CCBIO Opinion

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The Tumor Microenvironment: Barrier or Support?

The tumor microenvironement (TME) is a complex meshwork of extracellular matrix (ECM) macromolecules filled with a variety of cells including cancer-associated fibroblasts (CAFs), blood vessel associated smooth muscle cells, pericytes and endothelial cells, mesenchymal stem cells and a variety of immune cells. The mechanisms for the autocrine-, paracrine-, mechano-, and hypoxia-dependent signaling events in CAFs in the TME varies with the tumor type, tissue, the position of cells within the tumor and the type of dynamic cell-ECM interactions that the CAFs engage in.

In most studies, the stroma is found to be tumor supportive (tumor supportive function of TME). However, two recent reports might overturn this dogma by suggesting that the TME has a restraining or suppressive effect on tumor growth (barrier function of TME) (Ozdemir et al., 2014; Rhim et al., 2014). In the first study (Ozdemir et al, 2014), conditional deletion of αSMA-expressing myofibroblasts in experimental pancreatic cancer resulted in increased tumor growth. However, some of the data might have to be re-evaluated and re-interpreted. In a study from Öhlund et al (Ohlund et al., 2017), two major types of CAFs were identified in a mouse model and in human pancreatic cancer tissue. The peritumoral CAFs expressed fibroblast activation protein (FAP) and high levels of αSMA, and were denoted myofibroblastic CAFs (myCAFs). CAFs located at further distance from tumor cells and which expressed lower levels of FAP and αSMA were named inflammatory CAFs, iCAFs. The study convincingly indicated that CAFs can change from one state to the other (myCAFs to iCAFs and vice versa) in a dynamic manner. The findings in this study might have implications for the interpretation of the Ozdemir paper. It is for example possible that ablation of all cells expressing αSMA, in addition to deleting CAFs, also delete smooth muscle cells, interfering with blood vessel function. The study from Öhlund raises the possibility that preferential deletion of myCAFs (high α-SMA expression) could have an effect different from deletion of iCAFs (low α- SMA expression).

These findings present a strong rationale for continued in-depth profiling and subclassification of CAFs. Some interesting studies have already appeared using multiplexed FACS or single cell sequencing to identify functionally distinct and marker-defined CAF subsets

(Bartoschek et al., 2018; Costa et al., 2018; Costa-Almeida et al., 2018). Ongoing studies in our own laboratories also contribute to this field. A recent study demonstrated differential prognostic associations with PDGFR-defined CAF subsets in breast cancer (Strell, 2019; Östman group). Our studies continue to indicate that PDGFalphaR and PDGFbetaR define clinically relevant CAF subsets in other tumor types. Likewise, ongoing studies of the role of integrin α11 in a breast cancer model and a squamous carcinoma model strongly suggest that integrin α11 is an interesting CAF biomarker worthy of further investigation (Primac et al., 2018).

The final word on the tumor stroma being supportive or restrictive has thus not been said yet. However, one can still be optimistic that continued studies will ultimately present yet unknown biomarker and drug target opportunities in the CAF landscape. • •