Editorial

Circulating markers in metastatic cancer: new perspectives

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Metastasis is one of the leading causes of cancer-related death resulting from the final outcome of multiple processes such as epithelial-mesenchymal transition (EMT) and the reverse (MET), extracellular matrix (ECM) remodeling, immune system activation and reprogramming of the tumor microenvironment. This special issue on "Non-invasive strategies in metastatic dissemination" focuses on recent advances and novel studies in exosomes as well as other cellular processes influencing metastasis in cancer. The special issue highlights the areas covering novel insights into the role of phenotypic plasticity and EMT-associated heterogeneity in circulating tumor cells (CTCs), exosomes in cancer development and ECM remodeling in tumor progression and metastasis.

Intercellular communication via the cargoes carried by exosomes is a key facilitator to bridge between the primary tumor and the tumor microenvironment in metastasis. Extracellular vesicles (EVs) released by cells contain biomolecules involved in pro-tumorigenic processes. Recent studies support the role of EVs in promoting cancer incidence, progression and organ-specific metastasis. The comprehensive review by Visan *et al.* [1] covers the role of exosomes in EMT. In this article, the authors survey many aspects of EMT, metastasis, the mechanism of exosome-mediated EMT and the role of exosomes in conferring therapy resistance [1]. The article by Carvalho *et al.* [2] further discusses the potential of utilizing the EV proteome for biomarker profiling. The authors compared the EV proteome and cellular proteome from the NCI-60 human tumor cell line panel to identify the expression of cancer hallmark proteins. This meta-analysis suggests high abundance of cancer hallmark proteins in EV proteomes and a potential role for predicting tumor tissue of origin, cancer diagnostics and prognostics [2].

The next intrinsic cellular phenomenon that drives metastasis and cancer invasion is the epithelial to mesenchymal transition (EMT) which has been classified into three different biological subtypes based on the biological process: Type 1 EMT is involved in developmental processes, type 2 EMT in wound healing, tissue regeneration and inflammation, and type 3 is associated with metastasis and progression of cancer. The primary difference between the developmental EMT and cancer-associated EMT is the lack of molecular regulation in the latter. Dhar *et al.* [3] describe the physiologically controlled pseudo-malignant behavior of the trophoblast during development. The authors also describe the role of hypoxia, ECM and signaling cascades in the trophoblast EMT and invasion, and further compare it with type 3 EMT [3]. Understanding the molecular regulation of trophoblast EMT could further understanding the molecular mechanisms of cancer-related EMT. In another report on EMT, Roy *et al.* [4] further explain the transcriptional regulation of EMT and investigate the role of type 3 EMT in stemness and plasticity. Raja *et al.* [5] review recent evidence on the role of EMT in cell survival, immune evasion, resistance to anoikis and metastasis. Circulating tumor cells (CTCs) entering into the bloodstream through intravasation involving EMT results in extravasation and metastatic colonization. Thus, the deeper characterization of CTCs will provide an opportunity to understand the mechanism of metastasis in solid tumors. The review focused on the dynamic state of EMT and plasticity signatures across CTCs datasets. The review also discussed the importance of an intermediate phenotype and its

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correlation with cellular plasticity [5]. Recent studies provide evidence of the role of oncogenic miRNAs as EMT promoters by repressing epithelial characteristics and tumor suppressive signaling pathways. Kumar *et al.* [6] summaries studies on the crosstalk between miRNA, oncogenic signaling pathways and EMT in breast cancer progression, concluding that miRNAs play a vital role in tumor initiation, progression and metastasis. The review further considers the importance of circulating miRNA profiling from CTCs and its role in diagnosis and prognosis of breast cancer [6]. A CTC-based liquid biopsy enables non-invasive monitoring of drug resistance. Balakrishnan *et al.* [7] describe current methods for isolation and expansion of CTCs. The low number of CTCs in peripheral blood demands an *ex-vivo* expansion. The review details the importance of tumor cell plasticity in CTC isolation and emphasizes the need to establish a method which does not require prior enrichment of CTCs. The deeper characterization of these rare cell populations is essential for clinical utility and management of cancers [7]. Effective isolation and expansion of CTCs is the key to develop a functional assay which could be used for patient-specific treatment strategies. Assessment of gene expression profiles in CTCs sheds additional light on their heterogeneity and potential functionality in tumorigenesis and metastasis. Hassan *et al.* [8] review recent studies assessing gene expression profiles of CTCs. Several studies have employed different molecular platforms such as RT-qPCR, RNA-ISH and RNAseq to identify a CTC-based gene signature [8]. Recent advances in sequencing techniques have allowed researchers and clinicians to profile DNA, RNA and proteins at molecular levels to discover novel cancer drivers and therapeutic targets. Oncogenes and tumor suppressor genes are the major regulators of gene transcription, transition due to insertion or a deletion (indel), rearrangements or single nucleotide mutations. Walavalkar *et al.* [9] highlight the different kind of variations within the enhancers and the effect of these variations in cancer initiation. Sadasivam *et al.* [10] provide an in-depth description of the identification of cancer stem cells (CSCs) in oral cancers and the molecular features specific to oral CSCs. Sala *et al.* [11] provide a comprehensive review on the role of argonaute proteins (AGO) in cellular processes. The review primarily focuses on the canonical as well as non-canonical functions of AGO proteins in mammals. In addition, they also focused on the association of AGO proteins in cell invasion, survival and poor prognosis in cancer [11].

The complex interaction between the tumor microenvironment and cancer cells is one of the major determinants in tumor progression and metastasis. Proteoglycans are the major macromolecules present in the ECM, playing a crucial role in angiogenesis, proliferation, invasion, and metastasis. Singh *et al.* [12] review the role of arylsulfatase, an enzyme which mediates desulfation of proteoglycans in oncogenesis. This review also depicts the role of proteoglycan sulfatases in EMT and remodeling of ECM, further suggesting sulfatases as targets for therapeutic interventions [12]. Cancer-associated fibroblasts (CAFs) are an abundant stromal cell type found in the tumor microenvironment (TME) and their reciprocal interaction with tumor cells will lead to the remodeling of the ECM, thus promoting intravasation of tumor cells. Patel *et al.* [13] summarize the heterogenous origin of CAFs and their regulation in tumor progression. Normal fibroblasts are converted to CAFs through the growth factors TGFβ1, SDF1 and PDGFRβ secreted from tumor cells. CAFs also induce EMT through paracrine signaling and facilitate tumor growth by secreting growth factors and cytokines/chemokines [13].

Metastasis, which causes most cancer deaths, is a major challenge in translational advances. Understanding the molecular mechanisms underlying metastatic progression of disease will improve metastasis-oriented drug development strategies. In this issue, we integrated the current knowledge on various aspects of metastasis and the significance of multimodal liquid biopsy tools. This introduction has provided an overview of the utility of the different approaches described in these collected papers to deepen our understanding of the mechanisms of drug resistance, tumor progression and metastatic processes.

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