The pleiotropic cytokine, transforming growth factor-β (TGF-β), plays a critical role in suppressing the immune response in the periphery to prevent an autoimmune response. TGF-β is a potent cytokine with diverse effects on hematopoietic cells. Its pivotal function within the immune system is to maintain tolerance via the regulation of lymphocyte proliferation, differentiation, and survival. In addition, TGF-β controls the initiation and resolution of inflammatory responses through the regulation of chemotaxis and activation of leukocytes in the periphery, including lymphocytes, natural killer cells, dendritic cells, macrophages, mast cells, and granulocytes. Through its pleiotropic effects on these immune cells, TGF-β prevents the development of autoimmune diseases without compromising immune responses to pathogens. However, overactivation of this pathway can lead to several immunopathologies under physiologic conditions including cancer progression, making it an attractive target for antitumor therapies. This review discusses the biological functions of TGF-β and its effects on the immune system and addresses how immunosuppression by this cytokine can promote tumorigenesis, providing the rationale for evaluating the immune-enhancing and antitumor effects of inhibiting TGF-β in cancer patients.
Under physiologic conditions, active TGF-β, either as a cell surface-bound or intracellular soluble form, is liberated from these proteins following additional stimuli from acidic pH, integrins, thrombospondin-1, and proteases, enabling it to exert its function by binding to its receptor (17–21).

Signal transduction follows binding of TGF-β to a heterodimeric receptor complex consisting of type I and II transmembrane serine/threonine kinase subunits. Five type I (activin-like receptor kinase family) and seven type II receptors have been identified to form these TGF-βRs (Fig. 1; ref. 14). Intracellular signal transduction is mediated by phosphorylation of several transcription factors known as Smads as well as Smad-independent pathways involving kinase cascades, including Rho-Rac-cdc-42, Ras-extracellular signal-regulated kinase, Tak-MKK3/6-c-Jun NH2-terminal kinase, TAK-MKK4-p38, and phosphatidylinositol 3-kinase, and transcriptional regulators, such as TGF-β interacting protein, protein phosphatase 2A, elongation initiation factors, and the immunophilin, FK506 binding protein 12 (Fig. 1; refs. 22–25). Following TGF-β binding, the Smad-dependent pathway is activated when activin-like receptor kinase 5 phosphorylates Smad2 and Smad3, which translocate into the nucleus in a complex with Smad4 (Fig. 1). The resulting Smad complex binds to a target promoter and regulates gene expression through the recruitment of histone acetyl transferase or histone deacetylase (Figs. 1 and 2; refs. 26, 27). Negative regulators of this pathway include Smad7, which competes with Smad2 and Smad3 for activin-like receptor kinase 5 binding and degrades activin-like receptor kinase 5 through the recruitment of Smurf-containing E3 ubiquitin-ligase complexes. The Smad-independent pathways activated following TGF-β binding to its receptor are poorly understood and their relevance to immune cell regulation is unknown.

### TGF-β and T cells

CD8+ cytotoxic T cells (CTL) and natural killer (NK) cells play a critical role in the prevention, killing, and clearance of tumors and have been targeted in the development of anticancer immunotherapies (28, 29). As a pleiotropic cytokine, TGF-β exerts its effects on multiple immune cell types (1) and its role in controlling T-cell functions has been extensively studied. TGF-β inhibition of T-cell proliferation in vitro was first documented using activated human T cells (3). One mechanism behind TGF-β–mediated suppression of T-cell proliferation is through TGF-β blockade of the production of interleukin (IL)-2 (Fig. 2), a lymphokine known to activate T cells, NK cells, and other types of cells of the immune system (30, 31). This effect can be partially reversed by the addition of exogenous IL-2 (3). Further work has shown that TGF-β suppression of IL-2 production may be through directly inhibiting IL-2 promoter activity through a cis-acting enhancer DNA element (32). R-Smad3 has also been shown to be critical in mediating TGF-β inhibition of IL-2 production (33).

In addition, TGF-β inhibits T-cell proliferation through pathways not involving IL-2 suppression (3). For example, TGF-β also attenuates the expression of cell cycle regulators in T cells. Upon TGF-β treatment, cyclin-dependent kinase inhibitors, including p15, p21, and p27, are up-regulated, whereas cell cycle–promoting factors, including c-myc, cyclin D2, cyclin-dependent kinase 2, and cyclin E, are decreased.

**Fig. 1.** Summary of Smad-dependent and Smad-independent signaling following TGF-β binding to its receptor. Following TGF-β binding to an example of a heterodimeric receptor for this cytokine ([activin-like receptor kinase 5 (ALK5) and TGF-βRII]), several molecular signaling cascades occur. The Smad-dependent and Smad-independent pathways as well as negative regulatory feedback pathways through Smurf and Smad7 are shown. TF, transcription factor; HAT, histone acetyl transferase; HDAC, histone deacetylase; FBKBP12, FK506 binding protein 12; TRIP-1, TGF-βR interacting protein; PP2A, protein phosphatase 2A; eIFs, elongation initiation factors; JNK, c-Jun NH2-terminal kinase; Erk, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase.

**TGF-β and the Key Effector Cells in the Antitumor Response: T cells and Natural Killer Cells**

TGF-β and T cells. CD8+ cytotoxic T cells (CTL) and natural killer (NK) cells play a critical role in the prevention, killing, and clearance of tumors and have been targeted in the development of anticancer immunotherapies (28, 29). As a pleiotropic cytokine, TGF-β exerts its effects on multiple immune cell types (1) and its role in controlling T-cell functions has been extensively studied. TGF-β inhibition of T-cell proliferation in vitro was first documented using activated human T cells (3). One mechanism behind TGF-β–mediated suppression of T-cell proliferation is through TGF-β blockade of the production of interleukin (IL)-2 (Fig. 2), a lymphokine known to activate T cells, NK cells, and other types of cells of the immune system (30, 31). This effect can be partially reversed by the addition of exogenous IL-2 (3). Further work has shown that TGF-β suppression of IL-2 production may be through directly inhibiting IL-2 promoter activity through a cis-acting enhancer DNA element (32). R-Smad3 has also been shown to be critical in mediating TGF-β inhibition of IL-2 production (33).

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The functional significance behind these effects of TGF-β as well as how TGF-β modulates these genes in T cells awaits further evaluation.

In addition to suppressing T-cell proliferation, TGF-β also controls T-cell effector functions. The expression of effector molecules by CTLs, such as IFN-γ and perforin, is inhibited by TGF-β (Fig. 2; refs. 40–43). Recent studies have shown that TGF-β is important for the inhibition of the exocytosis of granules and cytolytic function of CD8+ T cells (44). For example, Mempel et al. (44) used multiphoton intravital microscopy in the lymph nodes of anesthetized mice to evaluate how CTLs interact with antigen-presenting target cells in the presence or absence of activated regulatory T cells (Tregs), a suppressive T-cell population identified by the constitutive expression of a forkhead family transcription factor, FoxP3 (44). CTLs killed their targets at a 6.6-fold faster rate in the absence of Tregs, which can inhibit cytotoxic granule exocytosis by these effector cells (44). This effect was dependent on TGF-β as CTLs refractory to signaling by this cytokine displayed normal killing in the presence of Tregs (44).

The critical physiologic role for TGF-β in regulating suppression of conventional T cells, TGF-β further contributes to immunosuppression by promoting the generation of Tregs. Tregs are frequently found at higher frequencies in the peripheral blood, lymph nodes, and tumor sites of cancer patients (47). Although TGF-β can promote the generation of Tregs in vitro, it has been controversial whether TGF-β is involved in the generation or maintenance of Tregs under physiologic conditions. One recent study showed that Tregs lacking the TGF-βRII developed normally in the thymus but were poorly maintained in the periphery (48). That same study also showed that TGF-βRII–deficient Tregs were found to proliferate faster than the wild-type counterparts in the periphery, suggesting that TGF-β signaling is required to promote peripheral Treg survival independent of its proliferation potential (48). These results contrasted with those in other animal models where Treg maintenance or development was unaffected in environments...
lacking TGF-β1 expression (49). The discrepancies between these studies may be related to different experimental systems and mouse genetic backgrounds used in the experiments. The development of EGFP-FoxP3 and FoxP3-mRFP knock-in mice and FoxP3 intracellular staining will provide improved tools to identify Tregs based on FoxP3 expression (48, 50, 51). These reagents will enable future studies evaluating the effects of TGF-β on Treg biology and how this cytokine and Tregs inhibit antitumor responses in mouse models and cancer patients.

**TGF-β and NK cells.** NK cells are lymphoid cells that participate in innate immunity and in early defense by recognizing and killing infected or tumorigenic cells and rapidly producing chemokines and cytokines. IFN-γ production by NK cells is considered essential for stimulation of the Th1 response, and TGF-β attenuates this activity as well as the cytolytic activity of these cells (52, 53). Although the mechanisms of TGF-β-mediated inhibition of NK production of IFN-γ are unknown, TGF-β blocks the expression of receptors vital for the cytotoxic function of NK cells. Targeted killing by NK cells depends on the engagement of the NK receptors and coreceptors Nkp46, Nkp30, Nkp44, and NKG2D (54, 55). Exogenous TGF-β inhibits the expression of Nkp30 and NKG2D receptors resulting in decreased killing function (56). Our preliminary studies using transgenic mice containing NK cells resistant to TGF-β signaling (10) have revealed enhanced tumor rejection in these mice compared with wild-type littermates. Furthermore, down-modulation of NKG2D has also been associated with elevated TGF-β levels in cancer patients (57). This observation shows an immunosuppressive effect of TGF-β on NK cells under physiologic conditions in cancer patients and suggests a mechanism by which these cells are less effective at killing tumor cells. Further studies are planned to evaluate the antitumor effects of specifically blocking TGF-β signaling in NK cells and to determine the contribution of these cells in antitumor responses enhanced by approaches blocking TGF-β more broadly.

**TGF-β and the Immune System, and Cancer**

High levels of TGF-β are produced by many types of tumors, including melanomas and cancers of the breast, colon, esophagus, stomach, liver, lung, pancreas, and prostate, as well as hematologic malignancies (60, 61). Also, both the TGF-βRS type I and II as well as Smad proteins are mutated in several cancers (reviewed in ref. 62). In addition, tumors can promote TGF-β production by the surrounding cells in the tumor microenvironment (63). In early stages of tumorigenesis, TGF-β seems to act as a tumor suppressor. Gastrointestinal tumors with microsatellite instabilities and mutations in the TGF-βRII and pancreatic cancers containing Smad4 mutations do not respond appropriately to ligand-receptor interactions and thus become resistant to the signaling and antitumor activity by this cytokine (64, 65). During later stages of tumorigenesis, TGF-β can foster tumor growth, progression, and metastasis by enhancing the epithelial to mesenchymal transition and promoting tumor angiogenesis (66, 67). Interestingly, higher levels of TGF-β expression are observed in metastatic breast and colon metastases compared with the primary tumors (68, 69), reinforcing its role in promoting tumor progression in later stages of the disease. Elevated TGF-β levels in gastric carcinoma patients have been correlated with earlier recurrence rates for this cohort (70). Retrospective analyses of archival tumors obtained from breast, colon, and lung cancer patients have suggested a relationship between high levels of TGF-β with increased disease progression, metastasis, and death in breast and colon cancer patients and a worse 5-year survival in lung cancer patients (71–73).

In addition to its direct effects on tumor cells and angiogenesis, TGF-β enables tumors to evade immune surveillance (74) and killing through the mechanisms reviewed above and summarized in Fig. 3. TGF-β promotes Treg generation on TCR stimulation and it is conceivable that tumors promote immune privilege by generating Tregs through TGF-β production. This may be clinically relevant as high levels of Tregs portend a poor prognosis in ovarian cancer patients (75) and these cells infiltrate tumors in patients with various cancers as previously discussed above.

The epidemiologic and biological studies implicating TGF-β in tumor promotion and progression provide a strong rationale

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4 Y. Laouar and R. Flavell, unpublished observation.
for developing TGF-β inhibitors as therapeutic agents for advanced cancer. Various inhibitors of TGF-β signaling are being evaluated in preclinical models and early clinical trials including soluble protein receptors, TGF-β antibodies, small-molecule kinase inhibitors, oligonucleotides, peptide aptamers, and tumor vaccines, which are summarized in Table 1. Currently, the majority of the TGF-β signaling inhibitors are in preclinical studies. However, a blocking oligonucleotide (AP12009), an antibody to all three isoforms of human TGF-β (GC-1008), a small-molecule inhibitor of the TGF-βRI kinase (LY573636), and a vaccine using allogeneic tumor cells have entered clinical cancer trials (76–78). The most advanced studies to date involve approaches inhibiting TGF-β locally, including the synthetic antisense oligodeoxynucleotide, AP12009, and allogeneic tumor vaccines (76–78). The antisense AP12009 can bind to TGF-β2 mRNA in tumor cells, ultimately leading to decreased expression of TGF-β2. In preclinical studies, AP12009 reduced proliferation in glioma, pancreatic cancer, and malignant melanoma cell lines (76). Animal studies further showed that intrathecal bolus injections and intracerebral infusions of AP12009 were well tolerated (76). Subsequent phase I/II open-label dose escalation studies showed that this compound was safe and well tolerated when administered as intratumoral injections to patients with high-grade gliomas (76). Following treatment with AP12009, patient-derived peripheral blood mononuclear cells showed enhanced immune cell–mediated cytotoxicity against tumor cells in vitro after stimulation with IL-2 and coinbucation with autologous glioma cells (76). These results suggest that this oligodeoxynucleotide may enhance antitumor responses in glioma patients and warrant further evaluation in larger clinical trials. To this end, an international phase II trial in adult patients with recurrent high-grade glioma has recently completed enrollment (76). Given that AP12009 also inhibits pancreatic cancer and malignant melanoma cell lines, phase I/II studies evaluating this compound in pancreatic carcinoma and malignant melanoma patients are also under way (76).

Clinical studies have also been initiated with an allogeneic whole-cell tumor vaccine that has been stably transfected with a TGF-β2 antisense plasmid vector. Expression of this vector leads to reduced TGF-β2 expression by the vaccine cells (77), which could be an advantage considering that the endogenous TGF-β generated by the whole-cell vaccine might inhibit its efficacy. Gliosarcoma (9L) cells were stereotactically implanted in the forebrains of Fisher 344 rats and the animals were immunized with irradiated 9L cells stably transfected with a TGF-β2 antisense vector (pCEP-4 TGF-β) 5 days later (79). All (11 of 11) of the vaccinated rats survived 12 weeks compared with 2 of 15 and 3 of 10 rats vaccinated with gliosarcoma cells transfected with an empty vector or the IL-2 gene, respectively (79). Furthermore, a cohort of surviving rats rechallenged with 9L cells 12 weeks following vaccination survived for 6 months compared with a 5-week survival for unvaccinated control rats.
To this end, monoclonal antibodies blocking TGF-β may be more effective at enhancing antitumor responses that would be inhibited by this cytokine. Systemic blockade of TGF-β would be in inhibiting antitumor responses by the immune system, suggesting that the vaccine induced a sustained antitumor response with immunologic memory. At necropsy, histopathology of the tumor implantation sites revealed no microscopic evidence of the originally implanted tumor cells (79). These results are surprising given that TGF-β was only inhibited in the vaccine tumor cells and not in the tumor bed and surrounding stroma where the cytokine could be readily produced and exert its immunosuppressive effects to promote tumor progression in the rats. Nevertheless, these preclinical studies led to early clinical trials showing that s.c. injections of these vaccines were well tolerated in phase I and II trials enrolling glioma patients and stage I, II, III, and IV lung cancer patients (77, 78). Elevated serum levels of either IFN-γ or immunoglobulins against vaccine cells were noted in some patients on these trials (77, 78). However, it was unclear whether any immune response was elicited against relevant tumor antigens. The authors reported clinical responses in vaccinated patients (77, 78), although assessment of response and clinical benefit is particularly difficult in this patient population. Therefore, larger clinical trials will be necessary to further characterize the activity of this approach.

Although TGF-β secretion from tumor cells may be important in inhibiting antitumor responses by the immune system, localized blockade of TGF-β in tumors may not be the most effective approach as several other cell types in the tumor microenvironment can produce this immunosuppressive cytokine, including Tregs and stromal cells. Systemic blockade of TGF-β via systemic administration of a small-molecule or antibody inhibitor may be more effective at enhancing antitumor responses that would be inhibited by this cytokine. To this end, monoclonal antibodies blocking TGF-β and small-molecule inhibitors of TGF-β signaling are also entering clinical trials. These approaches have shown acceptable safety profiles as well as improved antitumor activity in the preclinical studies summarized in Table 1. The results from these animal studies have led to the development of early clinical trials evaluating systemic blockade of TGF-β in cancer patients with refractory disease. A multicenter, open label, dose-escalation phase I study evaluating a monoclonal antibody, GC1008, in patients with advanced renal cell carcinoma or malignant melanoma opened last year and is accruing patients. Patients eligible for this study will receive up to four doses of GC1008. In addition to the antibody approach, LY573636, a small-molecule inhibitor blocking TGF-β kinase activity is currently being evaluated in clinical trials. Recently, a phase I clinical trial evaluating this small-molecule inhibitor in refractory ovarian cancer, non–small cell lung cancer, soft tissue sarcoma, and thymoma patients reported that this compound was well tolerated as a 2-h i.v. infusion administered every 21 days. The main dose-limiting toxicity was bone marrow suppression manifested as grade 3/4 thrombocytopenia and neutropenia. Subsequent phase II studies of metastatic melanoma patients and non–small cell lung cancer patients evaluating this approach are in progress.

Although systemic blockade of TGF-β has been well-tolerated in animal models, it is possible that significant toxicities including autoimmune disease will be observed in clinical trials, particularly if used in combination with other immune activators. Murine models in which TGF-β signaling is blocked in CD4+ and CD8+ lymphocytes develop autoimmune colitis as they age, suggesting that autoimmunity may be observed.

### Table 1. Summary of TGF-β signaling inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Target</th>
<th>Stage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP12009</td>
<td>Oligonucleotide</td>
<td>TGF-β2</td>
<td>Phase II</td>
<td>(76, 86)</td>
</tr>
<tr>
<td>AP-11014</td>
<td>Oligonucleotide</td>
<td>TGF-β1</td>
<td>Preclinical</td>
<td>(87)</td>
</tr>
<tr>
<td>Lerdelimumab (CAT 152)</td>
<td>Antibody</td>
<td>TGF-β2</td>
<td>Phase III</td>
<td>(88)</td>
</tr>
<tr>
<td>Metelimumab (CAT 192)</td>
<td>Antibody</td>
<td>TGF-β1</td>
<td>Phase II</td>
<td>(89)</td>
</tr>
<tr>
<td>GC-1008</td>
<td>Antibody</td>
<td>All isoforms of human TGF-β</td>
<td>Phase I</td>
<td>(90)</td>
</tr>
<tr>
<td>ID11</td>
<td>Antibody</td>
<td>All isoforms of murine TGF-β</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Ly550410</td>
<td>Small-molecule inhibitors</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
<td>(91-93)</td>
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<tr>
<td>Ly580276</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
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<td>Ly364947</td>
<td>Ly2109761</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Ly573636</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Phase II</td>
<td>†</td>
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<tr>
<td>SB-505124</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
<td>(87, 94)</td>
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<tr>
<td>SB-431542</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
<td>(95, 96)</td>
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<tr>
<td>SD-208</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
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<tr>
<td>SD-093</td>
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<td>TGF-βRI kinase</td>
<td>Preclinical</td>
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<tr>
<td>K26894</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
<td></td>
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<tr>
<td>Sm16</td>
<td>Small-molecule inhibitor</td>
<td>TGF-βRI kinase</td>
<td>Preclinical</td>
<td></td>
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<tr>
<td>Trx-xFoxH1b</td>
<td>Interacting peptide aptamers</td>
<td>Smads</td>
<td>Preclinical</td>
<td></td>
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<tr>
<td>Trx-Lef1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antisense-transfected tumor cells</td>
<td>Vaccine</td>
<td>TGF-β2</td>
<td>Phase I and II</td>
<td>(77, 78)</td>
</tr>
<tr>
<td>Soluble TBR2-Fc</td>
<td>Stabilized soluble protein</td>
<td>TGF-βRs</td>
<td>Preclinical</td>
<td>(100)</td>
</tr>
</tbody>
</table>

NOTE: Drugs listed include type of drug, their target, and stage in development.

1 http://clinicaltrials.gov/show/NCT00383292.
2 http://www.lillytrials.com/initiated/studies/initiated_9813.html.
4 http://clinicaltrials.gov/show/NCT00383292.
in patients following prolonged systemic blockade of this cytokine. Of note, antagonistic antibodies to CTLA-4, a molecule inhibiting T-cell proliferation following initial activation, have produced several autoimmune breakthrough events in advanced cancer patients, including dermatitis, enterocolitis, hypophysitis, uveitis, hepatitis, and nephritis (81). Other potential toxicities of TGF-β blockade may be related to its regulatory function in other tissues including angiogenesis and musculoskeletal development.

By understanding the roles of TGF-β in promoting tumorigenesis and developing inhibitors to selectively inhibit TGF-β during the specific time points when it promotes progression of later stages of disease, we may be able to design more effective immunotherapies augmenting the antitumor response in cancer patients. The clinical benefits from initial trials evaluating blockade of TGF-β are unclear and larger studies are necessary to determine the efficacy of these approaches. Monoclonal antibodies and small-molecule inhibitors have been evaluated in preclinical models and early clinical trials assessing systemic blockade of TGF-β signaling are in progress.

Although the preclinical murine studies discussed in this review have suggested that TGF-β blockade can enhance antitumor activity, the effect can be overcome by increased tumor burden,8 indicating that this approach will likely need to be combined with chemotherapies or other immunotherapies to effectively eradicate tumors in cancer patients. Other such strategies of this nature are being developed and are the subject of papers in this issue of Clinical Cancer Research Focus (82–85). However, the toxicities of systemic blockade of this cytokine remain unknown and may worsen with additional chemotherapies or immunotherapies. Preclinical studies evaluating combinatorial immunotherapies and chemotherapies with TGF-β blockade are under way. We anticipate that the results from these animal studies will guide future trials evaluating combinations of TGF-β blockade, immunotherapies, and chemotherapies in cancer patients.

Conclusions

Regulation of the immune response is vital to prevent the development of autoimmune diseases. As a critical immune suppressive cytokine, TGF-β has pleiotropic functions in regulating multiple immune cells in a context-dependent manner. However, dysregulation of the immunosuppressive function of TGF-β promotes tumorigenesis, particularly in later stages of cancer development. Further studies of the mechanisms and signaling pathways mediating TGF-β will lead to an improved understanding of how our immune system achieves self-tolerance and mounts effective immune responses against unsolicited foreign antigens and tumors. This knowledge may ultimately lead to the development of innovative therapeutic strategies to manipulate the effects of TGF-β on the immune system to treat cancer patients.

Acknowledgments

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Transforming Growth Factor-β and the Immune Response: Implications for Anticancer Therapy

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