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Phenotypic and functional heterogeneity of cancer-associated fibroblast within the tumor microenvironment☆

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ABSTRACT

Cancer microenvironment is created not only by malignant epithelial cells, but also by several kinds of stromal cells. Since Paget proposed the "seed and soil" hypothesis, the biological importance of the cancer microenvironment has come to be widely accepted. The main compartment of host stromal cells are fibroblasts (Cancer-Associated Fibroblasts; CAFs), which are the main source of the collagen-producing cells. CAFs directly communicate with the cancer cells and other types of stromal cells to acquire a specific biological phenotype. CAFs play important roles in several aspects of the tumor progression process and the chemotherapeutic process. However, CAFs have heterogeneous origins, phenotypes, and functions under these conditions. A crucial challenge is to understand how much of this heterogeneity serves different biological responses to cancer cells. In this review, we highlight the issue of how diverse and heterogeneous functions given by CAFs can exert potent influences on tumor progression and therapeutic response. Furthermore, we also discuss the current advances in the development of novel therapeutic strategies against CAFs.

Contents

1. Introduction

The "seed and soil" theory was proposed by Paget over a century ago [1], and the molecular features of the "seed (cancer cells)" have been thoroughly analyzed. Many oncogenes and tumor suppressor genes of cancer cells have been identified and characterized. Today, it is generally

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accepted that cancer cells are genetically and/or epigenetically modified. On the other hand, the "soil," which is created by the both cancer cells and the host stromal cells, has never been fully characterized, possibly because of its structural and functional complexity. However, the recent developments of molecular technologies have made it possible to reveal the biomedical significance of the "soil".

There is growing evidence that biological behavior of cancer cells, such as proliferation, invasion, and metastasis, is profoundly influenced by the characteristics of the host stromal cells. Inflammatory cells, vascular cells, and fibroblasts are the main constituents of the "soil" and these stromal cells are often found in association with cancer cells and acquire a specific biological phenotype *via* interactions with cancer cells. Although the host stromal cells have been considered as to be stable and non-tumorigenic, some indications are beginning to suggest that these cells also unstable both in terms of genetic and/or epigenetic backgrounds. Additionally, these unstable stromal cells may in fact play a critical role in cancer development. Using a conditional knockout of the transforming growth factor β (TGF-β) type II receptor in fibroblasts ($Tgfbr2^{FspKO}$), Bhowmick et al. revealed a significant role for TGF-β signaling in stromal cell-mediated tumor development. They found that the abrogation of TGF-β signaling in the fibroblasts caused the development of carcinoma of the fore stomach and prostatic intraepithelial neoplasia [2]. These results suggest that stromal cells undoubtedly contribute to tumourigenesis and tumor development.

Fibroblasts in cancer tissue, also known as Cancer-Associated Fibroblasts (CAFs), are major components of stromal cells that surround cancer cells (Fig. 1) and provide, not only a mechanical support, but also control proliferation and survival, angiogenesis, metastasis, immunogenicity, and resistance to therapies. However, CAFs have heterogeneous origins, phenotypes, and functions in these subject matters. In this review, we will introduce diverse and heterogeneous functions of CAFs on tumor progression and therapeutic response.

2. Cancer-Associated Fibroblasts (CAFs)

2.1. Heterogeneous origin of CAFs (Fig. 2)

CAFs are the main source of the collagen-producing cells, they directly communicate with the cancer cells and other types of stromal cells such as endothelial cells and inflammatory cells. Extensive clinical evidence and the use of experimental mouse models support the premise of the biological importance of CAFs in tumor progression. However, the biological properties of CAFs are heterogeneous and different types of CAFs make distinct functional contributions. Rønnov et al. found that breast cancer CAFs originate from residual fibroblasts, vascular smooth muscle cells, and pericytes, suggesting that CAFs are of heterogeneous origin [3]. Previous *in vivo* and *in vitro* studies indicated that there are several sources of origin, including local infiltrating fibroblasts, endothelial cells, pericytes or adventitial fibroblasts of the vascular system, or cancer cells themselves undergoing fibroblastic transformation, which may explain CAF morphological, phenotypical, and functional variability [4]. Using a bone marrow (BM) transplantation/transfer model, we confirmed that BM cells were recruited into human cancer xenograft in severe combined immune-deficient (SCID) mice. Moreover these recruited BM cells expressed α-SMA, indicating BM cells transdifferentiated into myofibroblasts within cancer microenvironment [5,6]. This demonstrates that CAFs arise from the immigrant cell population, *i.e.*, from progenitor cells from the circulating pool of

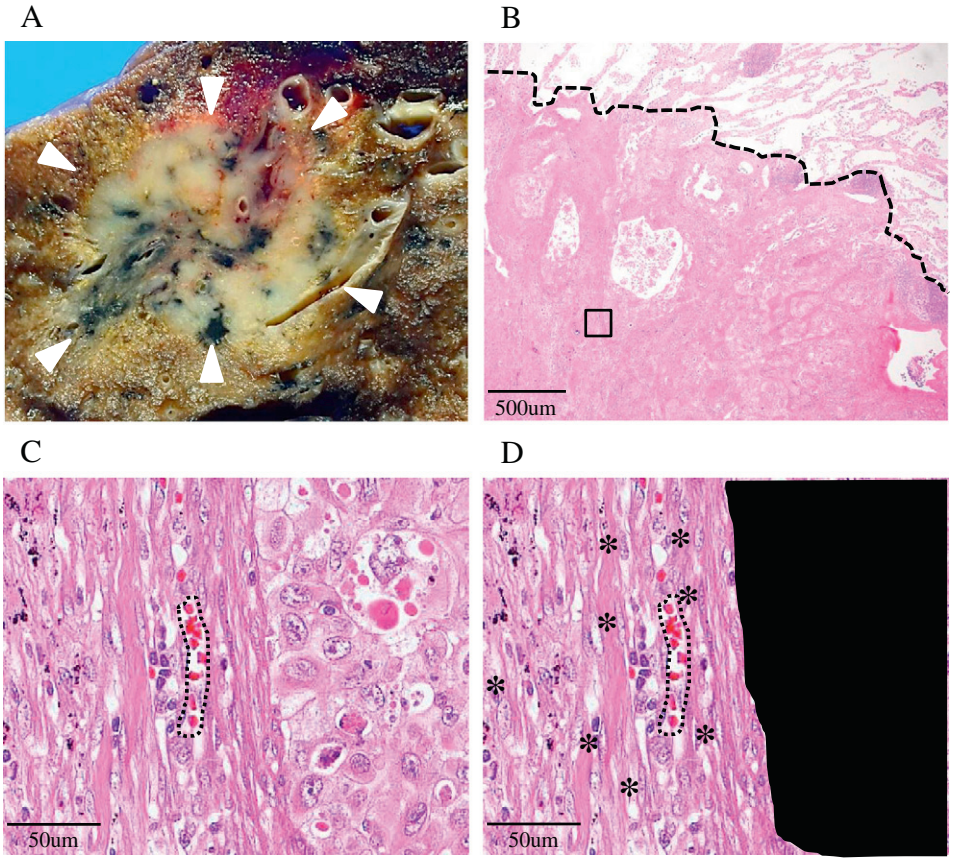

Fig. 1. Macroscopic and microscopic features of cancer (lung adenocarcinoma). A; Macroscopic feature of lung adenocarcinoma. White arrow heads point the tumor that has ill-defined borders. In contrast to non-cancerous lung tissue, the tumor is white in color. B; Microscopic feature of lung adenocarcinoma. Black dot lines indicate the boundary between cancer tissue and non-cancer tissue. Upper part is non-cancerous tissue (background lung tissue) and lower is cancer tissue (adenocarcinoma). C; Higher magnification of square area of Panel B. Tumor consists of heterogeneous elements including cancer cells and non-cancerous cells including many CAFs and a small number of lymphocytes. Dot lines indicate newly synthesized blood vessel. D; The same figure as the left; however, cancer cells are blacked out. Notice that many CAFs (spindle-shaped cells, asterisks) surround cancer cell nests.