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Review

Prognostic relevance of cancer-associated fibroblasts in human cancer

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ABSTRACT

Prognostication is an integral part of cancer diagnostic and helps oncologists to guide treatment decisions and therapy intensity. Accumulating evidence suggest that the stroma compartment also contains independent prognostic information, best exemplified by the impact of immune cells and cells of the vasculature on cancer progression. Similarly, strong experimental evidence exist that stromal fibroblasts, often designated cancer associated fibroblasts (CAFs), are actively involved in tumorigenesis. Thus, it can be anticipated that the molecular repertoire of CAFs is likewise important for the clinical behavior of the tumor. In this review we present recent studies addressing the prognostic impact of CAFs, with the focus on human lung and breast cancer. Several single markers have been suggested, either CAF specific or CAF derived, that in immunohistochemical studies have demonstrated independent association with survival. This includes members of the platelet derived growth factor receptor (PDGFR) family, CAF-markers like podoplanin and fibroblast activation protein (FAP) as well as transcription factors (FoxF1) and secreted factors (matrix metalloproteinases (MMPs), SPARC). However, most studies are based on explorative evaluations on single patient cohorts and require further validation. Using a more comprehensive approach, microarray studies have been employed to create gene expression signatures that detect an activated fibroblast state. These "stroma signatures" have been applied to identify specific CAF features associated with prognosis in several independent data sets of breast and lung cancer patients. Early studies in breast cancer have also demonstrated that fibroblast features influence therapy response.

Thus, many strategies have been used to present encouraging proof-of-concept findings that CAFs could be exploited for prognostication. However, these studies also highlight the difficulties to conclusively define an "activated stroma" and to identify the individual factors involved in clinically relevant tumor–stroma interactions.

1. Introduction

Based on strong experimental evidence, that the tumor stroma is central in tumorigenesis [1,2], researchers have tried to validate this concept in clinical samples. Obviously, if certain stroma characteristics exhibit tumor-promoting properties, this might also translate into a shorter survival time in cancer patients. This hypothesis may apply for single molecules, a set of factors or for the tumor stroma as a whole. Consequently, cellular and molecular stromal properties have been correlated with clinical parameters with the aim of identifying patient groups with different clinical outcome.

The identification of prognostic biomarkers would not only indicate, in clinical settings, functional relevance of the tumor stroma, but potentially also provide novel independent prognostic information. Finally, evidence for prognostic relevance would also suggest that the stromal factor is a suitable therapeutic target. In fact, clinically relevant molecular aberrations are frequently associated with prognostic information. Prototypic examples are EGFR mutations in non-small cell lung cancer (NSCLC) and HER2-overexpression in breast cancer [3,4].

Numerous studies have demonstrated that the cellular composition of the stroma carries significant prognostic information. This is best exemplified by the immune response: tumor infiltration by specific lymphocytes, macrophages, natural killer cells and plasma cells is associated either with longer or shorter survival in many solid tumors [5–8]. For colorectal cancer, an "Immunoscore" was demonstrated to be superior to the AJCC/UICC TNM classification, and is now validated for use in the routine clinical settings [9]. Similarly, the pattern of tumor vascularization has an impact

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on prognosis [10,11]. Notably, both angiogenesis and the tumor immune response are today successfully exploited for therapeutic intervention [12,13].

Another cellular component, often the most abundant in the tumor stroma of solid tumors, is the fibroblasts [2,14]. These fibroblasts are distinct from their normal counterparts in their "activated phenotype". Although, presumably heterogeneous in their origin and function, they are summarized as CAFs, and often characterized by the expression of α-smooth muscle actin (αSMA), FAP, PDGFRβ or PDGFRα. However these markers are often expressed only in a fraction of fibroblasts within the tumor and are not CAF-specific [14].

During the last two decades evidence has accumulated that CAFs not only build a scaffold for the tumor, but also actively promote tumor development and progression [15]. This paradigm is mainly based on co-culture experiments and sophisticated animal models in numerous different cancer types [16–18]. However, in contrast to the tumor vasculature and the immune response, the clinical relevance of the fibroblastic compartment is still not determined.

The aim of this review is to give an overview over prognostic biomarker studies related to the presence of CAFs or CAF-derived factors in human cancer. As prototypic cancer types, we focused on breast and NSCLC, both exhibiting a remarkable variable stroma response (Fig. 1). In the first part of the review, we describe selected "CAF-derived biomarkers" for lung and breast cancer separately; in the second part we integrate common findings and, finally, in the third part we critically discuss the evidence obtained from these studies and give future perspectives.

2. The prognostic role of CAFs and related markers in NSCLC

NSCLC presents a morphological and clinical heterogeneous cancer type, with adenocarcinomas and squamous cell lung cancer as the predominant histological subtypes. Earlier studies evaluating the prognostic association of the morphological stroma response, i.e. the amount and fibroblastic pattern, with clinical outcome have been inconclusive. In an initial study it was demonstrated that strong desmoplastic stroma response (fibroblastic proliferation with abundant extracellular matrix (ECM)) was associated with shorter survival of adenocarcinoma patients [19]. In contrast, the exact morphometric quantification of the stroma proportion revealed that higher stroma content was independently associated with longer survival [20]. Two other studies could not confirm these observations, though one at least found a correlation of increased desmoplasia with longer survival in the univariate analysis [21,22]. In squamous cell cancer it has been suggested that a fibrous stroma was associated with poor prognosis in stage I patients [23]. The inconclusive results indicate that the quantity of the tumor stroma and presumably also the total amount of CAFs are of minor relevance for prognosis in NSCLC. Hence, the quality of the stroma, i.e. specific characteristics of CAFs or certain CAF-derived factors, could be the critical aspect in the interaction.

Most of studies addressing the prognostic impact of CAF derived factors have used immunohistochemistry (IHC) analyses on archived NSCLC tissues. The IHC technique has the advantage that protein expression can be determined in the *in situ* environment under the microscope. The expression can directly be ascribed to a specific cell type (fibroblasts, cancer cells, immune cells),

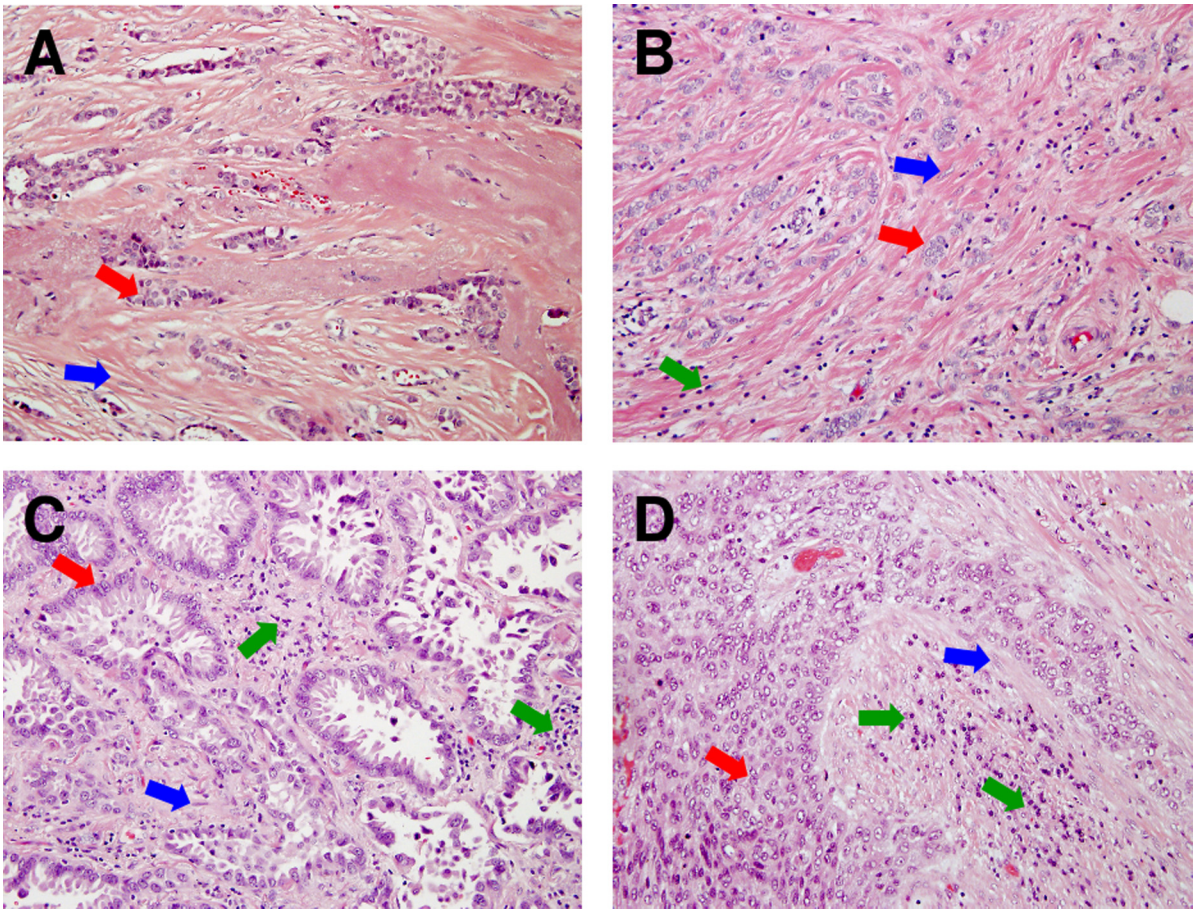

Fig. 1. Stroma reaction in breast (A and B) and lung cancer (C and D). Cancer cell growth (➔) is associated with a variable stroma response with proliferation of fibroblasts (➔) and infiltration of immune cells (➔). (A) illustrates a typical desmoplastic stroma with accumulation of collagen with low cellularity.