Abstract

Tumors present a complex composition of cancer and stromal cells that interact by direct cell-to-cell contact, extracellular matrix (ECM) proteins, cytokines, and growth factors. Fibroblasts represent a major cell type in the tumor stroma and participate actively in the process of tumorigenesis. These stromal cells, commonly termed cancer-associated fibroblasts (CAFs), are phenotypically different to their normal counterparts in physiological tissues, and often show myofibroblastic characteristics. Based on similarities with wound healing and inflammatory diseases, transforming growth factor-β (TGF-β) is considered to be the main factor involved in fibroblast recruitment, activation, and also differentiation to myofibroblasts. This review presents experimental evidence on the important role of TGF-β in fibroblast-epithelial interaction, as obtained from in vitro studies and from animal models. Additionally, global gene expression analyses of TGF-β stimulated fibroblasts and CAFs from the in situ environment suggest a TGF-β signature in the tumor stroma. While previous studies support a tumor stimulating effect of TGF-β via fibroblast activation, some recent studies utilizing genetically engineered mice models, indicate an opposite effect on tumor growth. Thus, similar to the dualistic effects of TGF-β on epithelial cells, the TGF-β response on CAFs is also highly context-dependent. The general connection between CAF biology and TGF-β function in tumorigenesis provides a new opportunity for novel stroma-based strategies in anticancer therapy.

Key Words: Stroma; cancer-associated fibroblasts; tumor-stroma interaction; myofibroblasts; targeted therapy; TGF-β-1; microarray; gene expression; cancer.
1. INTRODUCTION

Carcinogenesis is a multistep process accompanied by an accumulation of genetic mutations in tumors forming epithelial cells (1,2). This concept is supported by the identification of oncogenes and tumors suppressor genes detectable in nearly all stages of human neoplastic lesions. However, even if genetic alterations are an essential prerequisite for tumor development, it is generally accepted that additional factors, originating from the cancer environment, are necessary to initiate or promote both tumor growth and invasion, and the development of metastasis. The heterogeneous nature of cancer with the presence of a variety of nonmalignant cells in the tumor stroma indicates an organ-like interaction between malignant and nonmalignant cells embedded in a complex environment of extracellular matrix (ECM) components (3–6). In general, three major cell types can be distinguished in the tumor stroma: (I) cells of the vasculature, like endothelial cells and pericytes; (II) inflammatory cells (e.g. lymphocytes, histiocytes) and (III) fibroblasts (Fig. 1). These various cell types have been, to a very different extent, functionally explored for their involvement in tumorigenesis.

The strategy to inhibit tumor-angiogenesis has recently been successfully transferred to clinical practice with the approval of antiangiogenic drugs that significantly postpone tumor progression and increase patient survival (7). Similarly, tumor immunity has a long standing tradition in anticancer research. It is generally accepted that immunomodulation can influence tumorigenesis and therefore represents another promising principle in anticancer therapy (8,9). Surprisingly, cancer-associated fibroblasts (CAFs), often the most abundant cell type in the tumor stroma, were for a long time not recognized as relevant players, and consequently not adequately exploited as targets for anti-cancer therapy. With the development of more sophisticated molecular techniques and more organ-like in vitro models, it has become recognized that the interaction between fibroblasts and epithelial cells plays a significant role in tumorigenesis. This is reflected by the increasing amount of notable original publications and review articles during the last few years focusing on fibroblasts in the tumor environment (3,5,10–12).

A number of studies have investigated the molecular mechanisms involved in fibroblast-epithelial interactions. As one key regulator of this interaction, the cytokine transforming growth factor-β (TGF-β) has been identified. TGF-β exists in mammals in three isoforms (TGF-β-1, TGF-β-2, and TGF-β-3) that in generally share similar properties but different potencies in vitro and in vivo. TGF-β is secreted to the ECM as a latent complex consisting of bioactive TGFβ, the latency-associated peptide and the latent TGF-β-binding protein-1. Activation of TGF-β, after it has been released into the ECM, is regulated by proteases and other ECM proteins. Once activated, TGF-β signals through a heteromeric cell surface complex of two transmembrane serine/threonine kinase receptors, TGF-β receptor I and II (TGF-βRI and TGF-βRII). The biological responses to TGF-β are diverse and depend highly on the cellular context (13,14).

This review will provide the basic experimental evidence for the tumor-promoting effects of fibroblasts during cancer formation (see Section 2); introduce myofibroblasts and their role in cancer based on observations in wound healing and inflammation (see Section 3); link the action of TGF-β to specific phenotypical and functional properties of CAFs (see Section 4); discuss mechanisms responsible for the modulating effects of CAFs during carcinogenesis (see Section 5), describe recent global expression studies of TGF-β-stimulated fibroblasts and CAFs, and, based on the comparison of the available data, suggest gene targets of TGF-β that are also dominant in CAFs (see Section 6). Finally, we will discuss these data in the context of the therapeutic potential of TGF-β-mediated pathways in fibroblast-cancer cell interaction (see Section 7).