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TGFBR1 Signaling and Breast Cancer

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Abstract

Over the past decade mutations discovered in genes such as *BRCA1*, *BRCA2*, *TP53* and *PTEN*, have emerged as high-penetrance susceptibility genes and are clinically relevant for determination of breast cancer risk. Genetic counseling and subsequent screening for mutations and gene rearrangement has improved patient outcome through early detection and prophylactic interventions in patients with familial breast cancer syndromes. However, these high-penetrance genes only account for a small fraction of the hereditary linked breast cancers. It is currently believed that low-penetrance susceptibility alleles and/or environmental factors may play an important role in the remaining cases. *TGFBR1**6A (*6A) is a common hypomorphic variant of the type I TGF-β receptor gene (*TGFBR1*) that has been associated with risk for several forms of cancer, in particular breast cancer. Several epidemiological studies have suggested that patients who carry the *6A allele have an increased risk of breast cancer. Furthermore, functional analysis suggests that this mutation alters TGF-β signaling and promotes tumorigenesis. Although a decade of research has provided basic information in regards to the prevalence of this mutation in several cancer types and populations the molecular underpinning of its functional effects are poorly understood. A better understanding of the molecular mechanism of TGFBR1 signaling in breast cancer may have an impact on breast cancer risk assessment and breast cancer prevention.

Keywords

TGFBR1; Breast cancer; TGF-β; Cancer genetics; Low-penetrance susceptibility alleles; BRCA1/2; TP53; PTEN; CHEK2; Li Fraumeni syndrome; Cowden's disease; Hereditary breast and ovarian syndrome

Introduction to breast cancer

Breast cancer is the second leading cause of cancer death for women living in the United States. The American Cancer Society reports that in 2010, there were more than 209,000 new cases of breast cancer and more than 40,000 deaths [1]. Through advances in detection and treatment modalities, the number of breast cancer survivors has steadily increased. The high incidence and prevalence of breast cancer provides a strong rationale for studies into the biology of breast cancer. Screening recommendations, including mammography, MRI in

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high risk women and self-breast exams, have greatly increased the number of women who are diagnosed at early stage. Breast cancer outcome depends in great part on stage of disease at the time of diagnosis. Additional screening recommendations and new predictive markers of breast cancer risk will likely further decrease breast cancer mortality because of a shift towards diagnosis of early stage breast cancer. While treatments such as surgery, radiation and immunotherapy have proven very effective for localized disease, treatment for metastatic breast cancer remains a major challenge. Of the more than 200,000 cases diagnosed each year, it is estimated that 20%–25% are inherited [2]. Patients that acquire inherited mutations are at a greater risk for development of several cancer types including breast cancer. To date, about 100 genes have been linked to various Mendelian cancer predisposition syndromes [3]. *BRCA1*, *BRCA2*, *TP53* and *PTEN* mutations result in significant increase in lifetime risk for breast cancer. Additionally, mutations in several other genes, including *STK11/LKB1*, *CDH1*, *CHEK2*, *ATM*, *MLH1*, and *MSH2*, have also been associated with hereditary breast and/or ovarian tumors.

High-penetrance tumor susceptibility alleles

Mutations in *BRCA1* and *BRCA2* have been linked to a syndrome known as hereditary breast and ovarian cancer syndrome. *BRCA1* mutation is associated with a 65%–81% lifetime risk for breast cancer and a 35%–60% lifetime risk of ovarian or fallopian tube cancer [4–6]. *BRCA2* is associated with a 45%–85% lifetime risk for breast cancer and a 10%–27% lifetime risk of ovarian or fallopian tube cancer [4–6]. Both *BRCA1* and *BRCA2* are associated with an increased risk of male breast cancer [7]. Mutations in these two genes have been associated with ~20% of the familial breast cancer cases diagnosed [8]. Functionally, *BRCA1* plays a central role in the repair of double-strand breaks by homologous recombination, with *BRCA2* and a number of related proteins in a supportive role for the recognition of such DNA damage [9].

Rare *TP53* mutations have been linked to the Li-Fraumeni Syndrome (LS). The *TP53* gene encodes for a common tumor suppressor protein TP53, which is found to be mutated in more than 50% of all cancers. TP53 normally acts as a regulator of cell cycle progression in response to DNA damage. In breast cancer, the frequency of *TP53* gene mutations is approximately 20% to 30% [10]. Patients with Li-Fraumeni Syndrome also have increased risk to develop several additional forms of cancer including sarcomas, leukemia, and lymphomas. The exact prevalence of Li-Fraumeni is unknown; however, the estimated frequency of the TP53 mutation is 1 in every 20,000 persons [11].

Mutations in *PTEN* have been linked with a syndrome known as Cowden's disease. *PTEN* is a tumor suppressor gene that inhibits cell growth during the G1 phase of cell cycle by activating *CDKN1B* (KIP1) [12]. Individuals with Cowden syndrome are at increased risk for developing breast cancer as well as hamartomas and benign tumors of the skin, thyroid, breast, endometrium, and brain [12]. Although very rare, penetrance is thought to be nearly complete; it approaches 90% by age 20 years. Carcinoma of the breast occurs in 20%–36% of female patients and is one of the most serious consequences of Cowden disease

Although deleterious mutations in high penetrance genes, *BRCA1*/2, *TP53* and *PTEN*, are causative of a fraction of the familial breast cancer cases it is believed that environmental factors and low-penetrance susceptibility alleles account for the remainder of cases. Examples of genes harboring rare cancer-associated variants include *CHEK2, BRIP1* and *PALB2* [3]. Inherited deleterious mutations in the cell cycle regulator *CHEK2* are associated with a 2-fold increase in breast cancer risk [3, 6]. A recurrent mutation in the *CHEK2* gene (1100delC) was reported to be a cause of breast cancer by Meijers-Heijboer et al. [13]. Recent studies suggest that *CHEK2* may act as a modifier of risk of other susceptibility genes due to the strong correlation for patients with a family history of breast cancer. Serrano et al. reported a synergistic effect between *CHEK2* mutations and a missense variant in *BRCA2* [14].

TGFB signaling

Transforming Growth Factor-β (TGF-β) is one of the most commonly altered cellular signaling pathways in human cancer [15]. TGF-β often has opposing effects on these cellular processes, with its effects being both cell and context specific. A general scheme of TGF-β signaling is depicted in Fig. 1. There are three types of cell surface receptors involved in TGF-β signaling: TGF-β receptor 1, 2 and 3, all of which are dual specificity kinases [16]. TGF-β1 (TGFB1), 2 (TGFB2) and 3 (TGFB3) ligands all bind to the same receptors but with varying affinities. TGFBR3 binds to all three isoforms with very high affinity and may be important in sequestration of TGF-β to the cell surface and for ligand presentation [17]. TGFBR2 is a homodimeric receptor that binds to TGF-β ligand and then forms a heterotetramer with TGFBR1. Autophosphorylation of TGFBR2 causes phosphorylation of TGFBR1 to initiate intracellular signaling. Hence, TGFBR1 is the central propagator of TGF-β signaling.

The canonical TGF-β signaling pathway is mediated through SMAD proteins. The mammalian genome contains eight members of the SMAD family. The receptor-regulated SMAD (rSMADS) are activated through phosphorylation and direct interaction with TGFBR1. Once phosphorylated, these SMADs can complex to form heterodimers, which continue the intracellular signaling cascade. The rSMADs consist of SMAD1, 2, 3, 5 and 8, with SMAD2 and 3 being directly involved in the TGF-β signaling pathway. Co-mediator SMADs (co-SMADs) bind to the rSMAD complex and mediate entry into the nucleus to act as transcription factors. This class of SMADs includes SMAD4 in the TGF-β family signaling cascades. The third group of SMAD proteins inhibits this pathway and these proteins are known as inhibitory-SMADs (i-SMADs). SMAD6 and SMAD7 are members of this class and act to regulate TGF-β signaling and expression levels. While this classical signaling cascade has been shown to mediate many of the physiological effects of TGF-β, studies have shown that both TGF-β receptors and SMADs can interact with other signaling pathways to mediate effects. Studies have shown that signaling through MAPK8, MAPK14, PIK3, MAPK1/3 and RAS pathways may be involved in the physiological and pathological effects of TGF-β signaling [18, 19]. Some of the downstream targets of TGF-β signaling are important cell-cycle checkpoint genes, including *CDKN1A, CDKN1B, CDKN2B*, and their activation leads to growth arrest in normal cells [20]. Further investigation into the TGF-β

signaling through these non- SMAD pathways may help to develop a better understanding of the role of TGF-β in pathological conditions such as cancer and fibrosis.

TGFB signaling and breast cancer

The importance of TGF-β signaling in breast cancer progression is evident through numerous in vitro and in vivo studies in which the pathway is disrupted, as well as naturally occurring mutations are evaluated. In a study of TGF-β modulation of mammary tumor progression, mice transgenic for activated *Tgfbr1* and the *Erbb2* oncogene displayed reduced mitotic index and proliferation rates but enhanced pulmonary metastasis [21]. MCF-7 breast cancer cells overexpressing dominant negative TGFBR2 or treated with a TGFBR1 inhibitor exhibit increased apoptosis compared to normal breast epithelia [22]. Additionally, mutant TGF-β receptors have been associated with higher tumor grades and increased invasiveness. Studies have shown that overexpressing *TGFBR3* in a xenograft breast cancer model decreases angiogenesis in both the primary and metastatic tumor [23]. However, TGF-β upregulation of MMP-9 also induces angiogenesis in a breast cancer cell line [24]. In patients TGF-β ligand expression is elevated in the late stages of breast cancer and can be used as a prognostic marker [25]. Reduced nuclear levels of pSMAD2/3 have been associated with high tumor grade, high architectural grade, larger tumor size, and hormone receptor negativity [26], which suggest that decreased TGF-β signaling is associated with a worse outcome. These previous findings from in vitro, in vivo and patient samples illustrate the important role of TGF-β signaling as both a tumor suppressor and pro-oncogenic mediator of breast carcinogenesis. Newer studies which have focused on changes within the tumor microenvironment have highlighted a role for TGF-β signaling in tumor-stromal interactions. One study demonstrated, for example, that fibroblasts lacking *TGFBR2* are able to induce an invasive phenotype in adjacent carcinomas, featuring increased proliferation rate, greater angiogenesis, and reduced apoptosis [27]. Furthermore, *TGFBR2*-null fibroblasts grafted into the mammary fat pads of wild-type mice induced epithelial changes in the new local microenvironment [28]. Over the past few years, an increasing number of epidemiological studies have pointed to the possibility that genetic variants affecting TGF-β production and/or signaling may be related to the overall risk and survival of breast cancer patients. Several SNPs and/or mutations in *TGFB1* and *TGFBR1* have been associated with increased breast cancer risk and remain to be thoroughly evaluated. However, for the purposes of this review we will focus on mutations in *TGFBR1* and its potential implications for breast cancer risk.

Characterization of *TGFBR1**6A

The receptor serine/threonine kinase family in the human genome comprises 12 members—7 type I and 5 type II receptors—all dedicated to TGF-β signaling [16, 29]. *TGFBR1* gene maps to 9q22.33 [30] and is approximately 56 kb in length consisting of 9 exons [31]. Both types of the receptor serine/threonine kinases consist of about 500 amino acids, organized sequentially into an N-terminal extracellular ligand binding domain, a transmembrane region, and a C-terminal serine/threonine kinase domain [16]. Mutations in several components of the TGF-β signaling pathway have been associated with breast cancer, many of which involve *TGFBR2* and *SMAD* alterations. Mutation types such as frameshift and

missense mutations in the *TGFBRI* coding region are present in subsets of ovarian, esophageal, and head and neck cancers [32]. Additionally, decreased expression of *TGFBR1* or *TGFBR2* in gastric cancers has been linked to methylation of the *TGFBR1* promoter suggest epigenetic mechanisms may play a role [32]. Previously there was little evidence that mutations in the *TGFBR1* gene occurred in breast cancer, however at study by Chen et al. reported 2 of 31 primary carcinomas and 5 of 12 lymph node metastases carried a C to A transversion mutation resulting in a serine to tyrosine substitution at codon 387 (S387Y) of the *TGFBR1*. This *TGFBR1* mutant has a diminished ability to mediate TGF-β-dependent effects on gene expression as compared with wild-type *TGFBR1* [33].

There is growing evidence that a common variant of the type 1 TGF-β receptor, *TGFBR1**6A, may account for approximately 5% of all breast cancer cases, a fraction similar to that attributable to *BRCA1* and *BRCA2* [2]. *TGFBR1**6A is a common variant of *TGFBR1* which harbors a three alanine deletion within a stretch of nine alanines located in the 3′-end of exon 1 [30, 34, 35]. More than one in seven healthy individuals and one in six patients with cancer is a *TGFBR1**6A carrier making this a high frequency, low-penetrance susceptibility allele. In addition to the *6A variant, several deletions/additions within this same region have been identified, including *TGFBR1**10A, *TGFBR*1*8A and *TGFBR1**5A. The fact that a significantly higher *6A allelic frequency was found among patients with a diagnosis of cancer than among healthy controls prompted us to postulate that *6A may act functionally as a tumor susceptibility allele [35]. Early studies have shown that somatic acquisition of this allele is uncommon in breast cancer but not in other cancer types [26]. In an early study Baxter et al. investigated the possible influence of the *TGFBR1**6A allele on cancer risk in a cases-control study of 248 controls and 355 women with breast cancer occurring under the age of 40 years, bilateral breast cancer, or a family history of breast cancer. The *TGFBR1**6A allele was found to be significantly associated with breast cancer (odds ratio, 1.6; 95% confidence interval, 1.1–2.5) [36]. A meta-analysis performed by Colleran et al., found no association (genotypic OR=0.93, 95% CI=0.74–1.19, P=0.57; allelic OR=0.93, 95% CI= 0.74–1.15, P=0.49) for breast cancer risk [37]. However, a larger meta-analysis of 32 case control studies that included 13,662 cases and 14,147 controls showed significantly elevated cancer risk associated with *6A in all genetic models [38]. Overall cancer risk was increased by 11% for *6A heterozygotes and 30% for *6A homozygotes. This meta-analysis included 10,826 breast cancer cases and 12,964 controls and *TGFBR1**6A was significantly associated with breast cancer risk: O.R. 1.16, 95% CI 1.01–1.34 [38]. We have recently shown that *TGFBR1**6A is associated with constitutively decreased TGFBR1 expression and increased cancer susceptibility [39, 40].

The 9-alanine sequence is a component of the signal sequence peptide which is responsible for targeting and membrane insertion of secretory and membrane proteins. The signal sequence is normally cleaved following membrane insertion. Initial characterization of the *TGFBR1**6A sequence indicates that the 9-bp deletion in *TGFBR1**6A does not interfere with the normal cleavage site [35]. However, a secondary cleavage site, found in normal TGFBR1, is not present in the *6A sequence. An experimental model using dog pancreas microsomes confirmed that neither the 9-bp deletion in the *6A signal sequence nor the 3-bp insertion in the *10A signal sequence measurably affect either targeting to or translocation

across the endoplasmic reticulum membrane [35]. *TGFBR1**6A has also been shown to mediate TGF-β inhibitory signals less efficiently in reporter assays and growth inhibition assays in mink lung epithelial cells [34]. *TGFBR1**10A, another rare variant, transduces TGF-β growth-inhibitory signals as effectively at TGFBR1, which suggests that the 6 Ala repeat of *6A has specific biological properties [34, 35]. In MCF-7 breast cancer cells overexpressing *TGFBR1**6A there was an increase in cell proliferation, migration and invasion in response to TGF-β treatment [35, 41]. Furthermore, expression of *6A with abolished kinase activity stimulates MCF-7 cell growth in response to TGF-β providing strong support for the novel notion that *6A biological effects are, at least in part, caused by its shorter signal sequence [35]. An additional colon cancer cell line, DLD-1, which harbors the *6A mutation is also growth stimulated by TGF-β treatment [35]. That *6A was the only somatically acquired *TGFBR1* allele in primary and metastatic tumors suggests that, even if instability is present at the *TGFBR1* locus, the *6A allele provides selective growth advantage over other *TGFBR1* alleles, such as the previously reported *5A, *8A, and *10A alleles [35].

Several additional studies have been performed in a variety of cancer types, which have revealed no association of *TGFBR1**6A and cancer risk. Hu et. al recently published a study of *6A risk and osteosarcoma for a Chinese patient population in which no significant association was discovered [42]. Castillejo et al. reported results that suggest that the *TGFBR1**6A allele does not confer an increased risk of colorectal cancer in the Spanish population [43]. A small study in lung cancer did not show any significant increase in risk for *TGFBR1**6A mutation carriers [44]. However, several *TGFBR1* haplotypes were found to be associated with non-small cell lung cancer [45]. A 2007 report by Song et al. reported that in a Swedish population the *TGFBR1**6A variant may be associated with an increased risk of low-risk familial breast cancer and might be a marker for poorly differentiated breast cancer [46]. These differences may be attributed to variation in the ethnic populations selected for the various studies or may be due to synergistic effects of *TGFBR1**6A and other tumor susceptibility alleles present in some but not all cancer types. However, the most likely explanation is the lack of power of many of these studies given the low penetrance and high prevalence of this allele. Further analysis is warranted to determine the true mechanisms that govern the increased risk associated with *TGFBR1**6A in breast cancer patients.

To date, functional analysis of *TGFBR1**6A indicates that this mutation may confer a growth advantage to cancer cells by switching TGF-β growth inhibitory signals into growth stimulatory signals [47]. One study has confirmed that negative feedback regulation in terms of *SMAD3* expression was attenuated and radiation-induced cell death as a cellular endpoint was enhanced for cells harboring the *TGFBR1**6A mutation [47]. We have shown that *TGFBR1**6A enhances MCF-7 cell migration and invasion through RHOA and MAPK1 pathway activation and downregulation of ARHGAP5 and FN1 [41]. However, continued analysis using both in vitro and in vivo models will help to elucidate additional mechanisms of action. In addition to the *6A allele, an intronic SNP (Int7G24A, rs334354) in the TGFBR1 gene has also been investigated in relation to breast cancer risk. However, the

Int7G24A variant was not associated with breast cancer risk or clinical presentation of the disease including prognosis [48].

Potential clinical applications related to *TGFBR1**6A

Clinical options for women at high genetic risk of breast cancer include screening starting at a young age, the use of highly sensitive detection methods, and prophylactic surgeries of the ovaries or breast [6]. Identification of candidates for genetic counseling and genetic testing remains a central priority as only a small fraction of the estimated carriers has been identified to date [8]. The exact role of low-penetrance susceptibility alleles such as *6A, *TGFBR1* SNPs associated with constitutively decreased TGFBR1 expression and other SNPs identified through GWA studies remains to be defined. Investigation of low penetrance susceptibility alleles and breast cancer risk are complicated by the fact that the penetrance is highly influenced by other factors such as modifier genes, response to DNA damage, and environmental factors such as exposure to carcinogens, hormonal/reproductive factors, and weight [49].

Conclusions

TGF-β signaling plays an important role as both a tumor suppressor in early stage carcinogenesis and pro-metastatic factor in late stage tumorigenesis. It has been known to regulate many aspects of tumor biology including: apoptosis, cell cycle regulation, angiogenesis, immune suppression, migration and invasion. Its numerous roles have made this pathway an excellent candidate for targeted therapeutics. However, a new role for TGF-β signaling components has recently emerged as potential tumor modifiers of cancer susceptibility. Early studies have identified mutations in the receptors, ligands and intermediate signaling components which may be associated with cancer risk. Although some epidemiological studies have been inconclusive it is evident that variants such as *TGFBR1**6A play some role in mediating tumorigenic effects. Additional epidemiological and molecular studies of this mutation are warranted to determine its potential as a predictive marker for cancer risk and treatment response.

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Abbreviations

ARHGAP5	Rho GTPase-activating protein 5
ATM	Ataxia telangiectasia mutated
CDKN	Cyclin-dependent kinase inhibitor
ERRB2	Human Epidermal growth factor Receptor 2
FN1	Fibronectin
GWA	Genome-wide association

MAPK	Mitogen-activated protein kinase
PIK3	Phosphatidylinositol 3-kinase
PTEN	Phosphatase and tensin homologue
rSMAD	Receptor-regulated SMAD
coSMAD	Co-mediator SMAD
iSMAD	Inhibitory SMAD
STK11	Serine/Threonine kinase
TGF-β	Transforming growth factor beta
TGFBR	Transforming growth factor beta receptor

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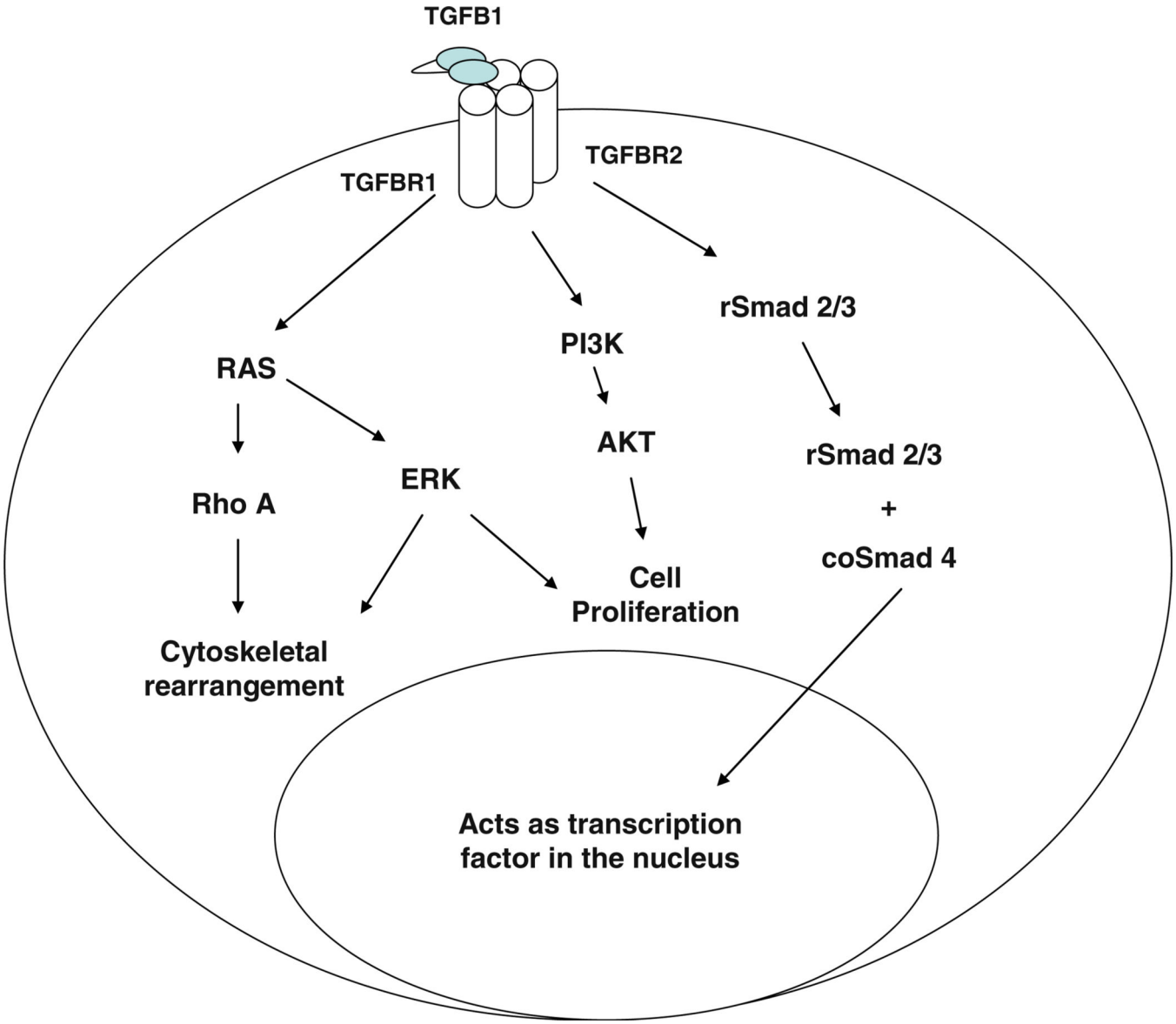

Fig. 1.
TGF-β signaling cascade