Tumor microenvironment revisited

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A number of authoritative reviews devoted to the role of the tumor microenvironment have been published in recent years [1,2]. It is evident that the tumor stroma can modulate many tumor characteristics including the response to therapy. We need to keep this in mind, especially now that there is an increasing tendency to base intervention strategies on the driver mutations present in the tumor cells. This diagnostic mutation analysis receives attention for a good reason: it allows stratification of patients on the basis of molecular parameters with predictive power. Furthermore, the complexity of tumor cell populations is already challenging enough given the presence of a multitude of different cell types and their genetic heterogeneity.

The contribution of stromal cells to a tumor tissue, including deposited matrices [3], can greatly vary, sometimes making up more than 90% of the tumor mass, for example as observed in pancreatic cancer. In addition, the relative presence of the different cell types, fibroblasts, immune cells, and vascular cells can also greatly vary and serve in many cases as independent parameters of prognosis and response to therapy. Therefore, gaining better insight into how stromal components interact with the tumor cells and how this influences their growth, progression to higher malignancy, and response to therapy is of significant importance.

The tumor microenvironment (TME) is shaped through a process that resembles a wound healing reaction in which mesenchymal cells, endothelial cells, and immune cells are recruited to the site of tumor growth. This can result in the physical containment of the tumor as is observed in a

carcinoma *in situ* in which a small tumor mass becomes encapsulated by fibroblasts and kept in check through signals emanating from these normal fibroblasts. However, tumor cells with their unstable genomes can acquire additional mutations that enable them to escape from this containment, for example by “instructive education” of the stromal components or by selective recruitment of other cell types that support tumor progression. In this way, stromal cells become true accomplices in the tumorigenic process [4]. This “instructive education” can endow stromal fibroblast with new features and such “indoctrinated” cancer-associated fibroblasts (CAFs) then clearly differ from their normal counterparts. Tumor cells and recruited stroma so establish a unique biotope with extensive paracrine signaling, built from scratch, exploiting the various cell types it can recruit from within the organism. It is the tinkering of evolution all over again. The stromal components might contribute to drug resistance by creating a physical barrier thereby limiting drug access, by secreting growth-promoting or anti-apoptotic factors, by providing niches for cancer stem cells, or by mediating immunosuppression. Each of these specific accessory activities could obviously also serve as target for intervention.

Deciphering this complex interplay between tumor cells and stroma seems a daunting task. However, like the frequent occurrence of particular mutations in distinct tumors, also the tumor-stroma interaction might largely rely on a limited set of preferred signaling cascades. Furthermore, one can also think of approaches to reduce this complexity, for example, by depleting stromal components as part of

the intervention [5]. Even though this might by itself not impair tumor growth, it might make the tumor more amenable for treatment either by small molecule interventions or by immunotherapy. Although a recent clinical trial in pancreatic cancer based on improving accessibility of the tumor to cytotoxic drugs by targeting the stroma has been disappointing and therefore prematurely terminated, other treatment modalities might benefit from such stromal degradation and therefore worth further exploring in mouse models. Combining treatments that degrade the tumor stroma with immunomodulation would be specifically of interest given the remarkable success of immunomodulation in a subset of tumors [6] and the notion that the tumor microenvironment plays an important role in immune suppression.

To this end, models of cancer (e.g., genetically engineered mouse models) and global genomic efforts (a la The Cancer Genomic Atlas or TCGA) will be invaluable to dissect the TMEs of different cancer types and genotypes derived from both models and primary tumor lesions (what we refer to as the “TME landscape”). Along the same line, it will be of great importance to assess how novel therapeutic interventions impact the TME landscape and how the primary tumor prepares distant sites for metastasis remodeling the TME.

Undoubtedly, many of these aspects will be discussed at the EMBO/EMBL symposium on tumor microenvironment held in the beginning of May 2014 in Heidelberg.

Conflict of interest

The authors declare that they have no conflict of interest.

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