a survival advantage[58]. For a final summary of DNA lesion type, repair mechanism and gene products (Table 2).

DEFECTS IN DNA REPAIR PATHWAYS ASSOCIATED WITH BREAST CANCER: FOCUS ON BRCA1, BRIT-1 AND PARP-1

The most common DNA damage response systems are tightly regulated and cause cells to stop cell cycle at a G1 checkpoint, during S phase (DNA Synthesis phase) portion of interphase of the cell cycle or during mitotic phase (cell division) of the cell cycle. One important gene

involved in DNA damage response to ionizing radiation or double strand breaks is the Ataxia telangiectasia mutated (ATM) gene. ATM is a serine/threonine kinase which is activated by DSB and which phosphorylates several key proteins that initiate activation of DNA damage checkpoints including *p53, Chk1,* and *Chk2*. ATM is also at the top of a regulatory cascade of DNA damage repair initiators such as *BRCA1*. ATM activation of downstream proteins can result in cell cycle arrest, DNA damage repair or apoptosis depending on downstream effector proteins.

Cells with dysfunctional *BRCA1* gene expression suffer defects in performance of double strand break (DSB) repair mechanisms including homologous recombination and non-homologous end-joining. *BRCA1* contains several domains which are effectors of DNA repair. Two of these domains include (1) a *BRCA1* c-terminal domain (BRCT)[59]; and (2) an N-terminal RING domain which interacts with BARD1 protein to allow for E3 ubiquitin-ligase activity[60-62]. The BRCT domain contains repeats which bind to unique phosphor-serine motifs of other proteins and which allow participation in DNA damage checkpoint and double strand break repairs[30,42,59,63]. BRCT domains are also found in other breast-cancer-related genes such as *XRCC4* or *FANCG*. It is normative for these gene products to form protein complexes that can mediate repair of DNA damage[10,64,65]. Mutations in the BRCT domain of *BRCA1* which inactivate its binding capacity, can result in increased single stranded DNA and hyper-recombination rates without changes to non-homologous end-joining DNA repair mechanisms[30]. It is currently unknown whether similar mutations in BRCT regions of other genes may also result in hyper-recombination effects. However, it is likely a redundant mechanism.

Another DNA damage response gene product-*BRCT-repeat inhibitor of hTERT expression (BRIT-1)*-is an early mediator of DNA damage response and repair systems through a wide variety of mechanisms ranging from regulation of the *BRCA1-Chk1* pathway to stabilizing chromatin architecture[42,66]. *BRCA1* is an important part of this DNA damage response system and *BRIT1* regulates early DNA damage responses as well as helping to maintain chromosomal integrity. *BRIT1* is required for the formation of irradiation-induced foci and for phosphorylation of ATM which then phosphorylates downstream effectors of DNA repair such as *BRCA1*[41,42,66,67]. Because of the role of *BRIT1* in controlling signal transduction through the *BRCA1-cdk1* pathway, there may be an intimate relationship between the function of *BRIT1* and *BRCA1* negative tumors. The downstream effector of *BRCA1* activity, *Cdk1* has recently been described as a potential biomarker of Paclitaxel sensitivity in several breast cancer cells lines when tested through xenografts in nude mice[68]. It remains undetermined whether *BRIT-1* negative tumors have chemo-resistance qualities.

Other mutated gene products conferring increased cancer risk and involved in HR-such as BLM (Bloom' s syndrome gene), a RecQ helicase-also give rise to genomic instability, mitotic hyper-recombination and increased mutations[69]. It is important to keep in mind that the DNA repair process itself can instigate mutations, especially in recombination events to resolve DSB. Recombination requires *de novo* synthesis of a portion of both DNA strands based upon a homologous template, and thus is generally considered "error free" but-when hyper-activated-HR can introduce anomaly in DNA. This phenomenon, as it relates to breast cancer, remains to be explored further.

PARP-1 is a protein which can detect single-strand DNA damage through its N-terminal RING finger domain. Upon sensing the break, *PARP-1* forms a homodimer with catalytic activity. *PARP-1* then has several roles such as recruiting repair enzymes to the site of the SSB, relaxing chromatin structure in order to allow for DNA damage repair and preventing DSB. Initial clinical studies suggest that *PARP-1* inhibitors will be a fruitful adjuvant therapy for TNBC and BLBC which are *BRCA1* negative as *PARP-1* inhibitors appear to re-sensitize cells to DNA damage.

BREAST CANCER TUMOR INITIATING CELLS AND DNA DAMAGE REPAIR

The current definition of tumor-initiating cells is cells which are resistant to chemotherapeutic intervention and which when transplanted into other parts of the body can form identical tumors. Data from studies of cancer cell lines support the concept that tumor-initiating cells are resistant to ionizing radiation and chemotherapy[18,40,70]. Future studies discovering the mechanism of resistance utilized by these cell populations may be vital in the development of treatment regimens for chemotherapy resistant cancer and breast cancers with poor prognosis such as TNBC or BLBC. It is likely that these cell types have enhanced DNA damage repair activity which confers a survival advantage.

CONCLUSION

Various classification schemes have guided treatment options for breast cancer patients but have not been sufficient to provide consistently successful individualized treatment regimens. In the future, what we now know regarding the complexities of DNA damage, the causal relationships between endogenous and exogenous factors and types of DNA damage as well as major genes involved in DNA damage will guide breast cancer treatments. Three gene candidates present important biomarkers of DNA damage resistance, namely BRCA1, BRIT1 and PARP-1. As personalized medicine becomes more sophisticated it may be that DNA damage "signatures" help physicians to choose the best targeted therapies for individuals with breast cancer.

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Murielle Mimeault, PhD, Department of Biochemistry and Molecular Biology, College of Medicine, Eppley Cancer Institute, 7052 DRC, University of Nebraska Medical Center, 985870 Nebraska Medical Center, Omaha, NE 68198-5870, United States

Vaclav Vetvicka, Professor, Department of Pathology and Laboratory Medicine, University of Louisville, 511 S Floyd St, MDR Bldg, Rm 224, Louisville, KY 40202, United States

Songsak Petmitr, PhD, Associate Professor, Department of Tropical Nutrition and Food Science, Mahidol University, 420/6 Ratchawithi Road, Bangkok 10400, Thailand

Steven A Rosenzweig, PhD, Professor, Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, United States

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Events Calendar 2011

January 13-14, 2011
3rd Breast-Gynecology International Cancer Conference BGICC, Cairo, Egypt

January 15-16, 2011
Melanoma 2011: 21st Annual Cutaneous Malignancy Update, San Diego, CA, United States

January 15, 2011
Current Trends in Breast Cancer: Updates From the 2010 San Antonio Breast Cancer Symposium, Dallas, TX, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011, San Francisco, CA, United States

January 21-23, 2011
8th Meeting of the EAU Section of Oncological Urology, London, England, United Kingdom

January 27-28, 2011
2nd National Conference: Recent Advances in Renal and Bladder Cancer, London, United Kingdom

January 27-28, 2011
8th Annual Cancer Drugs Research & Development, San Diego, CA, United States

February 10-12, 2011
17th Annual NOCR Meeting, Las Vegas, NV, United States

February 19-22, 2011
Scripps Cancer Center's 31st Annual Conference: Clinical Hematology and Oncology, San Diego, CA, United States

February 24-26, 2011
European Multidisciplinary Conference in Thoracic Oncology (Lung 2011-EMCTO), Lugano, Switzerland

February 25-27, 2011
7th European Congress on Hematologic Malignancies: From Clinical Science to Clinical Practice, Budapest, Hungary

March 02-05, 2011
64th Society of Surgical Oncology Annual Cancer Symposium 2011, San Antonio, TX, United States

March 04-06, 2011
8th Annual Oncology Nursing Advanced Practice: Innovation through Practice, San Diego, CA, United States

March 07-09, 2011
9th International Symposium on Targeted Anticancer Therapies, Paris, France

March 09-13, 2011
16th National Comprehensive Cancer Network Annual Conference (NCCN 2011), Hollywood, FL, United States

March 11-12, 2011
12th European Congress: Perspectives in Lung Cancer, Torino, Italy

March 14-18, 2011
Oncology Imaging Update in Costa Rica, Guanacaste, Costa Rica

March 17-19, 2011
International Cancer Prevention Update Symposium, New York, United States

March 18-22, 2011
Vienna, Austria 26th Annual EAU Congress

April 02-06, 2011
AACR 102nd Annual Meeting, Orlando, FL, United States

April 08-10, 2011
Asian Oncology Summit 2011, Hong Kong, China

April 20-23, 2011
9th International Gastric Cancer Congress, Seoul, South Korea

April 29-30, 2011
Cancer Survivorship Conference, Minneapolis, MN, United States

May 23-24, 2011
4th International Conference on Ovarian Cancer Screening, London, United Kingdom

June 03-07, 2011
47th American Society of Clinical Oncology Annual Meeting, Chicago, IL, United States

June 20-23, 2011
7th EADO Congress European Association of Dermato-Oncology, Nantes, France

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer, Barcelona, Spain

June 23-25, 2011
"MASCC/ISOO 2011 International Symposium, Athens, Greece

July 03-07, 2011
14th World Conference on Lung Cancer, Amsterdam, Netherlands

July 14-17, 2011
3rd World Congress of the International Academy of Oral Oncology 2011, Singapore, Singapore

August 15-17, 2011
International Conference and Exhibition on Cancer Science & Therapy, Las Vegas, Nevada, United States

September 1-3, 2011
Tri-Society Head and Neck Oncology, Singapore, Singapore

September 7-10, 2011
Hallmarks and Horizons of Cancer, Lausanne, Switzerland

September 23-27, 2011
Joint 16th ECCO and 36th ESMO Multidisciplinary Cancer Congress, Stockholm, Sweden

October 06-07, 2011
Current Status and Future of Anti-Cancer Targeted Therapies, Buenos Aires, Argentina

November 30-December 03, 2011
AORTIC 2011-Entering the 21st Century for Cancer Control in Africa, Cairo, Egypt

November 6-9, 2011
NCRI Cancer Conference, Liverpool, United Kingdom

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21st Asia Pacific Cancer Conference 2011, Kuala Lumpur, Wilayah Persekutuan, Malaysia

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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