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Carcinoma-Associated Fibroblasts in Lung Cancer

Roya Navab, Bizhan Bandarchi and Ming-Sound Tsao

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Abstract

There is growing evidence that carcinogenesis is influenced and controlled by the cellular interactions between tumor stroma, ECM, and neoplastic cells. Therefore, the stromal cells surrounding cancer epithelial cells, rather than being passive bystanders, appear to have an important role in modifying tumor development and progression. Clinical evidence also supports the significant contribution of stroma to the development of a wide variety of tumors. There is a higher incidence of tumor formation in tissues exhibiting a chronically inflamed stroma as well as those undergoing wound healing, in which the stroma plays a central role. The stromal microenvironment of human cancers is also different from that of the corresponding normal tissue. Studies have revealed reactive stroma that is characterized by modified ECM composition, increased microvasculature, inflammatory cells, and fibroblasts with “activated” phenotype. These modified fibroblasts are often referred to as activated fibroblasts, myofibroblasts, tumor-associated fibroblasts, or carcinoma-associated fibroblasts (CAFs). This chapter will focus its discussion on the characterization of CAFs, their role in human lung carcinogenesis and malignant progression, and as potential novel therapeutic targets.

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Introduction

Fibroblasts are the predominant stromal cells in connective tissues, particularly fibrous connective tissue. Fibroblasts in normal tissue are responsible for the intracellular assembly of various extracellular fibrillary and nonfibrillary structural proteins such as procollagen and glycosaminoglycans, which form the ground substance of stromal tissue (1). The main product of fibroblasts is collagen, predominantly collagen type I, which is the major constituent of extracellular matrix (ECM). Cancer cells grow in a biologically complex stroma composed of various types of stromal and inflammatory cells and ECM, creating a tumor microenvironment [1, 2].

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Cancer Stroma

During the early stages of carcinogenesis, the proliferation of neoplastic epithelial cells is contained within the boundary of a basement membrane and separated from the surrounding stromal tissue [17]. This growth that is confined by the basement membrane is called carcinoma in situ (CIS). During CIS progression to invasive carcinoma, the tumor cells invade through the basement membrane [18, 19] into the stroma and induce its “reactive” appearances [18, 20]. This is associated with the expansion of the tumor stroma by increased proliferation of activated fibroblasts and deposition of ECM [21], a histological observation referred as desmoplasia [22]. In fact, activated fibroblasts appear as one of the key features not only in cancer stroma but also in a variety of inflammatory conditions including wound healing [13]. The histological term for activated fibroblasts is myofibroblast, which indicates an intermediate phenotype between smooth muscle cells and fibroblasts [14, 23]. Myofibroblasts are widely distributed and easy to culture in vitro. Although pathologists have identified the presence of myofibroblasts in cancer decades ago, the scientific interest in evaluating them remains preliminary. Consequently, our knowledge on myofibroblasts and CAFs remains fragmented. It should be noted that myofibroblasts are not per se a pathological cell type and are present in various tissues under normal conditions (e.g., lung, brain, prostate, breast, heart) [24].

Markers of Fibroblasts and CAFs

Fibroblast remains poorly defined in molecular terms. A lack of reliable and specific molecular fibroblast marker(s) is a limiting factor in studying fibroblasts in vivo. Among all the well-established markers of fibroblasts, fibroblast-specific protein-1 (FSP-1) appears to provide the best specificity in vivo (see Table 1). In addition, several other proteins can be considered as site-specific markers. CAFs are normally defined by the expression of α -smooth muscle actin (α -SMA) [18, 23, 25].

Chung et al. [26] showed that fibroblasts in mammals are highly heterogeneous, and those isolated from different sites show diversity (Table 1). They compared the genome-wide expression patterns of 50 human cultured fibroblasts isolated from 16 different organs and showed that gene expression patterns from different anatomical sites are as divergent as the gene expression patterns observed among distinct lineages of white blood cells [26]. This diversity is evident from the secretion of specific extracellular matrix (ECM) constituents, growth factors, or differentiation factors. For example, fetal skin fibroblasts express high levels of collagen types I and V, whereas fetal lung fibroblasts do not but express exclusively the lung-specific forkhead family transcription factors FOXF1 and FOXP1 [26].

Heterogeneity in human lung CAFs has also been observed. Nazaret et al. [27] established human lung TAFs which are characterized by the expression of human FSP-1, Thy-1, α -smooth muscle actin, and fibroblast activation protein (FAP)

