Abstract

The inactivation of specific components of the transforming growth factor-beta (TGF-β) signaling pathway has been implicated in many types of hematological malignancies. These range from alterations at the level of TGF-β receptors to mutations, deletions or functional inactivation of downstream signaling components such as members of the Smad family of proteins. It is becoming increasingly apparent that, in addition to playing a role in the progression of certain leukemias, disruption of TGF-β signaling in the lymphoid compartment also has profound effects on tumor progression of epithelial cells. In this respect, the use of conditional knockout murine models has been particularly instructive. We review here well-documented examples where TGF-β signaling is thought to control leukemogenesis. More recent data from our laboratory and others are highlighted in support of a role for T-cell TGF-β signaling in regulating epithelial tumor progression. Finally, we review the link between TGF-β, regulatory T cells (Treg) and tumor immunotherapies, an understanding of which has significant therapeutic relevance.
1. INTRODUCTION

Transforming growth factor-beta (TGF-β) is the prototype of a large family of growth factors that includes the three mammalian TGF-β isoforms (1,2, and 3) as well as activins, inhibins, and bone morphogenic proteins (BMP). TGF-β family ligands signal through a membrane serine–threonine kinase receptor complex consisting of a ligand-binding type II receptor (TGF-βRII) and a signal transducing type I receptor (TGF-βRI). The principal intracellular transducers downstream of the receptor complex are the Smad proteins. The Smad family consists of receptor-associated R-Smads (Smad1,2,3,5,8), a common Smad (Smad4) to which activated R-Smads bind, and inhibitory Smads (Smad6,7). Smad2 and Smad3 relay signals initiated by TGF-β isoforms as well as activins and inhibins; whereas, Smads1,5, and 8 act to convey signaling events initiated by BMP ligands.

There are many means through which TGF-β, produced by the tumor itself or by other cells in the tumor microenvironment, can suppress immunosurveillance. TGF-β is a pleiotropic cytokine whose biological effects are highly context dependent, being influenced by such factors as: differentiation stage of the target cell; in the case of lymphocytes, activation status; local concentration; and other growth factors that are present. TGF-β is a potent suppressor of human hematopoietic progenitor cells; inhibits proliferation of activated B and T lymphocytes; triggers apoptosis of immature B and T lymphocytes as well as epithelial cells; protects activated T cells from activation-induced cell death; and inhibits differentiation of Th1 (1,2,3) and Th2 (4,5) CD4+ helper T-cell subsets (reviewed in /6). In addition, TGF-β has been shown to inhibit the acquisition of effector function of cytotoxic T lymphocytes (CTL) (7–9); inhibit release of pro-inflammatory cytokines by T cells and activated macrophages (10–15); and to inhibit activation of antigen presenting cells such as macrophages and dendritic cells (DC) (6).

We review some of the documented examples of disrupted TGF-β signaling in hematopoietic malignancies and their functional and therapeutic significance. There is evidence for mutations, deletions, as well as altered expression of key TGF-β signaling components. There are also data pointing to functional inactivation of TGF-β signaling intermediates in the etiology of certain leukemias.

Disruption of TGF-β signaling in lymphocytes can also have profound effects on the progression of solid tumors. Recent studies implicate TGF-β signaling in T cells in the regulation of proliferation of dysplastic epithelial cells in experimental colorectal cancer (16). We discuss the role of TGF-β signaling in stromal T cells in driving epithelial neoplasia and highlight recent work from our own laboratory, using gene-targeted mouse models. One of these studies has important potential implications for the treatment of tumors that develop in familial juvenile polyposis (FJP) patients.

More recent studies have described a role for TGF-β in supporting the differentiation and homeostasis of peripheral regulatory T cells (Treg) (6,17,18). Some controversy surrounds the role of TGF-β in the effector function of CD4+CD25+ Treg; namely, the mechanism through which they suppress proliferation of CD4+ T cells, with some studies supporting a role for TGF-β (17,19–22) and others not (23,24). These seemingly conflicting findings are likely reconcilable as there exist distinct populations of Treg, which are thought to suppress through different mechanisms (25–27). Treg have been implicated in the failure of many cancer vaccines to induce effective antitumor immunity and in fact, depletion of Treg prior to cancer immunotherapy improves patient outcome (28). Recent data concerning the role of Treg in tumor immunotherapy are discussed.