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Viewpoints and debate

Targeting breast cancer-associated fibroblasts to improve anti-cancer therapy

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ABSTRACT

In recent years, mass spectrometry-based proteomics has undergone significant development steps which may be divided into an exploratory phase, a consolidation phase and an application phase. We are in a stage now where we are able to apply mass spectrometric technologies to answer complex and clinically relevant questions. This is demonstrated here with respect to a current hot topic, namely the consideration of the cancer-supporting microenvironment as a target of new and more efficient anti-cancer therapy. Actually, the relevance of micro environmental stromal cells to tumor initiation and promotion has been clearly recognized. However, the individual kind and degree of stroma-derived tumor promotion can so far hardly be determined in patients, and hardly any therapeutic option exists to dismantle the cancer cells of the stroma-derived support. Quite remarkably, the response of stromal cells to standard chemotherapeutics is also rather unknown. In this Perspective, experimental strategies how to address such issues are outlined in detail. Different cell systems are presented as powerful models which allow identifying relevant marker molecules. Targeted proteomics is presented as method of choice for both, drug screening *in vitro* as well as monitoring drug responses in patients. By this means, a way of classifying different functional tumor promoting mechanisms, evaluating how current treatment strategies may affect cancer-associated fibroblasts, identifying effective drugs targeting these cancer-associated cells and, may be most importantly, demonstrating how combined therapeutic strategies may improve the efficiency of anti-cancer treatments are indicated.

Background and motivation

Breast cancer is the most common type of cancer in women, with incidence rates still on the rise [1]. Since recently, the cancer-associated stroma has gained an increasing importance for many aspects of carcinogenesis, including cancer development and growth, as well as establishment of drug resistance [2,3]. Cancer-associated fibroblasts (CAFs) seem to be especially critical for many aspects of carcinogenesis [4]. Treatment of these cells may therefore represent a new option for anti-cancer therapy [5,6]. However, talking about CAFs as one species may oversimplify the situation. These tumor-promoting cells may arise from local fibroblasts, from distant bone-marrow precursor cells recruited by tumor cells, or from epithelial–mesenchymal transition [7], and may thus display distinct phenotypes. So far, we were able, using proteome profiling, to distinguish already three different functional activities of CAFs resulting in tumor promotion: inflammatory processes in human hepatocellular carcinoma [8], remodeling of the extracellular matrix in multiple myeloma [9] and wound healing activities in breast cancer [10].

While the significance of CAFs is well recognized, the treatment of CAFs in clinical practice has not yet been established due to different reasons. So, first of all, it has to be clarified whether different subtypes of CAFs with corresponding cancer-supporting phenotypes may exist in a same tissue. Furthermore, a way to bring tumor-promoting CAF-phenotypes back to a “normal” rather tumor-suppressive phenotype [11] has to be established. As for the solution to these problems the main challenge will be to unequivocally characterize the underlying molecular processes. Only if we have identified relevant marker molecules which indicate the relevant cellular processes, we will be able to determine the *status quo*, to screen for drugs and to monitor desired drug effects in cell model systems as well as in patients. We consider proteome analysis techniques as method of choice to achieve such an aim, even though some frustration is apparent when talking about

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biomarkers and proteomics. However, many studies have been performed when proteomics was still in its exploratory phase. The introduction of standard sample preparation procedures [12] and quality control methods such as false discovery rate calculation [13] in addition to establishing the first mass spectrometry-based draft of the human proteome [14] are just about to consolidate the use of mass spectrometry for proteome analyses. We suggest that proteomics is now entering the application phase capable of coping with clinical challenges. Experimental strategies for solving problems in a systematic and stepwise fashion are outlined in detail in the following.

The research hypothesis

A rather simple hypothesis is the fundament of this Perspective (Fig. 1A). The classical therapeutic strategy rather targets cancer cells only. Indeed, in most cases the first-line chemotherapy is very successful in massively reducing the bulk of cancer mass. However, if the stromal microenvironment has adopted a tumor-promoting phenotype, the re-establishment of tumor growth from few cancer cells evading first-line chemotherapy is highly probable. It is actually the relapse of the disease what we are afraid of. Evidently, the cancer-supporting microenvironment is an important contributor for relapses. Targeted treatment of the tumor-promoting

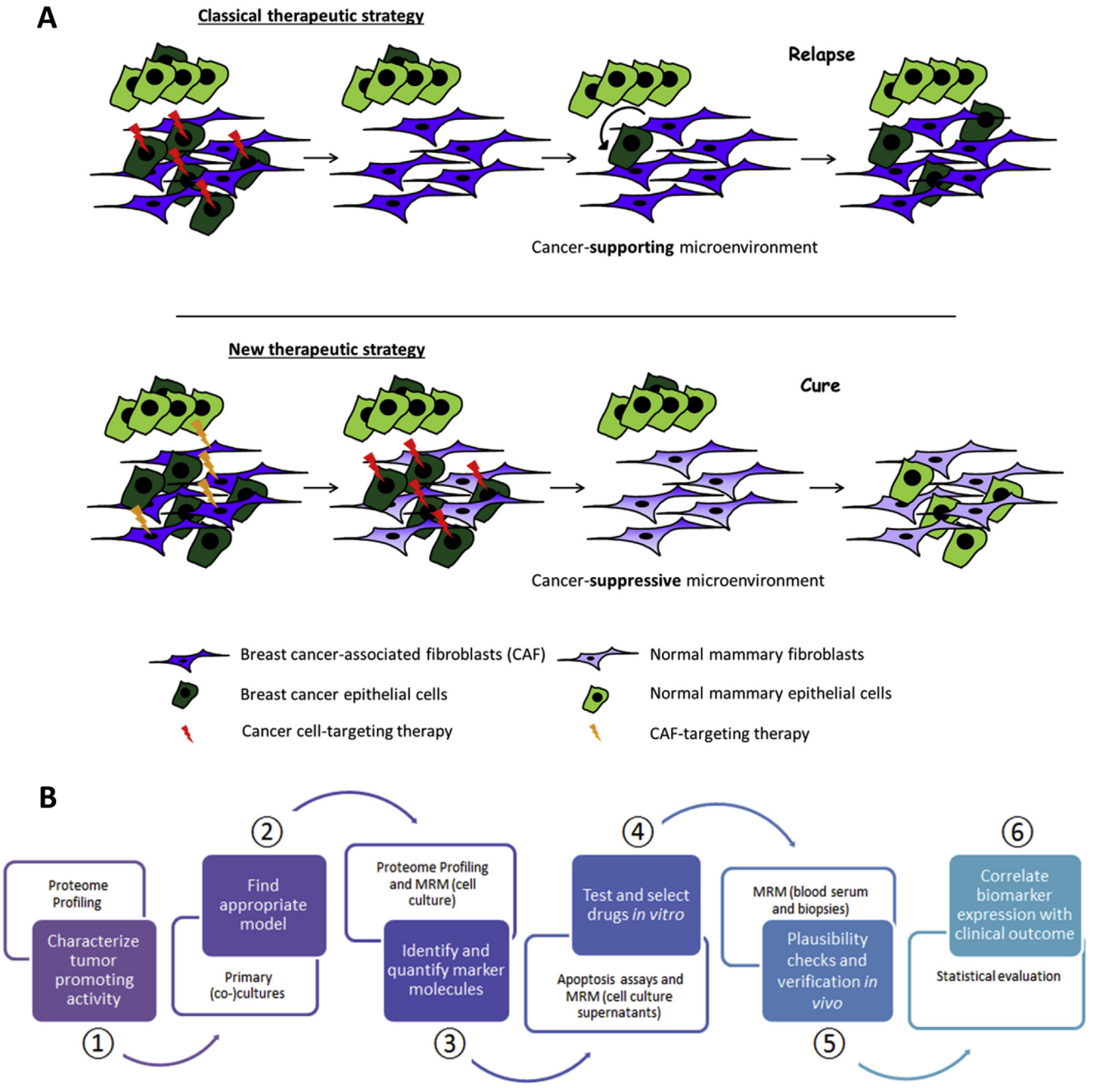

Fig. 1. Hypothesis and research strategy. A. Classical anti-cancer therapies rather target cancer cells only. The cancer-supporting stroma has so far hardly been considered. After an initially successful therapy, eventually surviving cancer cells will typically find a cancer-supporting microenvironment and may cause relapse. An improved efficiency of anti-cancer therapies may be achieved by combining cancer cell treatment with stroma-targeting treatment. If few surviving cancer cells are confronted with a rather cancer-suppressive microenvironment, relapse may be inhibited. **B**. From *in vitro* models to clinical verification: hierarchical evaluation steps.