Transforming growth factor-β (TGF-β) controls tissue homeostasis and mediates the repair response to tissue injury. While tumors escape from TGF-β's homeostatic function, many metastatic cancers coopt the tissue repair function to enhance their invasive/metastatic phenotype. These effects are due to an altered responsiveness of the tumor cells themselves (tumor cell autonomous effects) or to actions of tumor-associated TGF-β on the supporting host cell infrastructure. This discovery has resulted in great enthusiasm for developing TGF-β antagonists (TβA) for the treatment of metastatic cancer. Proof of concept has been provided by preclinical studies utilizing TGF-β neutralizing antibodies, TGF-β antisense molecules, soluble TGF-β receptors (TβR), and selective and potent chemical inhibitors of the TβR kinases. In vivo, TβA appears to impact on both cell autonomous and host cell effects of TGF-β. However, their antitumor activity has been modest in magnitude and limited to specific models, suggesting that only select tumors may be clinically susceptible to treatment with TβA. Moreover, as the oncogenic role of TGF-β signaling appears to come into play at a relatively late stage of tumor progression, blocking this pathway will likely have to be combined with inhibitors of oncogenes that drive tumor growth.

Key Words: Angiogenesis; cancer; motility; immune response; invasion; metastasis; TGF-β type I receptor kinase inhibitor; transforming growth factor-β; tumor growth.
1. THE TWO PRINCIPAL PHYSIOLOGICAL FUNCTIONS OF TRANSFORMING GROWTH FACTOR-β (TGF-β)

The TGF-β family of polypeptides comprises a group of highly conserved dimeric proteins with a molecular weight of approx 25 kDa (1). They are ubiquitously expressed in eukaryotes and have been isolated from the media and cell extracts of numerous transformed and non-neoplastic cell lines, as well as from most normal tissues (2,3). In self-renewing epithelia, which are the most common sites of origin of cancer, TGF-β appears to exert two major functions (Fig. 1).

1.1. Growth Control, Tissue Homeostasis, and Tumor Suppression

TGF-β plays a key role in maintaining the balance between cell renewal and cell differentiation and loss (4). This process probably involves a basal level of active (endogenous) TGF-β signaling, which protects against the development of early neoplastic lesions. For example, using a transgenic mouse model Cui et al. (5) showed that constitutive expression of TGF-β1 in suprabasal keratinocytes protects against 12-tetradecanoyl-phorbol-13-acetate-induced hyperplasia preceded by a strong induction of type II receptor (TβR-II) expression. Moreover, TGF-β protects keratinocytes against DNA damage (6,7). Thus, TGF-β1 and TβR-II are part of the endogenous homeostatic regulatory machinery in the mouse epidermis. Consistent with this, nonneoplastic epithelial cells in culture often express a low level of endogenous phosphorylated Smad2 (pSmad2). Furthermore, when these cells are treated with chemical inhibitors of the TβR-I kinase, pSmad2 becomes undetectable and cell growth is stimulated (8). Similarly, pSmad2 is detectable in normal noninjured lining and ductal epithelial as well as endothelial cells in human as well as mouse tissues (9–11). Even though most of the TGF-β secreted into the extracellular matrix (ECM) remains latent, these observations suggest that a small amount becomes activated at the cell surface of lining and ductal epithelial cells, presumably to control normal cell proliferation and differentiation in an autocrine manner. Finally, it is likely through this homeostatic function that TGF-β suppresses tumor development, and that its loss is an early event in epithelial carcinogenesis. This is clearly illustrated by mice that are homozygous for a hypomorphic allele of the latent TGF-β binding protein, LTBP-4. These animals fail to express pSmad2 precisely in those epithelial tissues that normally express this particular LTBP isoform, such as colon and lung (12). Furthermore, these mice are prone to developing colon cancer, supporting the idea of a tissue-specific failure of TGF-β’s homeostatic function. Finally, we have recently found that, in vivo, most human breast-, colon- and head-and-neck cancers continue to express pSmad2 (9–11). As these tumors are actively growing, they have presumably escaped from TGF-β-mediated homeostatic growth control.

1.2. Response to Tissue Injury and Tissue Repair

The second major role of TGF-β is in mediating the local response to tissue injury. Injury results in brisk local activation of TGF-β, which induces epithelial cells to assume a fibroblastoid and dispersed phenotype, epithelial-to-mesenchymal transdifferentiation (EMT), and to produce ECM components of what later becomes a scar (13). Normally, this process is self-limited in space and time, allowing epithelial cells to revert back to their cohesive epithelial phenotype (14). However, in chronic inflammatory conditions, loss of epithelial structures and the associated fibrosis have been attributed to persistent activation of TGF-β (15,16).

1.3. Mechanisms of TGF-β Activation

Two different integrin-mediated mechanisms appear to be involved in physiological activation of latent TGF-β in vivo (17). Mu et al. showed that latent TGF-β is sequestered