Review

Transforming growth factor-β in breast cancer: too much, too late
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Abstract

The contribution of transforming growth factor (TGF)β to breast cancer has been studied from a myriad perspectives since seminal studies more than two decades ago. Although the action of TGFβ as a canonical tumor suppressor in breast is without a doubt, there is compelling evidence that TGFβ is frequently subverted in a malignant plexus that drives breast cancer. New knowledge that TGFβ regulates the DNA damage response, which underlies cancer therapy, reveals another facet of TGFβ biology that impedes cancer control. Too much TGFβ, too late in cancer progression is the fundamental motivation for pharmaceutical inhibition.

Transforming growth factor-β in breast cancer progression

The breadth and scope of research to define the complex roles that transforming growth factor (TGF)β plays during mammary development and breast cancer now exceeds a thousand papers. Even by the time the elegant and oft-quoted study by Silberstein and Daniel in 1987 [1] put TGFβ on the mammary map as an important regulator of breast development, there was clear evidence that cancer could subvert this powerful growth inhibitory signal [2].

In the past decade or so, animal tumor studies that target over-expression or inactivation of various TGFβ signaling components to different epithelial compartments have resulted in a bewildering array of conclusions due to the pleiotropic and highly context-dependent action of TGFβ on cancer suppression or progression. It is now generally agreed that during early tumor outgrowth, elevated TGFβ is tumor suppressive, whereas at later stages there is a switch towards malignant conversion and progression [3,4], as shown in neu-induced mammary tumors [5]. Inactivation of tumor suppressor genes, the sequential acquisition of oncogenic mutations, and epigenetic changes within the cancer genome divert the canonical growth inhibitory arm of the TGFβ signaling pathway towards behaviors that increase motility, invasion and metastasis (reviewed in [4]). Consistent with the response to TGFβ evolving from growth inhibition to tumor progression during advanced malignancy, the majority of breast tumors, including their metastases, are positive for nuclear phosphorylated Smad2, indicating an actively signaling TGFβ pathway [6,7].

Loss of TGFβ growth inhibition and increased expression of TGFβ have been associated with malignant conversion and progression in breast, as well as gastric, endometrial, ovarian, and cervical cancers, glioma and melanoma (reviewed in [4,8]). But specific mutation of TGFβ signaling components occurs only occasionally in breast cancers. Rather, TGFβ growth response is abrogated by changes in the profile of other active signaling networks or the relative availability of transcriptional co-repressors or co-activators that bind to and modulate the canonical Smad pathway. Estrogens also appear to negatively regulate TGFβ signaling in breast cancer [9] and there is evidence that many pathway components may be epigenetically regulated during critical transitions in malignant progression [10].

TGFβ genetic predisposition to cancer

Genes encoding components of the TGFβ signaling pathway, including TGFβ1 [11], TGFBR1 [12] and TGFβ2 [13], are functionally polymorphic in humans. TGFβ1 harbors promoter and signal peptide polymorphisms that influence protein secretion and levels of freely circulating TGFβ1 [11,14]. Several groups have demonstrated an association between variant TGFβ1 alleles and breast cancer risk [11,15,16]. The L10P allele increases protein production when expressed in culture and has been associated with high TGFβ levels [11]. The Breast Cancer Association Consortium conducted combined case-control analyses for breast cancer risk, and found odds ratios of 1.07 and 1.16 for L10P heterozygotes and homozygotes, respectively [17]. A case-control study of over 3,900 Caucasian women with early onset invasive breast cancer (median age 50 years) and a similar number of matched controls [11] demonstrated association between

EMT = epithelial to mesenchymal transition; FACS = fluorescent-activated cell sorting; TGF = transforming growth factor.
homzygosity for the high producer TGFB1 L10P allele and an odds ratio of 1.25 for risk of invasive breast cancer. Similar associations have been found between hyperactive TGFB1 variants and invasive prostate cancer [18], nasopharyngeal cancer [19], malignant melanoma [20], and lung cancer [21]. Conversely, a cohort study of more than 3,000 women aged 65 to 75 years suggested that homozygosity for hyperactive TGFB1 appeared protective for breast cancer, suggesting that TGFβ1 has a breast tumor suppressing activity [15]. Pasche and colleagues [22] have proposed that hypomorphic variants of the TGFβ type I receptor interact with the hyperactive TGFB1 variant to create ‘high’ versus ‘low’ signalers, the latter being associated with elevated breast cancer risk.

The disparate conclusions from these studies may be related to the age of the women and tumor grades in different studies. More recently, this apparent genetic dichotomy has been explained in terms of the dual function of TGFβ1 in carcinogenesis evident during neoplastic progression, as demonstrated in mouse models [3]. In a case control study of Asian breast cancer patients stratified according to tumor grade, hyperactive TGFB1 was associated with decreased risk of early-stage breast cancer but increased risk of advanced breast cancer [23]. Given the complex biology regulated by TGFβ, there are probably other processes involved in mediating the TGFβ-associated risk of breast cancer. In different mouse strains, for example, homozygosity for a hypomorphic Tgfb1 variant is genetically linked to skin tumor susceptibility. However, this effect can be completely masked by interacting genetic variants at a distant locus elsewhere in the genome [24]. It is likely that Tgfb1 genotypes interact with other features in the genetic background [25].

Consequences of too much TGFβ
Elevated plasma TGFβ1 in hepatocellular carcinoma and breast, lung and prostate cancer patients correlates with poor outcome (reviewed in [26]). Systemic TGFβ1 levels have been used as a surrogate of tumor load and/or response to therapy [27,28]. Some circulating TGFβ1 may arise from the tumor; however, high plasma TGFβ1 levels can persist after tumor resection, suggesting that there may also be additional sources of the cytokine, such as blood cells, platelet degranulation or liver [29-31]. Compounding this, cancer therapy itself might induce TGFβ1 secretion by a number of routes (reviewed in [32-34]).

Epithelial to mesenchymal transition and the cancer stem cell
The tumor progressing activities of TGFβ are multifold, and involve effects on both the tumor cell and the tumor microenvironment [4]. It has been known for some time that TGFβ can induce epithelial to mesenchymal transition (EMT) in embryonic or neoplasic epithelial cells. This process is essential for normal embryonic development, and its exploitation during cancer progression has been thought to contribute to tumor invasion and metastasis [35]. In the mouse skin model of chemical carcinogenesis, overt EMT is a common occurrence, driven by TGFβ → Smad → Snail signaling, and resulting in the formation of highly aggressive, totally fibroblastic spindle carcinoma that have lost all the molecular markers of epithelial cells [3]. Radiation, a carcinogen of human breast, primes non-malignant human mammary epithelial cells to undergo TGFβ-mediated EMT [36]. Changes in motility elicited by cytoskeletal re-organization, and enhanced secretion of matrix-remodeling enzymes are classically considered the main driving forces in the contribution of reversible TGFβ-driven EMT to invasion and metastasis [37].

A recent paper from Polyak and colleagues [38] suggests an alternative mechanism. Expression profiling of fluorescent-activated cell sorting (FACS) sorted CD44HIGH CD24LOW marked cells, a population enriched for breast epithelial stem cells, showed transcripts associated with cell motility, cell adhesion, cell proliferation, chemotaxis and angiogenesis. The transcriptional similarity between FACS sorted populations enriched for normal and neoplastic stem cells was greater than that between them and the CD44LOW CD24HIGH population. The enrichment in transcripts for TGFβ and WNT signaling components was striking in these stem cells [38], suggesting preferential activation of these pathways and their functional involvement in stem cell biology. Indeed, putative stem cells were responsive to TGFβ and targeted by TGFβ inhibition, whereas the descendant CD44LOW CD24HIGH progenitor cells had lost responsiveness due to methylation of the TGFBR2 gene. These data suggest that TGFβ signaling plays a role in mammary stem cell maintenance [38].

Taking this observation one step further, Mani and colleagues [39] showed that Snail-driven EMT in human mammary epithelial cells induces stem cell-like properties in terms of expression of stem cell markers, increased mammosphere seeding activity in vitro and tumorigenicity in vivo. Excessive TGFβ levels in the tumor microenvironment may, therefore, not only maintain putative cancer stem cells, but also contribute to their formation if more differentiated progenitors undergo EMT. This latter possibility remains to be tested. However, clinical evidence demonstrates that tumor expression of a ‘TGFβ cassette’ of genes (expressed in CD44HIGH CD24LOW > CD44LOW CD24HIGH) is associated with shorter metastasis-free survival of patients with estrogen receptor-negative breast cancer [38]. These studies suggest that anti-TGFβ therapy could hold promise for targeting the cancer stem cell, especially within this TGFβ active sub-group of estrogen receptor-negative breast tumors.

Either as part of the stem cell ‘phenotype’ or independently of it, TGFβ can induce several other cell autonomous phenotypic changes that are conducive to tumor progression and metastasis. TGFβ signaling is clearly required for efficient
colonization of the lung by transformed cells [40], and expres-
sion of a TGFβ response expression signature in estrogen
receptor-negative primary breast tumors is clinically associ-
ated with metastasis specifically to the lung but not to the
bone [41]. One molecular mechanism responsible for this
organ-specific tropism is TGFβ/Smad-driven activation of the
gene encoding angiopoietin-like 4 (ANGPTL4). Angiopoietin-
like 4 is a secreted ligand that disrupts tight endothelial
barriers, such as those found in lung but not bone marrow,
thus specifically stimulating pulmonary trans-endothelial
migration of tumor cells [41]. Importantly, only transient
exposure to TGFβ is required to induce the TGFβ response
signature, which includes ANGPTL4, and to stimulate the
consequent enhanced ability for lung colonization in a mouse
metastasis model.

Tumor progression via microenvironment modification
Clearly, TGFβ has dramatic effects on epithelial phenotype,
growth regulation and cell fate. Importantly, TGFβ has com-
parable control of the microenvironment composition
mediated by effects on stromal, immune and vascular cells.
Many investigators have argued that disruption of the stroma
and tissue architecture can be a primary driver of carcino-
genesis [42-46]. Recent experiments published from the labs
of Weinberg [47], Moses [48], Sonnenschein [49] and
Coussens [50] provide additional evidence that micro-
environment composition is a critical determinant of cancer
progression, which underscores the flipside of the cancer
paradigm, that is, how the tissue becomes a tumor; TGFβ has
a significant role on this side of the coin.

Tgfb1 null mice crossed onto an immune deficient back-
ground (which prevents neonatal death from gross inflam-
atory disease shortly after birth [51]) show little evidence of
spontaneous cancer when housed under germ-free con-
ditions. However, under standard mouse husbandry, these
mice develop gastrointestinal cancer, supporting the concept
that non-target cells mediate this epithelial tumorigenesis via
TGFβ [52]. It is perhaps surprising to note that spontaneous
cancer is not elevated in Tgfb1 heterozygote mice up to 2
years, even though TGFβ production is severely compro-
mised, even in Balb/C mice that are highly susceptible to
breast cancer (MH Barcellos-Hoff and RJ Akhurst, unpub-
lished data).

One of the major stromal targets for TGFβ action in tumor
progression is the immune system. TGFβ acts in the tumor
microenvironment to blunt immune-surveillance via multiple
mechanisms, including suppression of both cytotoxic T and
natural killer (NK) cells (reviewed in [53]). TGFβ recruit-
ment of macrophages to the tumor also leads to a pro-inflammatory
micro-environment, further exacerbating TGFβ production
and the vicious cycle of tumor progression. Cell autonomous
effects of TGFβ on the tumor cell provide protection from
elimination by the immune system - for example, by down
regulation of the expression of death receptors, major histo-
compatibility complex (MHC) molecules and Rae-1γ, the
NKGD2 ligand required for NK cell activity. Recently, Wake-
field and colleagues [54] demonstrated that TGFβ stimulate
CD8+ T cells that infiltrate the tumor to produce interleukin-
17, that in turn acts as a tumor cell survival factor via the
interleukin-17 receptor.

These observations suggest that microenvironmental effects
of TGFβ, together with its roles in EMT and metastasis,
stimulate cancer progression and override any effects of
TGFβ as a tumor suppressor in epithelia. These studies under-
score the consensus opinion that TGFβ1 levels in cancer
mediate a neoplastic plexus, driving cancer cells towards
more aggressive behaviors and supporting their survival, while
simultaneously limiting suppression by the host and perhaps
augmenting normal tissue complications. The concept, put
forward by Wakefield and colleagues [54], is that since
excessive TGFβ action is mostly localized within the tumor,
TGFβ inhibition could be therapeutically advantageous.

TGFβ, a malicious bystander during cancer
therapy
TGFβ inhibition in either mouse or human mammary epithelial
cells increases the cytotoxic response to ionizing radiation
and several chemotherapeutic drugs [55-60]. Both radiation
and chemotherapy induce TGFβ activity [61]. More impor-
tantly, Teicher and colleagues [62] showed that tumors
secreting high levels of TGFβ are more resistant to chemo-
therapy. Cis-platinum treatment of MDA-MB-231 breast
cancer cells increased both TGFβ mRNA levels and the
secretion of active TGFβ, which the authors suggest
enhances growth arrest that facilitates repair of damage, thus
rendering these cells resistant to cis-platinum killing [63].
Furthermore, treatment of MDA-MB-231 cells with anti-TGFβ
antibodies greatly enhanced cis-platinum-induced DNA frag-
mentation, augmented cell cycle progression and restored
cellular sensitivity to cis-platinum [55]. Treatment of animals
bearing cis-platinum-resistant tumors with TGFβ neutralizing
antibody or with the TGFβ inhibitor decorin restored drug
sensitivity of the tumor [56,57]. These authors suggested that
inhibiting TGFβ-mediated cell cycle control would augment
therapeutic efficacy.

Recent data suggest an even more proximal role for TGFβ in
radiotherapy (reviewed in [64]). Breast cancer radiotherapy
targets the tumor with the goal of inducing DNA damage
resulting in cancer cell death, which increases long term
patient survival [65]. Radiation-induced DNA damage elicits a
signal transduction pathway that begins with sensor/activator
proteins that lead to the activation of transducers that further
convey the signal to multiple downstream effectors [66].
Recent studies have focused on ATM, a serine/threonine
protein kinase required for the rapid response to radiation-
duced DNA double strand breaks [67], as a means to
amplify the therapeutic efficacy of radiation. Remarkably,
the DNA damage response and subsequent cell fate decisions
are severely compromised if TGFβ is inhibited prior to irradiation in mouse epithelial tissues [59], human mammary epithelial cells [60,68] and lung cancer cells [60,68].

TGFβ depletion or signal inhibition does not affect ATM protein abundance, but actually blocks ATM kinase activity [60]. Both ATM autophosphorylation and phosphorylation of critical substrates, such as p53, Chk2 and Rad17, are abrogated, which in turn prevents cells from undergoing apoptosis or cell cycle arrest following DNA damage. As a consequence, epithelial cells are sensitized to radiation toxicity as assessed by clonogenic assays, just as if ATM is inhibited. Whether this potentially important therapeutic consequence will extend the use of TGFβ inhibitors in breast cancer treatment is unknown. Although a lung cancer cell line was rendered more resistant to radiation by use of small hairpin RNA inhibition of TGFβ receptors [68], preliminary studies using small molecule inhibition of TGFβ type I receptor kinase resulted in significant radiosensitization in four of five breast cancer cell lines (MH Barcellos-Hoff and A Pal, unpublished data). If TGFβ control of ATM is confirmed in tumors, then high tumor levels of TGFβ might actually amplify DNA damage signaling and repair, preventing tumor cell death, thereby limiting response to radiotherapy as Teicher and colleagues have shown for the response to chemotherapy [58].

Arteaga and colleagues [69] demonstrate that radiation-induced systemic TGFβ can also promote metastatic disease in breast cancer. In these studies, irradiated MMTV/PyVmT transgenic mice showed increased circulating levels of TGFβ1, circulating tumor cells, and lung metastases, which was abrogated by administration of a pan-neutralizing TGFβ antibody to the irradiated host. Hence, TGFβ inhibitors could block this tumor survival pathway and increase radio-sensitivity, as well as preventing metastasis [69].

Radiotherapy-induced TGFβ activity is also implicated in late tissue toxicities that limit the use of radiotherapy for cancer treatment (reviewed in [32,33]). Normal tissues are spared from radio-toxicity in large part by physical targeting of tumors with conformal and targeted radiotherapy. Nonetheless, in some individuals, fibrosis can develop several years after therapy, which can affect quality of life or, in the case of lung tissue, be life-threatening. Unlike tumor control mediated by cell killing, fibrosis results from aberrant cytokine cascades principally initiated by TGFβ. Recent studies by Anscher and colleagues [33] have shown that even a single dose of anti-TGFβ antibody blocked radiation-induced lung injury, inflammatory response, and expression and activation of TGFβ from 6 weeks to 6 months after irradiation. Interestingly, EMT can contribute to fibrotic processes [70], and radiation appears to sensitize cells to TGFβ-mediated EMT [36].

These studies demonstrating that TGFβ activation is an undesirable side effect of radiotherapy provide further impetus for therapeutic inhibition. Along with the idea that TGFβ promotes breast cancer cell survival and metastasis at multiple levels, these data support the use of TGFβ inhibition during radiotherapy and chemotherapy. If effective, increased tumor response and decreased late tissue effects would result in a vastly improved therapeutic index for radiation treatment in breast cancer.

Future directions
The dysregulation of TGFβ in breast cancer, which in turn deregulates cellular and multicellular interactions to promote cancer, underlies one rationale for pharmaceutical TGFβ inhibition for breast cancer treatment. Immediate gain could be achieved by using TGFβ inhibitors to improve the response to chemo- and radiotherapy. Attenuation of undesirable effects, such as fibrosis, is yet another benefit of TGFβ inhibition, based on directly blocking processes that initiate pathology, or indirectly due to the anticipated reduction in radiation dose or scheduling necessary because of improved tumor response.

Concerns about limiting the activity of a growth factor whose action is essential to normal development and that plays crucial roles in wound healing and inflammation are valid but have yet to be confirmed in experimental cancer models. Perhaps, as suggested by several studies, the high levels of both protein and activity in the context of cancer elicit very different effects to those found in normal tissues where TGFβ activation is highly controlled. As proposed by Wakefield and colleagues [54], the ‘locally distributed’ activity may be the key to rational targeting. TGFβ inhibitors that reduce, rather than eliminate, TGFβ effects, used in combination with either targeted delivery to the tumor or a targeted therapy like radiation, may spare normal tissue at the expense of tumors (reviewed in [34]).

TGFβ-specific inhibitors based on blockade of synthesis, ligand/receptor binding or receptor kinase signaling are in clinical trials (reviewed in [53]). Pre-clinical models using TGFβ inhibitors have not yet elicited overt toxicity, and have shown efficacy by suppressing tumor metastasis, enhancing tumor responses to radio- and chemotherapy, and reducing normal tissue late effects. Given its complex biology, the biological target in breast cancer may be stromal, immune, vascular, or cancer stem cells, or all of these. Further research can refine the therapeutic rationale by focusing on drug scheduling and delivery, identifying patients who will benefit most from such therapy, and combining therapeutic modalities such that cancer is eliminated without normal tissue toxicity or long term health effects.

Competing interests
The authors declare that they have no competing interests.

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References

1. Silberstein GB, Daniel CW: Reversible inhibition of mammary gland growth by transforming growth factor-ß. Science 1987, 237:291-293.

2. Basolo F, Fiore L, Ciardiello F, Calvo S, Fontanini G, Conaldi PG, Tonio A: Response of normal and oncogene-transformed human mammary epithelial cells to transforming growth factor factor beta 1 (TGF-beta 1): lack of growth-inhibitory effect on clone expressing the simian virus 40 large-T antigen. Int J Cancer 1994, 59:736-742.

3. Cui W, Fowlis DJ, Bryson S, Duffie E, Ireland H, Balmain A, Akhurst RJ: TGFß1 inhibits the formation of benign skin tumors, but enhances progression to invasive spindle carcinoma in transgenic mice. Cell 1996, 85:531-542.

4. Derynick R, Akhurst RJ, Balmain A: TGF-ß signaling in tumor suppression and cancer progression. Nat Genet 2001, 29:117-129.

5. Siegel PM, Shu W, Cardiff RD, Muller WJ, Massague J: Transforming growth factor beta signal transduction: molecular specificity and functional flexibility. Nat Rev Mol Cell Biol 2002, 3:790-792.

6. Kleuser B, Malek D, Gust R, Pertz HH, Potteck H: Concordant epigenetic silencing of transforming growth factor beta signaling pathway variants may predict breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005, 14:1567-1570.

7. Mao JH, Saunier EF, de Koning JP, McKinnon MM, Higgins MN, Nicklacs K, Yang HT, Balmain A, Akhurst RJ: Genetic variants of Tgfb1 act as context-dependent modifiers of mouse skin tumor susceptibility. Proc Natl Acad Sci USA 2006, 103:8125-8130.

8. Schmierer B, Hill CS: TGFbeta-SMAD signal transduction: molecular specificity and functional flexibility. Nat Rev Mol Cell Biol 2007, 8:568-582.

9. Beisser J, Buck MB, Fritz P, Dippon J, Schwab M, Brauch H, Zug-8 Schmierer B, Hill CS: TGFß1 inhibits the formation of benign skin tumors, but enhances progression to invasive spindle carcinoma in transgenic mice. Cell 1996, 85:531-542.

10. Basolo F, Fiore L, Ciardiello F, Calvo S, Fontanini G, Conaldi PG, Tonio A: Response of normal and oncogene-transformed human mammary epithelial cells to transforming growth factor factor beta 1 (TGF-beta 1): lack of growth-inhibitory effect on clone expressing the simian virus 40 large-T antigen. Int J Cancer 1994, 59:736-742.

11. Cui W, Fowlis DJ, Bryson S, Duffie E, Ireland H, Balmain A, Akhurst RJ: TGFß1 inhibits the formation of benign skin tumors, but enhances progression to invasive spindle carcinoma in transgenic mice. Cell 1996, 85:531-542.

12. Derynick R, Akhurst RJ, Balmain A: TGF-ß signaling in tumor suppression and cancer progression. Nat Genet 2001, 29:117-129.

13. Siegel PM, Shu W, Cardiff RD, Muller WJ, Massague J: Transforming growth factor beta signal transduction: molecular specificity and functional flexibility. Nat Rev Mol Cell Biol 2002, 3:790-792.

14. Kleuser B, Malek D, Gust R, Pertz HH, Potteck H: Concordant epigenetic silencing of transforming growth factor beta signaling pathway variants may predict breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005, 14:1567-1570.

15. Mao JH, Saunier EF, de Koning JP, McKinnon MM, Higgins MN, Nicklacs K, Yang HT, Balmain A, Akhurst RJ: Genetic variants of Tgfb1 act as context-dependent modifiers of mouse skin tumor susceptibility. Proc Natl Acad Sci USA 2006, 103:8125-8130.

16. Akhurst RJ: TGF beta signaling in health and disease. Nat Genet 2004, 36:790-792.

17. Teicher BA: Malignant cells, directors of the malignant process: role of transforming growth factor-beta. Cancer Metastasis Rev 2001, 20:133-143.

18. Anscher MS, Peters WP, Reisenbichler H, Petros WP, Jirtle RL: Transforming growth factor ß as a predictor of liver and lung fibrosis after autologous bone marrow transplantation for advanced breast cancer. New England J Med 1993, 328:1592-1598.

19. Kong F-M, Anscher MS, Murase T, Abbott BD, Iglehart JD, Jirtle RL: Elevated plasma transforming growth factor-b1 levels in breast cancer patients decrease after surgical removal of tumor. Ann Surgery 1995, 222:155-162.

20. Tsushima H, Ito N, Tamura S, Matsuura Y, Inada M, Yabuuchi I, Imai Y, Nagashima R, Misawa H, Takeda H, Matsuzawa Y, Kawata S: Circulating transforming growth factor beta1 as a predictor of liver metastasis after resection in colorectal cancer. Clin Cancer Res 2001, 7:1258-1282.

21. Barthelemy-Brichant N, David JL, Bosquée L, Bury T, Seidel L: Antitransforming growth factor-beta antibody 1D11 ameliorates breast cancer risk in Japanese women. Breast Cancer 2003, 10:63-69.

22. Cox A, Dunning AM, Garcia-Olmos M, Balasubramanian S, Reed MW, Pooley KA, Scollen S, Baynes C, Ponder BA, Chanock S, Lissowska J, Bronte L, Peplonska B, Southey MC, Hopper JL, McCreedie MR, Giles GG, Fletcher O, Johnson N, dos Santos Silva I, Gibson L, Bojesen SE, Nordestgaard BG, Axelson OK, Torres D, Hamann U, Justenhoven C, Brauch H, Chang-Claude J, Kropp S, et al: A coding variant in CASP8 is associated with breast cancer risk, 2007, 38:352-358.

23. Ewart-Toland A, Chan JM, Yuan J, Balmain A, Ma J: A gain of function TGFB1 polymorphism may be associated with late stage prostate cancer. Cancer Epidemiol Biomarkers Prev 2000, 9:755-761.

24. Wei Y-S, Zhu Y-H, Du B, Yang Z-H, Liang W-B, Lv M-L, Xiang T-H, Tai S-H, Zhao Y, Zhang L: Association of transforming growth factor-beta1 gene polymorphisms with genetic susceptibility to nasopharyngeal carcinoma. Clinica Chimica Acta 2007, 380:155-162.

25. Nikolova PN, Pawelec GP, Mihailova SM, Ivanova MI, Myhailova AP, Bandaljdeva DN, Marinova DI, Ivanova SS, Naumova EJ: Association of cytokine gene polymorphisms with malignant melanoma in Caucasian population. Cancer Immunol Immunother 2007, 56:245-251.

26. Shin A, Shu X-O, Cai Q, Gao Y-T, Zheng W: Genetic polymorphisms of the transforming growth factor-beta1 gene and breast cancer risk: a possible dual role at different cancer stages. Cancer Epidemiol Biomarkers Prev 2005, 14:1567-1570.

27. Shabtai SF, Kattan MW, Travell E, Andrews B, Zhu K, Wheeler TM, Slawin KM: Association of pre- and postoperative plasma levels of transforming growth factor beta1 and interleukin 6 and its soluble receptor with prostate cancer progression. Cancer Res 2004, 64:1492-1499.

28. Martin M, Lefaix J, Delanian S: Soluble transforming growth factor-beta1 in transgenic mice. Cell 1996, 85:531-542.

29. Shibutani M, Kinoshita I, Ishida K, Saijo S, Yamaoka M, Sawa S, Yamaoka Y: Function of transforming growth factor-beta1 in the response of normal and transformed cells to serum deprivation. J Biol Chem 1987, 262:155-162.

30. Barthelemy-Brichant N, David JL, Bosquée L, Bury T, Seidel L: Antitransforming growth factor-beta antibody 1D11 ameliorates breast cancer risk in Japanese women. Breast Cancer 2003, 10:63-69.

31. Cox A, Dunning AM, Garcia-Olmos M, Balasubramanian S, Reed MW, Pooley KA, Scollen S, Baynes C, Ponder BA, Chanock S, Lissowska J, Bronte L, Peplonska B, Southey MC, Hopper JL, McCreedie MR, Giles GG, Fletcher O, Johnson N, dos Santos Silva I, Gibson L, Bojesen SE, Nordestgaard BG, Axelson OK, Torres D, Hamann U, Justenhoven C, Brauch H, Chang-Claude J, Kropp S, et al: A coding variant in CASP8 is associated with breast cancer risk, 2007, 38:352-358.

32. Ewart-Toland A, Chan JM, Yuan J, Balmain A, Ma J: A gain of function TGFB1 polymorphism may be associated with late stage prostate cancer. Cancer Epidemiol Biomarkers Prev 2000, 9:755-761.

33. Wei Y-S, Zhu Y-H, Du B, Yang Z-H, Liang W-B, Lv M-L, Xiang T-H, Tai S-H, Zhao Y, Zhang L: Association of transforming growth factor-beta1 gene polymorphisms with genetic susceptibility to nasopharyngeal carcinoma. Clinica Chimica Acta 2007, 380:155-162.

34. Nikolova PN, Pawelec GP, Mihailova SM, Ivanova MI, Myhailova AP, Bandaljdeva DN, Marinova DI, Ivanova SS, Naumova EJ: Association of cytokine gene polymorphisms with malignant melanoma in Caucasian population. Cancer Immunol Immunother 2007, 56:245-251.
35. Thiery JP: Epithelial-mesenchymal transitions in development and pathologies. Curr Opin Cell Biol 2003, 15:740-746.

36. Andarawewa KL, Erickson AC, Chou WS, Costes SV, Gascard P, Mott JD, Bissell MJ, Barcellos-Hoff MH: Ionizing radiation predisposes nonmalignant human mammary epithelial cells to undergo transforming growth factor beta induced epithelial to mesenchymal transition. Cancer Res 2007, 67:8662-8670.

37. Thiery JP: Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2002, 2:445-454.

38. Shiloh Y: ATM: Sounding the double-strand break alarm. Cold Spring Harb Symp Quant Biol 2000, 65:527-533.

39. Andarawewa KL, Chytil A, Plieth D, Gorska AE, Dumont N, Shappell BS, Werb Z: Inhibition of TGFβ1 signaling attenuates ATM activity in response to genotoxic stress. Cancer Res 2006, 66:10861-10868.

40. Pandey J, Umphress SM, Kang Y, Angdisen J, Naumova A, Mercer KL, Jacks T, Jakowlew SB: Modulation of tumor induction and progression of oncogenic Kras-positive tumors in the presence of TGF-β1 haploinsufficiency. Carcinogenesis 2007, 28:2599-2608.

41. Padua D, Zhang XHF, Wang Q, Nadal C, Gerald WL, Gomis RR, Massagué J: TGFbeta primes breast tumors for lung metastases: survival seeding through Angiopoietin-like 4. Cell 2006, 125:86-97.

42. Rubin H: Tumor evolution as a dynamic developmental disorder. Cancer Res 1985, 45:2935-2942.

43. Barcellos-Hoff MH: The potential influence of radiation-induced microenvironments in neoplastic progression. J Mammary Gland Biol Neoplasia 1998, 3:165-175.

44. Sonnenschein C, Soto AM: Somatic mutation theory of carcinogenesis: why it should be dropped. Mol Carcinog 2000, 29:205-211.

45. Basell MJ, Radisky D: Putting tumours in context. Nat Rev Cancer 2004, 4:11-11.

46. Wiseman BS,WEB zb: Stromal effects on mammary gland development and breast cancer. Science 2002, 296:1046-1049.

47. Kupervasser C, Chavarria T, Wu M, Magrane G, Gray JW, Carey L, Rhim J, Weinberg RA: Reconstruction of functionally normal and malignant human breast tissues in mice. Proc Natl Acad Sci USA 2004, 101:4966-4971.

48. Bhovmick NA, Chytli A, Pleth D, Gorska AE, Dumont N, Shappell S, Washington MK, Neilson EG, Moses HL: TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. Science 2004, 303:848-851.

49. Maffini MV, Soto AM, Calabro JM, Ucci AA, Sonnenschein C: The stroma as a crucial target in rat mammary gland carcinogenesis. J Cell Sci 2004, 117:1495-1502.

50. Teicher BA, Ikobe M, Ara G, Keyses SR, Herbst RS: Transforming growth factor-beta 1 overexpression produces drug resistance in vivo: reversal by decorin. In Vivo 1997, 11:463-472.

51. Liu F, Menon K, Alvarez E, Lu K, Teicher BA: Transforming growth factor-beta and response to anticancer therapies in human liver and gastric tumors in vitro and in vivo. Int J Oncol 2000, 16:599-610.

52. Ewan KB, Henshall-Powell RL, Ravani SA, Pajares MJ, Arteaga CL, Watters RL, Akhurst RJ, Barcellos-Hoff MH: Transforming growth factor-β1 mediates cellular response to DNA damage in situ. Cancer Res 2002, 62:5627-5631.

53. Kroshner J, Jobling MF, Pajares MJ, Ravani SA, Glick A, Lavin M, Koslov S, Shiloh Y, Barcellos-Hoff MH: Inhibition of TGFβ1 signaling attenuates ATM activity in response to genotoxic stress. Cancer Res 2006, 66:10861-10868.

54. Kakeji Y, Maehara Y, Ikobe M, Teicher BA: Dynamics of tumor oxygenation, CD31 staining and transforming growth factor-beta levels after treatment with radiation or cyclophosphamide in the rat 13762 mammary carcinoma. Int J Radiat Oncol Biol Phys 1997, 37:1115-1123.

55. Teicher BA, Maehara Y, Kakeji Y, Ara G, Keyses SR, Wong J, Herbst R: Reversal of in vivo drug resistance by the transforming growth factor-beta inhibitor decorin. Int J Cancer 1997, 71:49-58.

56. Hirohashi S, Kanai Y: Cell adhesion system and human cancer morphogenesis. Cancer Sci 2003, 94:575-581.

57. Teicher BA, Ikobe M, Ara G, Keyses SR, Herbst RS: Transforming growth factor-beta 1 overexpression produces drug resistance in vivo: reversal by decorin. In Vivo 1997, 11:463-472.