

Advances in breast cancer therapy and chemoprevention: current strategies and new approaches

Review Article

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Abbreviations: estrogen receptor, (ER); selective estrogen-receptor modulator, (SERM); double strand breaks, (DSB); Nonsteroidal anti-inflammatory drugs, (NSAIDs); cyclooxygenase, (COX); human telomerase reverse transcriptase catalytic subunit, (hTERT); human telomerase RNA component, (hTR); cyclophosphamide-methotrexate-fluorouracil, (CMF)

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Summary

Breast cancer is the most frequent cancer and the second leading cause of cancer mortality in women, with approximately one in eight being affected over their lifetime. One successful breast cancer therapy is inhibiting the function of the estrogen receptor (ER). In addition, the use of tamoxifen is showing promise as a new chemoprevention strategy. However, not all breast tumors respond to anti-estrogen therapy or even contain ER. Furthermore, current therapies for breast cancer include treatments that exert significant toxicity and often result in drug resistance. Thus, there is a need for new drug developments in breast cancer therapy and chemoprevention. These novel strategies should exploit the hallmarks of breast cancer including self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genomic instability (Sledge and Miller, 2003). This review discusses some of the recent general strategies in cancer therapy and chemoprevention with the intention to promote the exploitation of the hallmarks of cancer, such as the limitless replicative potential via telomerase.

I. Introduction

Conventional breast cancer therapy, such as cytotoxic chemotherapy and radiation, has relied on the long-standing observation that cancer cells divide more rapidly than normal cells. In addition, the use of anti-estrogen therapy has long since been used for the treatment of estrogen receptor positive (ER+) breast tumors. These conventional therapies have shown much success and significant survival advantages in breast cancer patients (Kim, 2003). However, the therapies directed towards rapidly dividing cells will also result in the killing of cells lining the gastrointestinal tract or hemtopoietic cells. The toxicity encountered during treatment can hinder the quality of life in breast cancer patients to a point where the negatives outweigh the benefits. Furthermore, drug resistance can occur leaving

the patient and doctor hopeless in controlling tumor growth.

It is thus time that clinicians and basic researchers come together to take advantage of the growing knowledge of the mechanisms underlying cancer. As Hanahan and Weinberg (2000) discussed in their review, there are seven critical features, or a "tool box" that give a cancer cell its recognizable phenotype (**Figure 1**). These hallmarks of cancer include self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genomic instability. A recent review by Sledge and Miller (2003) suggests the hallmarks of malignancy as a conceptual framework for understanding novel breast cancer therapies. Herein, some of the current therapies for breast cancer will be discussed, including chemoprevention

strategies, with the proposal to develop novel approaches for the treatment of breast cancer by targeting a hallmark of cancer such as the limitless replicative potential.

II. Current therapies for breast cancer

Adjuvant, systemic therapies have greatly improved the prognosis of patients with breast cancer, especially early breast cancer. Systemic therapies include chemotherapy and hormonal therapy before or after surgery. The classes of chemotherapeutics include alkylators, antimetabolites, and antimicrotubules and use cytotoxicity to attack the proliferation of cancer (Table 1). Treatment strategies have shown that using chemotherapeutics in combination are more effective than just one drug alone (Hortobagyi, 1998). For example, cyclophosphamide is typically used in combination with methotrexate and fluorouracil (collectively termed CMF) for the adjuvant treatment of breast cancer. While successful, these therapies have adverse side effects which make the use of targeted therapies in combination with lower nontoxic doses of the standard chemotherapeutic agents more desirable.

It has been well established that estrogen promotes the growth of some breast cancers, especially those that contain the estrogen receptor. Therefore, one of the most successful modes of therapy is either through ovarian ablation, which is a major source of estrogen, or through the use of antiestrogen drugs such as tamoxifen or related drugs. Hormonal therapy has been effective in both premenopausal and postmenopausal women whose cancers are positive for steroid receptors (Early Breast Cancer Trialists' Collaborative Group, 1998; Coleman, 2003). Tamoxifen is a selective estrogen-receptor modulator (SERM) in that it is an antagonist in the breast but agonist in the uterus. Tamoxifen, typically given as adjuvant treatment for five years, has been shown to have a 26% reduction in recurrence and a 14% annual reduction in deaths (Early Breast Cancer Trialists' Collaborative Group, 1998; Coleman, 2003). While the use of tamoxifen has shown success, an undesirable effect is the stimulation of uterine or endometrial carcinomas. Under current evaluation as substitutes to tamoxifen are second generation SERMs, such as raloxifene and aromatase inhibitors, which block the production of estrogen and has been shown to be superior to tamoxifen or even be beneficial for combination treatments (Coleman 2003).

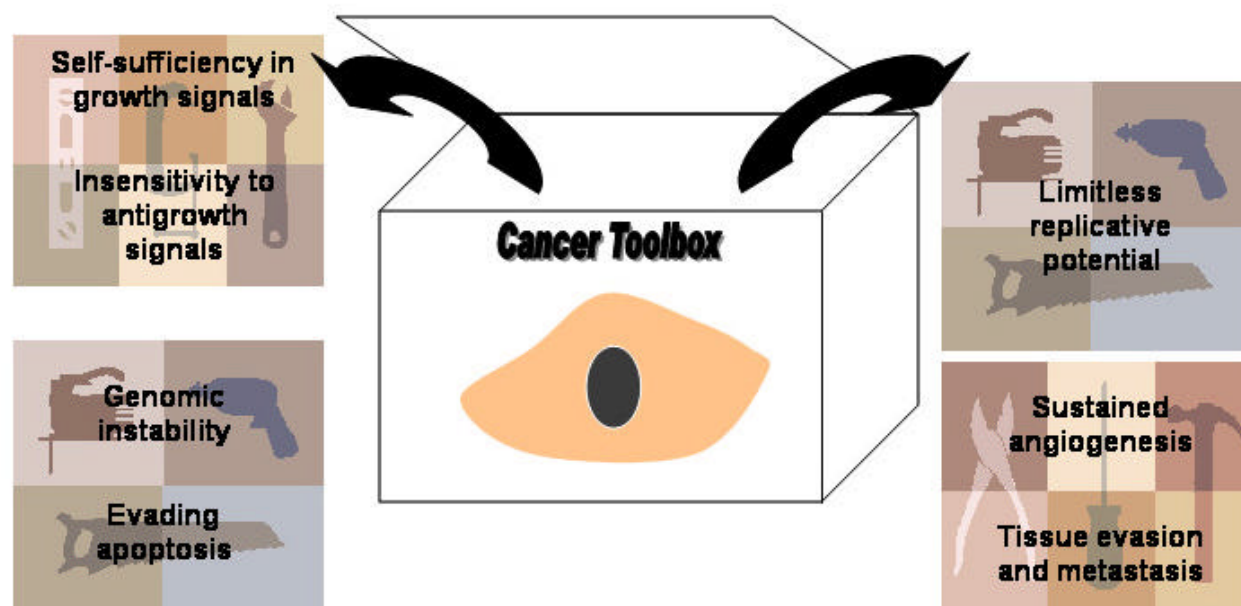


Figure 1. The breast cancer therapy toolbox: targeting the hallmarks of cancer. The hallmarks of cancer include self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genomic instability (Hanahan and Weinberg, 2000). Using our knowledge about the hallmarks of cancer, clinicians are encouraged to exploit these components in order to improve breast cancer treatment strategies (Sledge and Miller, 2003).

Table 1: Common chemotherapy strategies

<u>Drug Class</u>	<u>Mechanism</u>	<u>Examples</u>
Alkylators	control proliferation	Cyclophosphamide (Cytosan)
Antimetabolites	interfere with cell division	Methotrexate, 5-FU
Antimicrotubules	disrupt mitotic events	paclitaxel (Taxol) Docetaxal (Taxotere) Vinblastine
Antitumor antibiotics	DNA damage	doxorubicin (Adriamycin)

Raloxifene has shown promise for treating breast cancer since it is antagonistic in breast and uterine, but agonistic in bone. Osteoporosis can develop from estrogen deprivation and the use of raloxifene not only helps treat breast cancer, but also helps prevent bone loss. SERMs have also been tested for their affect to prevent breast cancer, as discussed below.

Finally, another current successful therapy is immunotherapy with the use of monoclonal antibodies against the receptor HER2/neu. HER2/neu, an epidermal growth factor receptor family member, is overexpressed in approximately one quarter of breast cancers and is associated with poor prognosis (Slamon et al, 1987). The use of the monoclonal antibody to HER2, known as trastuzumab or herceptin, in combination with conventional chemotherapy resulted in higher response rates and prolonged survival in patients with metastatic breast cancer (Slamon et al, 2001). It is now understood that the HER2 and ER pathways share considerable cross-talk. For instance, HER2 can regulate ER coactivators and result in tamoxifen resistance (Schiff et al, 2003). With the increase of knowledge of the HER2 and ER signaling pathways, the use of inhibitors of HER2 signaling has been shown to reverse tamoxifen resistance (Witters et al, 2002). Therefore, integrating our understanding of the molecular mechanisms of cancer with standard chemotherapy can improve therapeutic outcomes. However, we need to ensure that patient selection is taken into account in order to monitor the success of combination targeted therapy (Kim, 2003; Sledge and Miller, 2003). For instance, use of HER2 targeted therapies in combination with tamoxifen would not be successful in ER- or HER2-negative breast cancer patients. Molecular profiling of breast cancer patients, described below, would thus be of clinical significance.

III. Radiation therapy

Radiation therapy is an important and integral part of the management of breast cancer patients. This therapy may be used to destroy any residual breast cancer after surgery or to aid in shrinking the tumor before surgery. Radiation therapy is delivered as ionizing radiation (IR) with high-energy photons and charged particles (Gudkov and Komarova, 2003). The ionizing radiation causes ionization of atoms in the biological target tissue because electrons traveling through the target tissue collide with atoms and release energy. The key to the success of radiation therapy is by IR-induced DNA damage. In general, double strand breaks (DSB) induced by ionizing radiation could lead to genome instability, such as translocated chromosomes, broken chromosomes, end-to-end fusions, dicentric chromosomes, inversions, duplications, and deletions. Without the regulatory mechanisms to repair damaged DNA, tumor cells are sensitive to ionizing radiation. Thus, radiotherapy plays a key role in the treatment of many tumors, but the radiosensitivity of different tumors varies considerably. The effectiveness of using radiation therapy in the clinic have been the result of decades of experiences and empirical development (Gudkov and Komarova, 2003).

Even with the effectiveness of tumor cell killing, damage to normal tissues can occur. Indeed, if the local irradiation dose (usually 100-300 cGy) was given to the whole body, it could be lethal (Gudkov and Komarova, 2003). In addition, radiation therapy for breast cancer would be delivered to an area which may include some surrounding normal tissue. The current radiation delivery protocols are most likely optimal even with a typical course of fractionating multiple doses. However, the therapeutic index can be improved by understanding the molecular mechanisms of radiation response and exploiting the hallmarks of cancer in order to sensitize cells to irradiation.

IV. Advances in breast cancer chemopreventive strategies

Unlike chemotherapy, which focuses on halting or eliminating malignant cell growth, chemoprevention focuses on preventing the process of carcinogenesis by the use of pharmacological agents (Sporn and Newton, 1979). With the development of improved screening methods, increased detection, and incidence of breast cancer the need for prevention has grown. Indeed, the number of chemopreventive trials has increased tremendously over the years and has shown some success, particularly in the case for tamoxifen.

Tamoxifen became the first chemopreventive agent to earn FDA approval, based on the positive results of National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer prevention trial (Fisher et al, 1998). However, two smaller trials in Europe showed negative results. The main differences between the NSABP and the European trials were that the NSABP had a larger and more diverse population, while the European trials each had their own specialized population of either younger with strong family history and concurrent use of hormone replacement therapy or a low-risk population with poor compliance (Decensi and Costa, 2000). Currently, the NSABP is conducting a Study of Tamoxifen and Raloxifene (STAR), with strong support for the use of raloxifene for similar reasons as mentioned above for the therapy trials.

Another chemoprevention agent that is currently in Phase III trials is fenretinide. Fenretinide is a synthetic retinoid that has proven potent chemopreventive activity in breast carcinogenesis models with low toxicity, unlike other natural retinoids tested (Costa et al, 1994). Retinoids bind to specific nuclear receptors that can bind to DNA and influence transcription of proteins involved in proliferation, differentiation, or death via apoptosis (Sporn, 1986). Each retinoid, upon binding to a certain retinoid receptor, can have a different effect on the cell. For example, unlike the differentiating agent retinoic acid, fenretinide induces apoptosis in tumor cells. The agent can act on ER-positive or ER-negative breast cancer cells and remains stable in the body for prolonged administration (Sporn and Newton, 1979). With the onset of chemoprevention trials using this synthetic retinoid, additional agents that do not use an antiestrogen

mechanism are being evaluated for chemoprevention potential.

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, sulindac, and celecoxib, have recently been studied for their potent chemopreventive effects on a number of solid tumors. NSAIDs block the biosynthesis of prostaglandins by inhibiting the cyclooxygenase (COX) activity of the enzyme prostaglandin G/H-synthase (Thun et al, 2002). COX-1 and COX-2, two cyclooxygenase isoforms, are expressed in a variety of normal tissues, and COX-2 has been implicated as having a role in breast cancer as well as other cancers by stimulating cell growth through prostaglandins, suppressing apoptosis by increasing Bcl-2, and enhancing angiogenesis and cell invasiveness (Singh et al, 2002). The expressions of COX-1 and COX-2 were found to be high in human breast cancer (Hwang et al, 1998). Hwang et al (1998) found that COX-2 expression was particularly high in breast epithelial tumors, while COX-1 was primarily localized to the adjacent stromal cells, which also contained some COX-2. On the other hand, Hwang et al found that normal epithelial tissues do not express COX-2. While most chemopreventive studies have been performed with prostate and colon cancer, there is potential for NSAIDs in breast cancer chemoprevention. For example, celecoxib, NS-398, and sulindac sulfone prevented mammary carcinogenesis in mice and rats (Harris et al, 2000; Rozic et al, 2001; Thompson et al, 1997).

It is widely accepted that chemopreventive agents may prevent or hinder the occurrence of cancer (Sporn and Suh, 2002). Unfortunately, this approach may not be truly prevention, but only a delay of an undesirable outcome. It is important to note, however, that a practical goal of chemoprevention should be to decrease the incidence and death from invasive breast cancer. Extending the quality of life and advancing the life expectancy of individuals predisposed to breast cancer is still a highly desirable strategy (Sporn and Suh, 2002). To obtain a goal of being truly prevention, further research is needed looking at other endpoints and targets of carcinogenesis. Combination chemoprevention may be just as useful as combination therapy in that they use standard treatments in conjunction with agents that specifically target a mechanism(s) of cancer.

V. Novel targets for breast cancer therapy: telomeres and telomerase

A. Telomerase and telomerase inhibitors

One of the hallmarks of breast cancer is its limitless replicative potential, predominantly achieved by telomerase, a reverse transcriptase/ ribonucleoprotein complex that maintains the ends of chromosome (telomeres). Briefly, almost all normal human cells gradually lose telomeric DNA as cells age. Under rare circumstances, immortalized cells emerge when telomerase or another mechanism to maintain telomere stability is activated (Wright et al. 1989; Bryan et al, 1997; Duncan and Reddel, 1997). Telomerase is a protein

complex consisting of a human telomerase reverse transcriptase catalytic subunit (hTERT) that uses the human telomerase RNA component (hTR) of the complex as a template for adding TTAGGG repeats to the end of the chromosome (Greider and Blackburn, 1985). Once telomerase is activated, it may preferentially elongate critically short telomeres, stabilize telomere lengths and permit continued cell division. This hypothesis is supported by the observation that ectopically introduced telomerase activity can extend telomeres and indefinitely prolong cellular lifespan (Vaziri and Benchimol, 1998; Bodnar et al, 1998).

The activation of telomerase occurs in the vast majority of breast cancers (>90% of breast tumors), but is not detected in normal adjacent tissues (Shay and Bacchetti, 1997; Carey et al. 1998; Yashima et al, 1998, Herbert et al, 2001b for review). Therefore, the inhibition of telomerase is an attractive anticancer therapeutic target because treatment with telomerase inhibitors should potentially have less toxicity than other chemotherapeutic agents due to telomerase being absent in most somatic cells. As telomerase is re-expressed in almost all breast cancer cells, the critically short telomeres may be favored to be elongated by telomerase. The average telomere length in these cells becomes stable at lengths well below normal cells. These shorter lengths are at a critical length for cell survival. The difference in telomere lengths between normal and cancer cells thus provides for a mechanism and a window of opportunity to specifically target telomerase and inhibit the growth of cancer cells.

Telomerase inhibitors that actually work through a telomere-based mechanism should (i) reduce telomerase activity, but initially not affect cell growth rates; (ii) lead to progressive shortening of telomeres with each cell division; and (iii) cause cells to die or undergo growth arrest. In addition, the time necessary to observe decreased proliferation should vary depending on initial telomere length, and chemically related molecules that do not inhibit telomerase activity should not cause decreased cell proliferation or telomere shortening (White et al, 2001 for review).

Telomerase inhibitors have been previously shown to inhibit growth and induce apoptosis in cancer cells (Gyraznov et al, 2001; Hahn et al, 1999; Herbert et al, 1999; Herbert et al, 2001; Herbert et al, 2002; Zhang et al, 1999). Preparations for Phase I clinical trials are currently in progress. Unfortunately, the shortening of telomeres occurs only during cell division and the time necessary to see cells die due to telomerase inhibition is on the order of weeks and months, depending on the initial telomere lengths. It is thus necessary to develop a regimen that takes advantage of the universal expression of telomerase in breast cancer cells while not compromising the patient with the continued growth of the tumor during the weeks of anti-telomerase treatment. The next approach is to examine whether the combination of telomerase inhibition and low doses of other therapeutic agents, such as cytotoxic chemotherapeutic agents, angiogenesis inhibitors, and radiation therapy, can have a greater effect at inhibiting breast cancer growth than either reagent alone. Data supporting this hypothesis has recently been

shown in cancer cells treated with telomerase inhibitors in combination with various antiproliferative agents such as topoisomerase inhibitors, cisplatin, and doxorubicin, or irradiation (Figure 2; Ludwig et al, 2000; Mo et al, 2003; Chen et al, 2003). Treating the cells for a short time with telomerase inhibitors induced enough telomere dysfunction to render the cells even more sensitive to irradiation (Figure 2). Therefore, new strategies for breast cancer treatment can be designed using telomerase inhibitors. Telomerase inhibitors can be used to prevent residual tumor recurrence, in between rounds of chemotherapy, or in the early stages of tumor growth to

sensitize cells to chemotherapy or radiation therapy (Figure 3).

B. Telomere dysfunction and breast cancer therapy

Genomic integrity plays an important role in breast cancer progression and is one of the critical hallmarks in cancer. Telomere dysfunction may also play a role in genomic instability seen during carcinogenesis (Artandi et al, 2000; Wu et al, 2003). The maintenance of functional telomeres (repetitive DNA sequences at the ends of chromosomes, consisting of TTAGGG in humans) protect

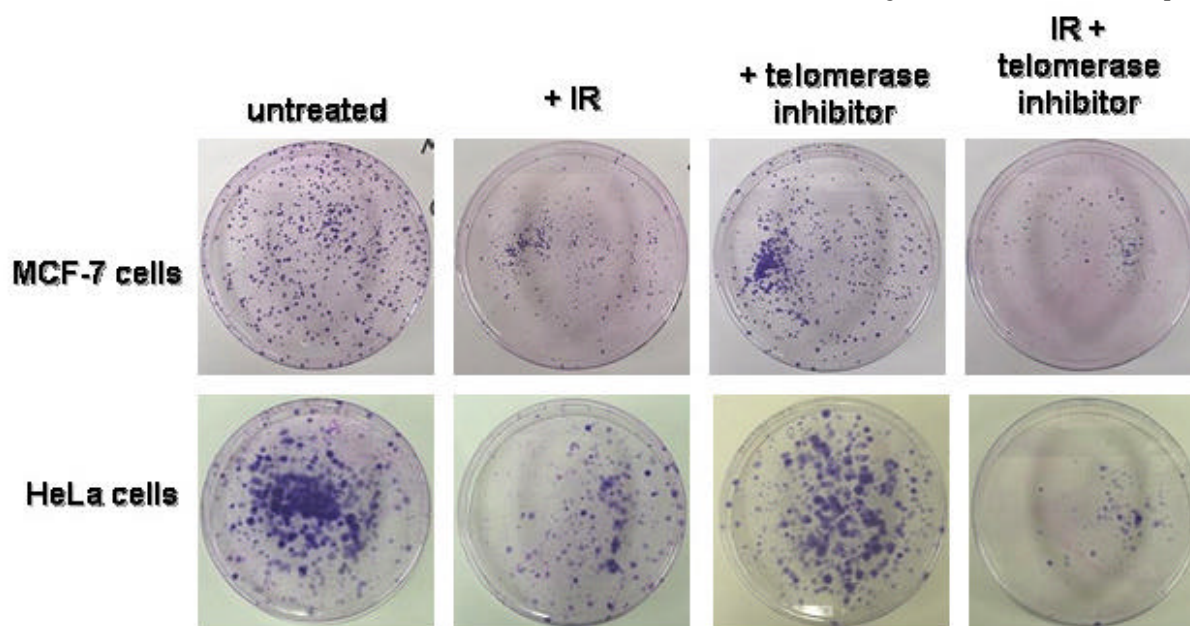


Figure 2. Combination of irradiation and telomerase inhibitors decreases colony formation of HeLa cervical and MCF-7 breast cancer cells. HeLa and MCF-7 breast cancer cells were either treated with 4 Gy of gamma irradiation (+IR), telomerase inhibitor alone, combination of 4 Gy irradiation and telomerase inhibitors (IR + telomerase inhibitor), or no treatment (untreated). After four days of telomerase inhibitor treatment or no treatment, cells were irradiated and then stained with Geimsa seven days later. The amounts of stained colony circles on treated dishes were compared to untreated stained dishes.

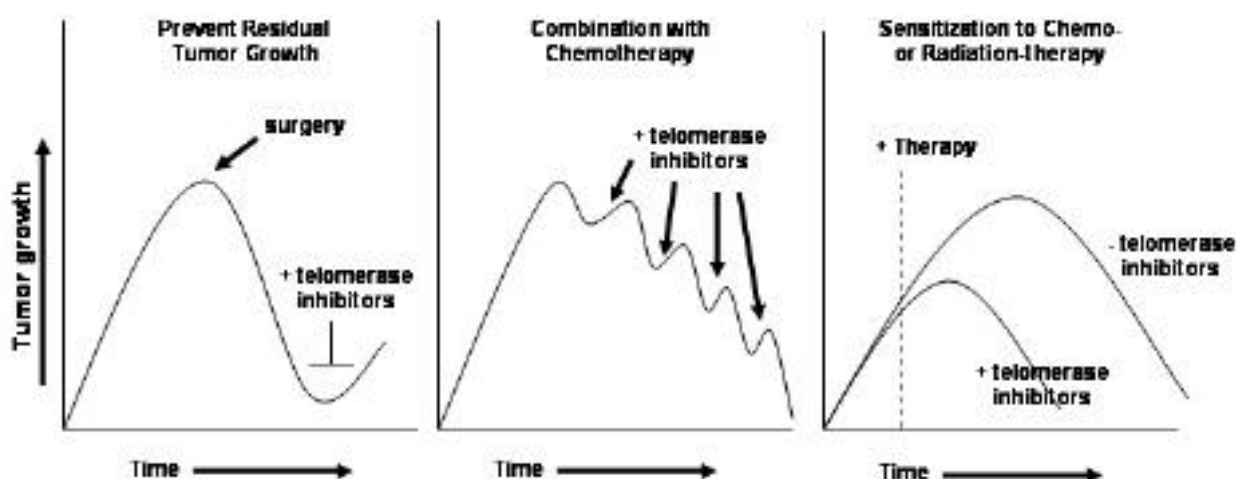


Figure 3. New strategies for breast cancer treatment using telomerase inhibitors. In order to have maximum potential, telomerase inhibitors need to have a dividing cell population within the tumor. Thus, telomerase inhibitors can be used to prevent residual tumor recurrence, in between rounds of chemotherapy, or in the early stages of tumor growth to sensitize cells to chemotherapy or radiation therapy.

the ends of eukaryotic chromosomes from end-to-end fusions and being recognized as DNA strand breaks needing repair (de Lange 2002). Without this protection, chromosomal ends may fuse together or be recognized as broken DNA needing unnecessary repair, leading to the same genomic instability seen during carcinogenesis. Telomeres have a 3' G-rich single stranded overhang that is approximately 200 nucleotides in mammals (Wright et al, 1997). The overhang can displace one strand of the telomeric repeat and hybridize to its complementary sequence (Griffith et al, 1999). This structure, containing the folded DNA and associated proteins, is called the t-loop and may function to prevent the G-rich overhang from activating DNA damage checkpoint activation and repair (Goytisolo and Blasco, 2002). Loss of the G-rich overhang is thought to induce telomere dysfunction through loss of the t-loop structure.

The telomerase complex has also been shown to maintain telomeres and the vast majority of human breast cancers maintain their chromosomal ends by telomerase. Telomeres, telomerase, and proteins that bind to telomeres have recently been implicated in being associated with the same proteins that are involved in the response to repair damaged DNA, thus providing a link between DNA repair mechanisms and telomere biology. For example, the DNA damage repair complex, Rad50/MRE11/NBS1, has been shown to associate with telomere-binding proteins and telomeres (Zhu et al, 2000).

Taken together, while telomere dysfunction can cause the genomic instability seen in early breast tumorigenesis, disrupting the maintenance of telomeres in breast cancer cells can be advantageous for therapeutics. Dysfunctional telomeres in cancer cells will lead to a DNA damage response. This DNA damage response can push cancer cells over the edge and lead to apoptosis. Cancer cells with critically short and dysfunctional telomeres could be more susceptible to genomic instability and other insults. Multiple insults inflicting DNA damage and other stresses would trigger cell death to the tumor population. Recent evidence supporting this idea suggests that disrupting a cancer cell's ability to maintain functional telomeres can sensitize cells to death (Gonzalez-Suarez et al, 2003). Thus, targeting the maintenance of telomeres will be important in cancer therapeutic strategies (Shay, 2003).

VI. A different approach for studying chemoprevention *in vitro*: using immortalization as an endpoint

As mentioned above, current chemoprevention trials have been encouraging, especially to those who are at a high risk for breast cancer. Unfortunately, results from clinical trials take many years to generate. It is therefore attractive to design and test agents that act on specific molecular targets and to develop preclinical models with a measurable endpoint to examine the effects of potential chemopreventive agents and their mechanisms of action (Sporn and Suh, 2002). Since cancer is mostly a disease of epithelial cells, a system of normal and spontaneously immortalized human breast epithelial cells can provide a good model system to examine the effects of potential

chemopreventive agents *in vitro*. Inhibition and/or reversal of the immortal phenotype and other endpoints such as early genomic instability and telomere stability should provide insights into the earliest stages of cancer development, leading to more effective cancer prevention measures.

Spontaneous immortalization of human cells *in vitro* is an extremely rare event, requiring mutations in several genes and cellular pathways normally involved in cellular senescence (Wright et al, 1989; Hara et al, 1991; Shay et al, 1991). Normal cells have a limited lifespan and undergo replicative senescence, in which cells cease to proliferate (Wright and Shay, 2001; Harley et al, 1990; Harley 1991; Campisi et al, 2001). Because of the end replication problem where lagging strand synthesis cannot copy all the way to the very end, almost all normal human cells gradually lose telomeric DNA as cells age (Blackburn, 1991; Blackburn, 1994; Greider, 1994). Senescence occurs when cells contain at least some critically short telomeres. Cells that lose critical cell-cycle checkpoint functions escape this initial growth arrest and divide until they enter crisis, when telomere lengths become extremely short, and chromosome end fusions and apoptosis occur (Blasco et al, 1997; Hande et al, 1999; Harley, 1991; Sedivy, 1998). During crisis, cells undergo a period of balanced cell growth and cell death usually followed by a decrease in the total number of surviving cells. Under extremely rare circumstances, when telomerase or another mechanism to maintain telomere stability is activated, an immortalized cell emerges (Blasco et al, 1997; Kim et al, 1994; Bryan et al, 1997). Limiting the number of cell divisions because of telomere shortening functions as an antitumor protection mechanism by preventing premalignant cells, which have used up their divisions acquiring a few mutations, from being able to continue to proliferate.

While normal human breast epithelial cells *in vitro* rarely ever spontaneously immortalize, Li-Fraumeni Syndrome (LFS)-derived (p53 +/-, telomerase silent) breast epithelial cells have been shown to spontaneously immortalize at a relatively high and reproducible frequency of approximately five in ten million (Shay et al, 1998; Herbert et al, 2001). The fact that the LFS-derived breast epithelial cells can reproducibly spontaneously immortalize allowed for the investigation of the effects of different agents, such as tamoxifen, retinoids, NSAIDs, and telomerase inhibitors, on the immortalization frequency *in vitro* (Herbert et al., 2001, 2003). Treatment of LFS-derived breast epithelial cells just prior to crisis with low (nM range), non-toxic dosages of some, but not all chemopreventive agents reduced the frequency of spontaneous immortalization. Examining the ability to prevent spontaneous immortalization offers a new intermediate endpoint for validating novel chemopreventive agents.

VII. Molecular profiling of breast cancer

Improved technologies in genomic and proteomic techniques have allowed us to unravel the complex

heterogeneity of breast cancer. Gene-expression profiling by cDNA microarrays uses nucleic acids, which are immobilized on a solid surface or chip, as probes for gene sequences. Proteomics include 2-dimensional gel analyses, yeast two-hybrid and protein chip microarrays (Lopez and Pluskal, 2003). Indeed, genomic and proteomics arrays are now being used to create a molecular portrait of breast cancers and normal breast epithelia (Perou et al, 2000; Sorlie et al, 2001; van't Veer et al, 2002; West et al, 2001; Hedenfalk et al, 2001; Gruvberger et al, 2001, Sotiriou et al, 2003). Several of these reports have been shown to predict clinical outcome and recent reports show microarray being able to predict chemotherapy response *in vitro* or a small sample size from fine needle aspirates (Sotiriou et al, 2002; Kudoh et al, 2000).

Only time will tell if molecular portraits can readily predict the outcome and best treatment strategy for breast cancer patients. Unfortunately, specimens collected during routine surgical pathology are usually formalin-fixed or paraffin-embedded to preserve tissue histology. This process makes the recovery of intact RNA for microarray analyses difficult (Chung et al, 2002). The ability to apply microarrays to peripheral blood, fine needle aspirates, and breast core needle biopsy samples will be an important step. Furthermore, microarrays were developed to scan the genome in a large-scale fashion and the results can be daunting. Only when microarrays are analyzed carefully to identify a subset of clinically relevant genes can microarrays be useful for clinical diagnosis (Chung et al, 2002). In the meantime, both microarrays and proteomic arrays will continue to provide insights for the molecular basis of cancer which can be of clinical significance.

VIII. Conclusions

This review covered a few of the advances in breast cancer therapies and chemoprevention strategies. Another promising therapy under development not mentioned was the use of angiogenesis inhibitors that can block metastasis of breast cancer. Improved technology allows for a molecular profiling of breast cancer patients or those predisposed to breast cancer so that an optimal treatment strategy can be determined for each individual. While current strategies have shown success, clinicians are encouraged to use new approaches that attack more than one hallmark of breast cancer. Novel strategies include combining telomerase inhibitors with conventional chemotherapy or radiation therapy in order to take advantage of dysfunctional telomeres. With the increase in our understanding of the molecular basis for breast cancer, at experimental stage improved treatment strategies will continue to give hope to breast cancer patients.

Acknowledgements

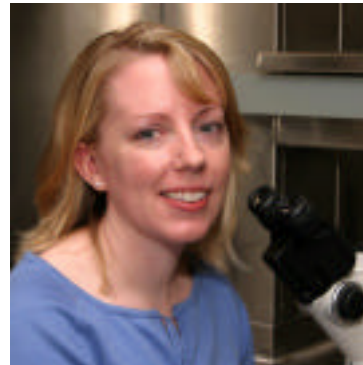
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