

Tumor microenvironment indoctrination

An emerging hallmark of cancer

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Nastiness of cancer does not only reside in the corruption of cancer cells by genetic aberrations that drive their sustained proliferative power—the roots of malignancy—but also in its aptitude to reciprocally sculpt its surrounding environment and cellular stromal ecosystem, in such a way that the corrupted tumor microenvironment becomes a full pro-tumorigenic entity. Such a contribution had been appreciated three decades ago already, with the discovery of tumor angiogenesis and extracellular matrix remodeling. Nevertheless, the recent emergence of the tumor microenvironment as the critical determinant in cancer biology is paralleled by the promising therapeutic potential it carries, opening alternate routes to fight cancer. The study of the tumor microenvironment recruited numerous lead-scientists over the years, with distinct perspectives, and some of them have kindly accepted to contribute to the elaboration of this special issue entitled *Tumor microenvironment indoctrination: An emerging hallmark of cancer*.

The Tumor Microenvironment: Stromal Cells and Extracellular Matrix

Indoctrinated stromal ecosystem. The discovery of oncogenes and tumor suppressors as the driving forces of malignancy acted in some respects as blinders on cancer biology and shaped the reductionist view that mutationally transformed cells can do it alone. Obviously, they can't, in most of the cases. Worse still, cancer cells recruit and indoctrinate numerous normal stromal cell types, whose collaboration shapes and catalyzes local and distant metastatic dissemination. The stromal ecosystem is discussed by Horimoto et al. and is composed of a variety of cell types such as angiogenic endothelial cells, infiltrating immune cells and fibroblasts among many others.¹ Cancer-associated fibroblasts can be either resident, recruited, mechanically or chemically activated. Otranto et al. provide a historical perspective on the origin, the activation and the role of cancer-associated fibroblasts (CAFs).² In particular, this very detailed review teaches us that cancer-associated myofibroblast can be activated from many distinct progenitor cells, including resident fibroblasts, pericytes, epithelial and endothelial cells but also bone marrow-derived circulating fibrocytes and mesenchymal stem cells (MSCs). How the latter rise in prominence and to what extent they serve the tumor cause is described in Cui et al.³ Notably, we learn that MSCs are recruited to the tumor by systemic factors released by tumor cells or surrounding disrupted tissues.

Hijacked extracellular matrix. The stromal compartment is however not only composed of cellular components but also filled with extracellular matrix (ECM) proteins that are used by both stromal and neoplastic cells to encourage tumor dissemination. As presented by Tripathi et al., ECM represents a highly dynamic scaffold made of fibrillar proteins, proteoglycans, glycoproteins

and non-fibrillar proteins.⁴ In addition to providing structural integrity to those organ-like structures that are solid tumors, the ECM is hijacked and exploited by both stromal and neoplastic cells. Although differences exist between composition of normal and cancer stromal ECM (such as deposition of basement membrane in normal organs), Otranto et al. insist on the parallels that exist between cancer and wound healing that had been postulated three decades ago.² Boudreau et al. suggest that similarities are also shared for example by normal branching morphogenesis and breast tumor invasion.⁵ Indeed, in both scenarios, the ECM is proteolyzed, aligned and remodeled as the epithelium invades the stroma. Normal and tumor-associated ECM nevertheless differ in terms of their mechano-topographical properties. Using again breast cancer as a snapshot of desmoplastic tumors and nonlinear optics to detect collagen—an abundant ECM protein—in situ, Conklin et al. describe the tumor-associated collagen signatures (TACS) and how their classification can be used as markers of mammary carcinoma progression.⁶ We also learn that some ECM proteins such as Tenascin-C, fibronectin and collagens are found at increased levels in tumor stroma.

Corrupted crosstalk. As discussed by Tripathi et al., a highly regulated crosstalk between tumor-associated ECM, neoplastic epithelial cells and stromal cells is needed to foster tumor progression.⁴ Initiation of this crosstalk may take place at the level of the early tumorigenic epithelia where the coordinated dialog between cell-cell and cell-matrix interactions is altered upon cell transformation. Indeed, as discussed by Epifano et al.,⁷ harmony mediated by cadherin and integrin adhesion receptors is a key feature of homeostatic epithelial tissues and drives their remodeling during morphogenesis and tissue repair. As soon as their activity is perturbed, such as during tumorigenesis, a stromal response is initiated, via chemico-mechanical means

such as secretion of soluble factors and changes in the ECM composition.

Tumor Microenvironment: How it is Being “Hacked” by the Tumor

Tumor-associated stroma contributes to the hallmarks of cancer in many ways. The range of its input includes self-evident angiogenesis to tumoral immuno-tolerance. Notably, invasion and metastasis appear as the favored hallmark of cancer and CAF one of the chosen and favored conductor of it. As discussed in several papers of this issue,^{1,2,4-6} CAFs can be activated by and in the vicinity of the tumor by both chemical (e.g., TGF β 1) and mechanical cues (ECM stiffening). They are however not the only players. Using breast cancer as reference, Boudreau et al. describe how the concerted action of the stromal ecosystem at play during normal breast development (fibroblasts, adipocytes, immune cells, ECM molecules, chemokines, proteases, etc.) is mirrored, hijacked and exaggerated during breast cancer progression.⁵ Using the same model, Conklin et al. describe how increased tumor cellularity and deposition of ECM molecules fosters mammographic density.⁶ They further discuss the importance of force-dependent matrix remodeling by CAFs (in particular collagen alignment) during tumor invasion and how this topographical remodeling correlates with tumor invasiveness. Matrix remodeling is mainly driven by CAFs' contractility. Using another parallelism, this time between tumor progression and wound healing, Otranto et al. explain how CAF are being activated in the tumor vicinity.² Among multiple mechanisms, they explain how mechanical stress imposed by tumor growth, tissue stiffening but also increased interstitial flow are sensed by CAFs and how their subsequent contractility forces tissue stiffening and thereby tumor growth and invasion.

The experimental evidence that biomechanical contribution of the tumor-associated stroma rises thus in prominence and additional methods to quantitatively measure it are required. Kraning-Rush et al. describe a novel method based on patterned polyacrylamide hydrogels for simultaneously controlling matrix stiffness, ligand density and topography.⁸ Its suitability for dissecting the cellular response to both structural and mechanical cues will increase our knowledge of the effects of substrate stiffness on tumor cell behavior. Cells sense mechano-topographical cues mediated by the ECM mainly via integrin receptors, which play prevalent roles in cell adhesion and migration. Integrins act as bi-directional linkers and relay both ECM-mediated extracellular cues to intracellular cytoskeletal contractility, both events being essential in tumor and especially CAFs behavior. Yu et al. describe a method where the use of mobile Arg-Gly-Asp (RGD) peptide ligands on lipid bilayers with nano-fabricated physical barriers defines the importance of integrin clustering and its dependence on force.⁹

Stromal cells do not only influence metastasis formation at the primary site by favoring invasion, they also favor metastatic niche formation as discussed by Horimoto et al. and Tripathi et al.^{1,4} These niches are composed of hematopoietic bone marrow progenitors and ECM molecules, which favor growth of healthy



About Dr Jacky G. Goetz

Dr Jacky G. Goetz graduated in Pharmacology and Cell Biology from University of Strasbourg (France) where he studied astrocytoma cell migration in the laboratory of Ken Takeda. He then moved to the laboratory of Ivan Robert Nabi in Montreal (University of Montreal, Canada), and later in Vancouver (University of British Columbia, Canada), where he first studied the interaction between the endoplasmic reticulum and mitochondria. He was in parallel interested in glycosylation of membrane proteins, in particular integrins, and described its importance, in concert with Caveolin-1 (Cav1), in fibronectin fibrillogenesis, focal adhesion dynamics and tumor cell migration. He received his PhD degree in 2007 from both University of Montreal and University of Strasbourg. He then moved to the CNIC in Madrid (Spain) in the laboratory of Miguel Angel del Pozo where he led a study on the implication of Cav1 in biomechanical remodeling of the microenvironment and showed its importance in normal tissue architecture but especially during tumor progression. He then joined the team of Julien Vermot at the IGBMC in Strasbourg (France) to pursue his interests in mechanotransduction phenomena using zebrafish as a model. He is about to start his team where he will develop his growing interest for the role played by biomechanical forces during tumor progression.

metastatic foci by creating hospitable tissue microenvironments. They provide both mechanical and signaling cues to the emigrating metastatic cells and thereby support their survival. Description of the implication of stromal cells and ECM in metastatic niche formation is however still in its infancy and sensibly unexplored. Many questions remain such as to what extent is a stromal reaction needed to initiate a premetastatic niche and sustain metastatic growth. Nevertheless, deeper understanding of the behavior of those niches will undoubtedly open new avenues in metastasis targeted therapies.

Tumor Microenvironment and Therapy: Ally or Foe?

The increasingly well-defined contribution of the tumor microenvironment to tumor aggressiveness identifies it as a promising target for cancer therapy. Care should however be taken and some mine clearing will be required to pave the way to success. The best example of such a mine is the very promising anti-angiogenic therapies, whose great potential had been shadowed by the progressive development by tumors of adaptive

resistance. Cukierman et al. open the debate and recapitulate some of the known stromal effects that account for drug resistance.¹⁰ With an emphasis on cell-adhesion mediated drug resistance, this nice perspective describes therapeutic efforts directed to increase the success of current therapies and identifies targets that could reduce this resistance. It also provides us with a detailed depiction of multiple stages of development of environment-dependent drug resistance. Such pitfalls are however grounds for hope and might lead to combinatorial strategies that would target tumor microenvironment in addition to cancer cells. Tumor microenvironment might also lead to the development of improved and integrative diagnostic tools. Using again breast cancer as an example, Conklin et al. show that mechanotopographical evaluation of the tumor stroma carries hope for fine-tuning of diagnosis and customization of treatment.⁶ They also discuss the promising discovery that the gene expression profile of the stroma may be a better predictor of patient outcome than the tumor epithelium itself. Some studies indicate that stroma, and not the epithelium, carries intrinsic protumorigenic abilities that carcinogens could exploit to develop a neoplasm. Furthermore, Boudreau et al. discuss the evidence that the multigene signatures currently used to model cancer heterogeneity and clinical outcome largely reflect signaling from

a heterogeneous microenvironment and propose that this could be exploited therapeutically.⁵

The fact that scientists increasingly became aware of the importance of microenvironment in tumor progression drastically changed the way it is being perceived and studied and opened a breach for successful therapeutic targeting. As can be judged from this special focus, scientists have grasped the importance of this emerging phenomenon and actively participate to the dissection of its underlying mechanisms. There is however a plethora of discoveries that lies ahead for this scientific community. Increasing our knowledge of the role of the microenvironment in tumor progression will fill the gap that exists between preclinical optimism and clinical truth. With the vast majority of cancer-targeted drugs sadly never fulfilling clinical expectations, the tumor microenvironment offers new hope. There is however still a long way to go and crucial questions need to be answered. Two important facts emerge from the recent discoveries. Success might reside in personalization of the diagnostic tools that would allow customization and fine-tuning of the treatment. One-size-fits-all drugs that target the sole cancer cell-intrinsic properties are obsolete and there is an urgent need for integrated and resistance-free approaches targeting also the reactive tumor microenvironment if one wants to improve the clinical benefit.

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