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Comments on roles of circulating tumor cells in the metastatic cascade and tumor immune escape: biology and clinical translation

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Liquid biopsy (LB) is, without a doubt, one of the fundamental pillars of precision medicine. In this context, Circulating Tumor Cells (CTCs) are one of the more important LB components and one of the more unknown and 'misunderstood'. In this review, Alix-Panabieres and Pantel described and discussed the biological complexity of CTCs and their great potential as prognostic biomarkers.[1]

In this work, the authors emphasized the influence of the immune system (IS) on CTCs. The IS can be the 'best enemy or best friend' of the metastatic process (dual effect); in other words, it can eliminate CTCs, or on the contrary, help their survival.[2] What biological properties CTCs acquire for their survival and how they manage to acquire such properties are probably the most critical questions related to this issue. If we could know these properties, we would be able to eliminate CTCs.

The prognostic role of CTC in tumor patients is under investigation. Several studies highlighted that CTCs detection is associated with a bad prognosis.[3 4] However, the presence only informs about the disease status or assesses the treatment efficacy. Still, this information is insufficient to know how we could remove them. The authors address two essential characteristics of these tumor cells: (1) the ability of these CTCs to acquire new phenotypes through the epithelial-mesenchymal transition (EMT) process or even under treatment pressure and (2) their ability to remain under dormancy (tumor cell latency).[5] Regarding the first question, we know that the induction of the EMT process promotes CTC's transformation from the epithelial to mesenchymal status. However, this transformation can involve a diversity of EMT phenotypes, where we can find both epithelial, mesenchymal, or semimesenchymal phenotypes combined or not with stemness features. This question is essential, are the CTCs under EMT able to induce a metastasis? This question could associate with the second important point that addresses the authors, cell dormancy. Some studies relate the EMT process with the dormancy status of these CTCs. And the CTCs under dormancy do not proliferate but show an extraordinary ability to survive, and these types of cells are refractory to treatment action. Some studies have demonstrated that the CTCs under the EMT process cannot induce metastasis.[6] A reversion of the EMT process is necessary to allow the proliferation of the CTCs. Interestingly, the EMT process reversal does not involve the acquisition of the original epithelial phenotypes; on the contrary, the EMT reversal induces 'Frankenstein' phenotypes, promoting the presence of multiple diverse subpopulations of CTCs. The presence of this cell heterogeneity makes it difficult they're removing and, consequently, control the disease.

Here, the authors discuss how different components of IS can activate the EMT process enabled to impact on CTCs survival in hostile microenvironments. Interestingly, components of IS present in the blood system, such as leucocytes, macrophages, platelets, or neutrophils, favor the CTC survival and can mediate the immune scape. CTCs can interact with the different components through direct and indirect strategies. The indirect interaction is the most analyzed and involves the induction or inhibition of different pathways to promote the expression of markers such as CD47 or PD-L1 or elicit the secretion of various cytokines.[7] The direct interaction involves the transference of biomolecules from IS cells, such as platelets,

to CTCs. These interactions encourage phenotypic, genetic, and functional changes on CTCs, promoting the immune escape (camouflaging) and survival. The transference of biomolecules (lipids, proteins, and nucleic acids) involves pathway activation related to the EMT program and genetic pathways activation associated with stemness characteristics. More interestingly, this interaction can promote the production of extracellular vesicles with hybrid cargo, which could have the ability to 'infect' neighbor cells.[8] As regards, CTCs' interaction with IS is crucial to understand their clinical role. As demonstrated for primary tumor cells, escaping mechanisms are activated by CTCs to overcome immune-cell system identification. Particularly, membrane receptors play a pivotal role in the guidance of this molecular event. The comprehension of heterogeneous and complex membrane receptor profile may also represent a viable approach to introduce CTCs in clinical practice. Because this crosstalk has implications for the therapy (chemical, immunological, or biological), the analyses of CTCs should include new approaches for their characterization, including the potential presence of typical features of IS cells.

Indeed, we need to go deep into the biology of these interactions to understand how we can combat the CTCs' presence as essential components of the metastatic process. Remarkably, CTC detection may represent an encouraging biomarker able to clinically administrate solid tumor patients. Particularly, CTCs may play a pivotal role in a comprehensive management of solid tumor patients in diagnostic, prognostic and therapeutic setting.[4] As regards, technical limitations of yet available handling procedures and partial identification of biological mechanisms under the CTCs diffusions in biological samples still require a deep investigation.

Finally, the review promotes using CTCs as an excellent clinical tool for monitoring patients. Its potential utility as prognostic and predictive markers represents an hot topic for the identification of several studies that promote this concept. New clinical evidence has shown that their detection can be beneficial for monitoring minimal residual disease in early cancer. This ability has been widely demonstrated in patients with metastatic disease for disease monitoring and treatment assessment. New automatized and improved strategies for isolating and characterizing these CTCs are now commercialized, facilitating their clinical implementation. In this setting, a harmonization of technical procedures able to isolate and manage CTC from scant biological matrix is currently an opening challenge.

In this landscape the role of the scientific societies, like as International Society of Liquid Biopsy and European Liquid Biopsy Society, in the dissemination of CTC as a fundamental component of Liquid Biopsy Family represent the key weapon to boost their clinical practice implementation.

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