Editorial

The Tumor Microenvironment: A Druggable Target for Metastatic Disease?

What defines a druggable target for the treatment of cancer? This sounds like a difficult question to answer but is rather simple: a desirable target for the treatment of cancer should be exposed in the cancer and absent in healthy tissue. Such a target meeting these requirements was recently discovered in the tumor microenvironment (TME). An antibody recognizing a component of the TME, the extra domain B (EDB) of fibronectin, was put on the top ten list of “Antibodies in 2018 to watch” as therapeutics for late-stage cancer by Janice Reichert, the executive director of The Antibody Society. This antibody is currently in a Phase 3 clinical trial for advanced stage IIIb/C melanoma. So, what makes the TME such a good target for the treatment of cancer?

The TME includes the cellular and the non-cellular components of solid tumors. The cellular compartment comprises many diverse cell types: cancer cells make up the bulk of the tumor which can be infiltrated by cancer-associated fibroblasts (CAF s), endothelial cells and immune cells. The non-cellular part contains various types of extracellular matrix (ECM) proteins. Both compartments form close interactions with each other and changes in the TME composition occur constantly generating a highly dynamic, localized tumor.

Cancer cells within a single tumor can be genetically and functionally heterogeneous. This heterogeneity arises from the acquisition of mutations and can be influenced by external factors such as drug treatment or by the TME affecting the cells’ survival, expansion and metastatic potential. CAF s progress from normal fibroblasts which in healthy conditions maintain tissue integrity but in the TME can promote tumorigenesis and metastatic progression. CAF s are characterized by augmented ECM deposition and cytokine secretion which in turn, attracts endothelial cells to connect the tumor to the vascular network of the body. Immune cells are recruited to the tumor by neoantigens generated by the mutational load of cancer cells. The presence of tumor-infiltrating lymphocytes (TILs) is associated with tumor regression and better patient prognosis. However, the TME provides an immunosuppressive environment via activation of inhibitory T cell receptors on cancer cells which can dampen the TIL response. Immunosuppression by the tumor is not only regulated by cancer cells but also, as recently demonstrated by Mechta-Grigoriou and colleagues in Cancer Cell, by specific subgroups of CAFs. In this study, different subgroups of CAFs were identified in breast cancer which exhibited immunosuppressive features by attracting and retaining TILs to the stroma rather than releasing them into the tumor mass. This exemplifies the complexity and dynamic nature of the TME and how the entire cellular ecology can affect the responses of one cell type.

Recent clinical studies have explored the therapeutic use of autologous TILs engineered to recognize the neoantigen signature from individual patient’s tumors. This therapy extracts T cells from the patients’ blood, followed by in vitro expansion of cancer-specific T cells and infusion back into the patient. This approach has shown great potential in the treatment of leukemia and lymphomas. It is based on the idea that T cells in the blood have been exposed to the tumors’ neoantigens to initiate a specific immune response. This method has remained challenging for the treatment of solid tumor and especially for tumors with low mutational load, such as ovarian cancer. A new study by Harari, and colleagues in Nature Communications demonstrates that TILs directly isolated from ovarian tumors, rather than taken from the blood, exhibit higher avidity to tumor-specific neoantigens. With this method, the success rate to isolate and expand active TILs which have been exposed to neoantigens was improved. This approach is currently being tested in the clinic for the treatment of various solid cancers. For example, TILs are being isolated from the metastatic lymph nodes for the treatment of late-stage melanoma. Although promising, such clinical interventions are still in their early phases and need to be tested for efficacy and safety before becoming available in the clinic.

The cellular and the noncellular compartment of the TME interact closely with each other. The noncellular component is made up of the ECM and provides the structural support of the tumor. The composition of the ECM can change depending on the tumor origin, genotype and during malignant cancer progression. Collagens are the most abundant proteins in the ECM and their alignment and elevated cross-linking into thick bundles is directly correlated with a more aggressive phenotype and metastatic progression. Such collagen bundles can be found at the invasive tumor front initiating cancer cell dissemination. Other ECM proteins such as tenascin C and fibronectin can function as signaling molecules to promote survival and proliferation and thus can form a pre-metastatic niche. Overall, the composition as well as the physical properties of the ECM play an important role in the regulation of cancer cell phenotypes, metastatic potential and ultimately patient’s outcome.

Tenascin C and a specific splice variant of fibronectin, EDB, are highly enriched in metastatic cancer including the primary as well as the metastatic site. Both proteins are expressed during embryonic development but are downregulated in healthy adult tissue. Re-activation of tenasin C and EDB have been reported during wound healing processes in the adult body as well as in various tumor types. Tenascin C is dramatically increased during lung cancer progression but is absent in normal lung tissue. Furthermore, tenasin C expression levels correlate with enhanced metastatic potential and poor prognosis in lung cancer patients. EDB has been detected in various cancers such as lung, breast and colorectal cancer and has been shown to be correlated with poorly differentiated and metastatic breast tumors. These properties make tenasin C and EDB an attractive target for therapeutic intervention.

Tenasin C and EDB can be explored as a specific delivery target for cancer drugs that otherwise might be administered systemically. This has the advantage to reduce side effects with higher drug concentration and to increase the efficiency of the treatment. Several drugs are being developed and tested in preclinical studies including the use of tenasin...
C- and EDB-antibody drug conjugates (ADCs) as well as in combination with traditional chemotherapeutics or to activate a tumoral immune response. Preclinical studies on mice bearing human subcutaneous carcinoma xenografts showed that tenasin C-specific ADCs can eliminate the tumor mass. Although the preclinical results look promising, clinical studies in humans are needed to evaluate the full potential of this targeted approach. An antibody recognizing the specific fibronectin splice variant, EDB, conjugated with IL2 and TNF to recruit immune cells to the tumor is currently tested in the clinic for late-stage melanoma. In a previously completed phase 2 study, this antibody showed efficacy in terms of complete and partial response of metastases. A phase 3 study (clinicaltrials.gov: NCT02938299) is currently been carried out testing the recurrence free survival as primary outcome of the EDB-antibody tagged with IL2 and TNF. Altogether, such developments support the feasibility of ECM-targeted drug delivery systems and highlight its unique potential for the treatment of metastatic cancer.

Overall, the treatment of solid tumors has remained challenging and novel approaches are desperately needed. The complex TME is constantly evolving and responding to external influences making cancer a highly adaptable disease. Targeted drug delivery via tumor-specific ECM proteins to locally deliver high drug concentrations or targeted cell-transfer to recruit the body’s own immune system to the tumor could help eradicate cancer in the future.