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Molecular pathology 2020: Targeting Tumor Microenvironment and Epigenome; Diagnostic, Prognostic and Therapeutic Implications

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Abstract

The dynamic interactions of cancer cells with their microenvironment consisting of stromal cells (cellular part) and extracellular matrix (ECM) components (non-cellular) is essential to stimulate the heterogeneity of cancer cell, clonal evolution and to increase the multidrug resistance ending in cancer cell progression and metastasis. The reciprocal cell-cell/ECM interaction and tumor cell hijacking of non-malignant cells force stromal cells to lose their function and acquire new phenotypes that promote development and invasion of tumor cells. Understanding the underlying cellular and molecular mechanisms governing these interactions can be used as a novel strategy to indirectly disrupt cancer cell interplay and contribute to the development of efficient and safe therapeutic strategies to fight cancer. Furthermore, the tumor-derived circulating materials can also be used as cancer diagnostic tools to precisely predict and monitor the outcome of therapy. This review evaluates such potentials in various advanced cancer models, with a focus on 3D systems as well as lab-on-chip devices.

The process of tumor formation and progression is influenced by two factors, namely genetic/epigenetic changes in the tumor cells and the rearrangement of the components of the tumor microenvironment (TME) through mutual and dynamic crosstalk [1]. TME consists of tumor cells, tumor stromal cells including stromal fibroblasts, endothelial cells and immune cells like microglia, macrophages and lymphocytes and the non-cellular components of extracellular matrix such as collagen, fibronectin, hyaluronan, laminin, among others [2, 3]. As the heart of TME, tumor cells control the function of cellular and non-cellular components through complex signaling networks to use the non-malignant cells to work for their own benefit. The consequence of such crosstalks is reflected in tumor formation and maintenance as well as deficient response to therapy and multi-drug resistance (MDR). The non-malignant cells in the TME are known to promote tumorigenesis in all phases of cancer development and metastasis [4, 5].

The source of intercellular communication is a complex network of cytokines, chemokines, growth factors, inflammatory mediators and matrix remodeling enzymes, but other fascinating mechanisms of interaction are now emerging. These include circulating tumor cells (CTCs), exosomes, cell-free DNA (cfDNA) and apoptotic bodies as novel horizontal gene transfer (HGT) mediators derived from tumor cells and delivering information to distant target cells including tumor cells and/or normal cells [6, 7].

Recent advances in tumor biology have shown that a comprehensive analysis of the multiple exchanges between tumor cells and their neighboring microenvironment is essential to understand the different underlying mechanisms of tumor growth and metastasis [8]. The loss of tissue integrity, carcinogenesis and further progress occurs as a consequence of reciprocal interactions between tumor cells with non-cellular (ECM) and cellular components of the TME [9, 10]. Therefore, on the other side of the argument, interactions in reactive non-neoplastic cells, genetically-altered tumor cells, and ECM control the majority of the stages of tumorigenesis effectively including clonal evolution, cancer heterogeneity, epithelial-mesenchymal-transition (EMT), migration, invasion, development of metastasis, neovascularization, apoptosis and chemotherapeutic drug resistance [11,12,13,14].

Due to the compelling role of TME in malignancy, many efforts are focused on this area [15, 16]. That is, a better understanding of the ways in which TME affects cancer progression is expected to make new targets available for the cancer cell isolation and cancer treatment. This can be achieved by interfering with the complex crosstalks established between cancer cells, host cells, and their surrounding ECM [10].

The recapitulating of TME is an important challenge in the development of experimental cancer models. In order to develop a reliable tool for personalized cancer therapy and drug development, it is essential to preserve the key characteristics of the original tumor. Recent advances on three dimensional (3D) platforms through the use of lab-on-chip and microfluidic devices [17] have provided an enormous opportunity to better stimulate the function and biology of TME and to bridge the translational gap between preclinical and clinical settings [18].

In this review, we look into the molecular interactions between cancer cells and their microenvironment and evaluate the effect of such interactions on the fate of cancer cells. The effect of tumor-derived circulating materials as novel cancer theranostics are also highlighted. To this end, we review the feasibility of implementing an innovative strategy pattern based on the interruption of these crosstalks to build an effective anti-cancer approach.

The cornerstone of the current review compared to the previous ones is its comprehensiveness. Previous reviews in this area are focused, for example, on recapitulating the gradual process of cancer metastasis by discussing advanced biomaterials and microtechnologies [19]. Also, they may highlight the mechanics of tumor metastasis [20]. And most of them only discussed a limited number of players/strategies such as anti-angiogenic therapies or targeting ECM yet fail to discuss the newly formed gadgets of cell-cell interactions such as cfDNA, apoptotic bodies, CTCs as well as exosomes [21, 22]. This review also evaluates the potential of disrupting tumor cells interactions in various cancer settings, in particular the newly emerging cancer models including 3D models and microfluidic platforms that allow to study different aspects of cancer cell behavior and biology, similar to the physiological environment in which they naturally occur.
I am working with my Team on Epigenetics. We have many papers regarding our work on Epigenetic. Our work is basically on DNA methylation. We are on ongoing Clinical phase I and Phase IIa Trials Regarding Anti UPAR and SAM (hypermethylating agent) We are also working on development of DNA methylation signature or tumor markers for breast and Prostatic cancer. DNA methylation till now seems very promising regarding its Diagnostic Therapeutic and prognostic implication.

I want to discuss Epigenetics focused on DNA methylation.

In my talk I want to focus on the following:

Why Patients metastasize even on hormonal therapy.
Functions of uPA-uPAR System
uPA/uPAR as a Focal Point in Tumor Progression
System to assess uPAR/PAI expression

Development of uPA/uPAR Targeted Therapeutics
ATN-658 is a fully humanized anti-uPAR antibody
uPA Promoter Methylation

Epigenetic regulation of gene transcription. DNA Methylation
Hypermethylating agents; S-adenosylmethionine (SAM)
Effect of SAM on Osteosarcoma metastasis in vivo
Early Non-invasive Biomarkers of Breast and Prostate Cancer

- Development of “epigenetic signature” for patients with breast, prostate and other common cancers.
- Validation of identified “epigenetic signature” in a large cohort of patients in multi-centre trial.
- Comparison of identified “epigenetic signature” in patients with different ethnic, racial and geographical background.
- Approval and marketing of identified approach for clinical use in normal and high risk subjects with various malignancies.

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