Commentary
Heterogeneity of stromal fibroblasts in tumor
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It is now widely accepted that stromal fibroblasts present within a tumor play
significant contributions to carcinoma growth.¹-⁴ However, the biological properties of
these fibroblasts still incompletely understood. In the December, 2006 issue of
Cancer Biology & Therapy, Sugimoto and colleagues⁵ indicate the existence of a
heterogenous cell population of stromal fibroblasts in tumors based on
immunohistological observation using various fibroblastic makers. We discuss the
implications of these findings here.

Fibroblasts are a major stromal cell type that is usually present within human epithelial
carcinomas. The dominant contribution of these fibroblasts to the stroma has encouraged
scientists to study the roles of stromal fibroblasts during tumor progression. For example,
several research groups have determined whether stromal fibroblasts act to promote tumor
growth and progression. Indeed, these studies demonstrated that stromal fibroblasts,
specifically termed carcinoma-associated fibroblasts (CAFs), that have been extracted from
human carcinomas mass can promote the growth of admixed epithelial carcinoma cells in
immunodeficient mice, doing so far more potently than control fibroblasts extracted from
non-cancerous tissues. Moreover, such CAFs showed an ability to inhibit cancer cell
apoptosis, induce cancer cell proliferation, and stimulate tumor angiogenesis.⁶,⁷
Alpha-smooth muscle actin (α-SMA)-positive myofibroblasts have long been recognized
as a prominent component of the activated fibroblasts present in both tumors and in sites of
tissue injury.⁸ Various growth factors, cytokines, and extra cellular matrix (ECM) proteins
produced by myofibroblasts play pivotal roles in tissue repair by stimulating growth of
nearby epithelial cells and facilitating angiogenesis.⁷,⁹ Such myofibroblasts secrete stromal
cell-derived factor 1 (SDF-1), which is an angiogenic chemokine, in order to promote
tumor growth and stimulate neoangiogenesis.⁷,¹⁰
In addition to α-SMA, various other markers have been used to detect stromal fibroblasts
in tumors. Included among these are vimentin, fibroblast-specific protein-1
(FSP-1/S100A4),\textsuperscript{11} NG2 (Neuron-Glial Antigen-2), chondroitin sulfate proteoglycan,\textsuperscript{5} PDGFR-\(\beta\),\textsuperscript{5} fibroblast-activation protein (FAP),\textsuperscript{12} fibroblast-associated antigen,\textsuperscript{13} prolyl 4-hydroxylase\textsuperscript{14} (Fig. 1). Of these, \(\alpha\)-SMA and FAP\textsuperscript{12} are especially useful markers to resolve myofibroblasts in tumor stroma from stromal fibroblasts, whereas several of the other markers can be used to reveal both the myofibroblasts and fibroblasts that together form CAF populations (Fig. 1).

Sugimoto and colleagues\textsuperscript{5} have now immunostained sections prepared from experimentally generated tumors in mouse and found unique FSP-1-expressing CAF subpopulations distinct from the \(\alpha\)-SMA\textsuperscript{+} myofibroblasts present in tumor stroma (Fig. 1). Recently, it was shown that fibroblast-produced FSP-1 promotes tumor metastasis and that mammary carcinoma cells injected into FSP-1\textsuperscript{-/-} mice showed significant delay in tumor uptake and decreased tumor incidence\textsuperscript{15}. Interestingly, coinjection of carcinoma cells with FSP-1\textsuperscript{+/+} mouse embryonic fibroblasts (MEFs) partially restored the kinetics of tumor development and the ability to form metastases.\textsuperscript{15} This suggests that it would be of interest to determine whether FSP-1-expressing CAF populations can promote tumor progression compared to those of FSP-1-negative CAF populations.

Another example of the heterogeneity of stromal fibroblasts is provided by a subpopulation of SA\textsuperscript{\beta}-gal-positive, senescent fibroblast populations that are present among the stromal fibroblasts in human ovarian carcinomas; these senescent fibroblasts play pivotal roles in enhancing carcinogenesis through paracrine signaling mechanisms.\textsuperscript{16,17} In yet other studies, a mouse prostate tumor model indicates that carcinoma cells

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**Figure 1. Immunohistological markers of stromal fibroblasts in tumor**

Carcinoma-associated fibroblasts (CAFs) are stromal fibroblast populations present within tumor and these CAFs include populations of both myofibroblasts and fibroblasts. Various fibroblastic markers are used to detect stromal fibroblasts in tumor: \(\alpha\)-SMA, fibroblast-activation protein (FAP), vimentin, NG2 (Neuron-Glial Antigen-2) chondroitin sulfate proteoglycan, PDGFR-\(\beta\), fibroblast-associated antigen, prolyl 4-hydroxylase, and fibroblast-specific protein-1 (FSP-1/S100A4). Of these, \(\alpha\)-SMA and FAP seems to be specific markers for myofibroblasts.
prefentially induce the clonal expansion of a small fraction of fibroblasts that lack p53, eventually generating the majority stromal fibroblast population within a tumor; this absence of p53 allowed stromal fibroblasts to generate highly proliferative fibroblasts, resembling CAFs, that further promote tumor progression. Supporting this line of observation, mutations of the p53 gene were indeed found in stromal regions microdisected from human breast carcinomas. Further work will elucidate molecular mechanisms by which loss of p53 in stromal fibroblasts influences nearby epithelial carcinoma growth.

Stromal fibroblasts within tumors seem to be originally derived from heterogenous cell types that include bone marrow-derived progenitors, smooth muscle cells, preadipocytes, fibroblasts, and myofibroblasts. Sugimoto and colleagues’ observation may reflect the various distinct cells-of-origin that have been responsible for generating stromal fibroblasts. Alternatively, a particular fraction of stromal fibroblasts might be selected or transdifferentiated into FSP-1-expressing cell populations during tumor progression. Ideally, future studies should address whether these FSP-1+CAFs exist in human carcinomas in which they provide a tumor-promoting fraction.

Because stromal fibroblasts are genetically more stable than rapidly mutating tumor cell populations, tumor immunotherapy specifically targeting these fibroblasts expressing FAP-1 has been attempted and has been found to successfully attenuated tumor progression in mouse models. In a larger sense, research on stromal fibroblasts will help us promote understanding of the complex tumor-stroma cell interactions in tumor-prone tissue microenvironments and will provide clues for the development of new types of anti-tumor therapeutics.

References


