Increasing information is available on immune cells infiltrating human tumors, an important piece of knowledge expected to inform and guide immune-based therapeutic approaches.7,3 However, our understanding of immune cells populating the tumor microenvironment in the metastatic setting is limited. This gap has only started to be filled, and it represents a critical issue when considering that immune-based therapeutic strategies are being largely tested in the context of metastatic disease.

In this issue of Cell Reports Medicine, Martinek et al.1 provide a window into the regional specialization of macrophages infiltrating metastatic melanoma. Combining histo-cytometry and transcriptomics, they identify a signature of stromal macrophages with dendritic cell features and clinical relevance.

By studying melanoma metastasis, Martinek et al.1 provide some new insights of considerable significance. Proving the hypothesis that CD14+ macrophages may have distinct transcriptional profiles depending on their location was a demanding objective. To achieve this goal, authors took advantage of state-of-the-art technology to conduct single-cell analysis in situ, without separation of the cells, a strong methodological aspect. Histo-cytometry on whole-tissue scans and laser capture microdissection were key resources that aided in drawing the cellular maps of metastatic melanoma. Several multiparametric analytic approaches are being used in prognostic studies, and here, the authors were exploiting the advantages of these technologies to accomplish a relevant objective, i.e., the definition of the prognostic value of different myeloid populations.9

Another point of attention of the study is the tissue site of metastasis. Martinek et al.1 analyzed melanoma metastasis that were localized in different organs (lymph nodes, skin, lung, intestine).
Interestingly, the transcriptome of the discrete CD14 populations (iCD14+ and sCD14+) were homogeneously conserved across tissues. This point is interesting and needs to be further explored. Although macrophage infiltration is a common denominator of different tumors, macrophages infiltrating secondary lesions in different organs are substantially different. It has been suggested that the tissue-intrinsic properties of the metastatic lesions imprint the macrophage profile. Here, the authors report that in melanoma, macrophages at different metastatic sites are homogeneous, suggesting that they may be shaped more by the melanoma cells rather than by the intrinsic properties of the tissue.

The study by Martinek et al. provides new vistas on the importance of topology as a correlate of the diversity of myelomonoctytic cells in metastatic melanoma and on the clinical significance of diversity. As usual, this study also raises a few questions. The ontology of different macrophages remains to be defined. The signals responsible for the differential phenotype and significance of macrophages are, at the moment, a matter of speculation. Finally, this report draws attention to the fact that the diversity and topology of macrophages in metastatic disease should be taken into consideration in the development of myeloid-cell-centered strategies.

DECLARATION OF INTERESTS

A.M. reports personal fees over the last 10 years from Ventana, Pierre Fabre, Verily, AbxVie, Astra Zeneca, Myeloid Therapeutics, Third Rock Venture, Imcheck Therapeutics, Ellipses, Novartis, Roche, darlane Laboratories Ltd, HyCult Biotechnology, eBioscience, BioLegend, Abcam Plc, Novus Biologicals, Enzo Life, and Affymetrix, outside the submitted work. In addition, A.M. is inventor of patents related to cellular and humoral innate immunity.

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