The relationship between malignant and tumor-associated cells provides a new strategy for targeted diagnosis and therapy

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Here, we discuss the intimate relationship that exists between malignant and tumor-associated cells, providing a new strategy for targeted diagnosis and therapy via the screening of single-chain antibodies and aptamers that interact with target cells.

The tumor microenvironment is composed of a variety of cell types in addition to neoplastic cells, including fibroblasts as well as endothelial, perivascular and immune cells. Malignant cells and these tumor-associated cells reciprocally influence each other, and their interactions play an essential role in oncogenesis, tumor progression, and response to therapy.1,2 We have recently determined that lung stem-like cells give rise to endothelial cells of the tumor vasculature. Thus, understanding the origin, differentiation pathway, and regulatory mechanisms of tumor-associated cells, as well as identifying specific (surface) markers, has important implications for the implementation of novel diagnostic and therapeutic paradigms against cancer.

A single-chain antibody is a recombinant protein that can be generated by connecting the variable fragments of the heavy and light chains of a given antibody to each other with a short linker peptide. Single-chain antibodies are advantageous in that they have a relatively low molecular weight, they are poorly immunogenic, and they penetrate quickly into tissues (including malignant lesions), enabling them to serve as targeting moieties (upon fusion) for effector molecules that exhibits antitumor activity. Aptamers are short single-chain nucleic acids that can recognize target cells with high specificity and affinity. Also aptamers are small, stable, and virtually non-immunogenic. Through advances in nanotechnology and genetic engineering, it has become possible to screen single-chain antibodies and aptamers for their ability to specifically interact with target cells, enabling the development of diagnostic reagents and effective therapeutic strategies.3,4 In such a context, we have identified single-chain antibodies and aptamers specific for endoglin, a cell-surface protein with a prominent role in angiogenesis also known as CD105. This might represent a significant advance in the development of novel diagnostic and therapeutic tools against cancer.

Cell-based immunotherapy is a major strategy of anticancer immunotherapy that involves the use of autologous immune cells. Most often, immune cells are collected from patients, expanded and exposed in vitro to specific stimuli, and eventually re-infused into patients. Such re-infused cells are expected to activate the host immune system against cancer by breaking immune tolerance.5,6 The efficacy of cell-based immunotherapy can be improved by the use of immune cells that target not only malignant cells but also tumor-associated cells. Furthermore, increasing the number of re-infused cells and combining them with the administration of targeted anticancer agents may further improve the clinical activity of cell-based immunotherapy. We have recently developed a new method to prepare highly efficient dendritic cell/cancer cell fusions for use in cell-based immunotherapeutic settings. Thus, studying new approaches whereby immune cells can be effectively manipulated in vitro, as well as identifying interventions by which the efficacy of immune cell targeting can be improved in vivo, is essential to overcoming the obstacles that currently limit the clinical efficacy cell-based immunotherapy.

Oncolytic viruses can exert significant antineoplastic effects as they efficiently infect and lyse malignant cells. These viruses are often engineered to express cytotoxic or immunostimulatory factors that assist them in tumor eradication. Oncolytic virotherapy has received

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much attention over the last decade and substantial achievements have been realized. We have generated several anticancer viruses with distinct functional properties. Thus, selecting and generating new oncolytic viruses, choosing effective antitumor factors for their genetic engineering and developing new carriers for the delivery (be them physical or cellular) warrant further investigation.

In summary, exploring the interactions between neoplastic and tumor-associated cells, defining the molecular cascades underpinning their behavior, and screening single-chain antibodies or aptamers that specifically interact with these cells will enable the development of new strategies for the diagnosis and therapy of cancer (Fig. 1). This will have prominent clinical implications, facilitating the design of novel, highly efficient therapeutic regimens for use in cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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