Cell Reports Medicine

CellPress
OPEN ACCESS

Preview

A topology perspective on macrophages in melanoma metastasis

Alberto Mantovani[1,2,3,*] and Federica Marchesi[2,4]
[1]Department of Biomedical Sciences, Humanitas University, 20090 Pieve Emanuele, Milan, Italy
[2]Department of Immunology and Inflammation, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089, Rozzano, Milan, Italy
[3]The William Harvey Research Institute, Queen Mary University of London, London EC1M 6BQ, UK
[4]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy
*Correspondence: alberto.mantovani@humanitasresearch.it
https://doi.org/10.1016/j.xcrm.2022.100643

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.

Increasing information is available on immune cells infiltrating human tumors, an important piece of knowledge expected to inform and guide immune-based therapeutic approaches.[2,3] 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] present data exploring the diversity of myeloid cells (defined as cells expressing CD14) in relation to their localization in metastatic melanoma. They demonstrate that the transcriptional profile of $CD14^+$ myeloid cells (including monocytes, macrophages, and dendritic cells) depends on their location, i.e., it is different whether they are localized in the tumor nests (iCD14+) or in the stroma (sCD14+). This topology perspective is interesting and conducive to relevant observations.

The authors first obtained a cellular map of 20 metastatic melanoma tumors from different organs by multiparametric immunofluorescence, considering, in the first place, only major populations identified by common lineage markers, such as CD45, CD3, CD14, and CD19/CD138. The choice of CD14 as a marker (instead of the commonly used CD68) is justified as an attempt to consider the largest fraction of myeloid cells, without restricting to mature macrophages. Not surprisingly, $CD14^+$ cells were the most abundant leukocyte subset. However, only iCD14+ cells, deeply localized in the melanoma nests, displayed intracytoplasmic unprocessed melanoma proteins and were in strategic proximity to both $CD3^+$ T cells and melanoma cells. We are observing here an example of myeloid diversity,[4] whereby myeloid cells respond to distinct microenvironmental cues (here, the ones provided by the tumor or the stroma) and acquire localization-dependent phenotype and function. The diversity of myeloid cells—macrophages in particular—has been the object of several studies[4–7] and is progressively incorporating new features (e.g., morphology, transcriptional profiles, metabolism) and drivers (including location in the tissue), as shown in this report, increasing the number of macrophage subtypes documented.

To what extent are these macrophage subtypes linked to a specific function? Provided that the distinct populations are isolated, the analysis of their transcriptome can help answer this question. Along this line, Martinek et al.[1] analyzed the transcriptome of iCD14+ and sCD14+ cells carefully harvested from distinct regions and found regional signatures, a relevant feature that was not present in $CD3^+$ T cells, whose transcriptional program was irrespective of their localization. What emerged was that iCD14+ were more like tissue macrophages, while sCD14+ seemed involved in the organization of the tumor stroma.

What about the clinical significance of this diversity? Notably, despite iCD14+ cells being capable of internalizing products of melanoma cells and juxtaposed to $CD3^+$ T cells, their signature did not stratify patients in The Cancer Genome Atlas datasets. Only a sCD14+ signature (*LY75-CD2-CD14*) correlated with survival benefit in melanoma patients. Figure 1 The signature, particularly *LY75* (encoding for the DEC-205 receptor), suggests that macrophage-derived dendritic cells may be present and traces back to a macrophage-dendritic cell connection previously documented by the authors.[8]

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).

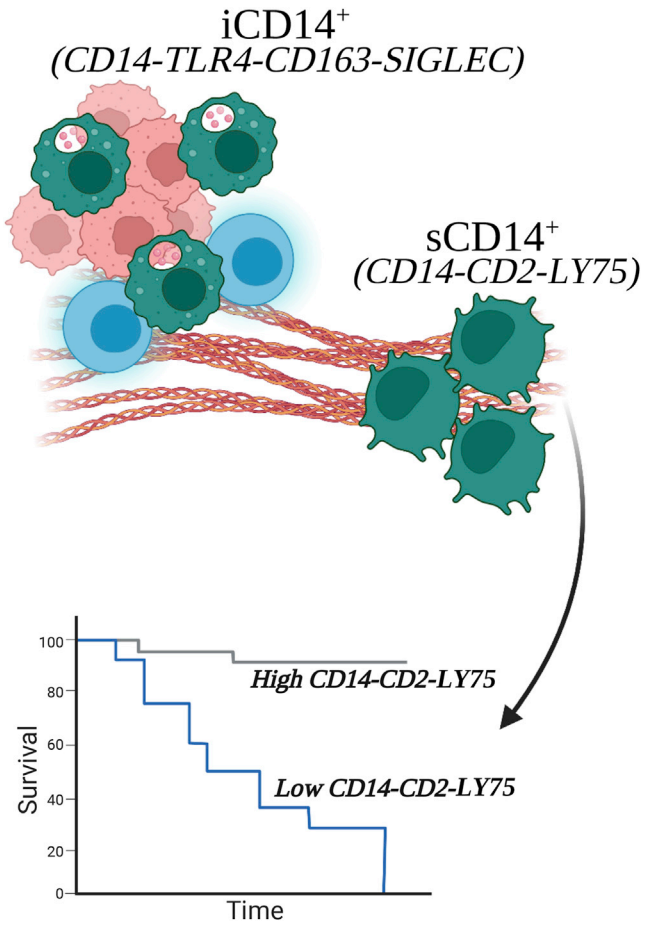

Figure 1. Regional specialization of macrophages in melanoma metastasis

Two distinct types of macrophages infiltrate melanoma metastasis. iCD14+ macrophages (expressing *CD14*, *TLR4*, *CD163*, and *SIGLEC1*) are close to tumor and T cells and present intracellular indigested tumor antigens, while sCD14+ macrophages localize in the stroma. A signature of sCD14+ (*Cd14-CD2-Ly75*) correlates with better survival for melanoma patients. Created with BioRender.com.

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,[2,10] 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 at al.[1] provides new vistas on the importance of topology as a correlate of the diversity of myelomonocytic cells in metastatic melanoma and on the clinical significance of diversity. As usual, this study also raises a few questions. The ontogeny 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.[4]

DECLARATION OF INTERESTS

A.M. reports personal fees over the last 10 years from Ventana, Pierre Fabre, Verily, AbbVie, Astra Zeneca, Myeloid Therapeutics, Third Rock Venture, Imcheck Therapeutics, Ellipses, Novartis, Roche, Macrophage Pharma, BiovelocIta, Merck, Olatec, Principia; royalties from sale of reagents from Cedarlane 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.

REFERENCES

1. Martinek, J., Lin, J., Kim, K.I., Wang, V.G., Wu, T.-C., Chiorazzi, M., Boruchov, H., Gulati, A., Seeniraj, S., Sun, L., et al. (2022). Transcriptional profiling of macrophages *in situ* in metastatic melanoma reveals localization-dependent phenotypes and function. Cell Rep. Med. *3*, 100621-1–100621-15.
2. Mantovani, A., Marchesi, F., Malesci, A., Laghi, L., and Allavena, P. (2017). Tumour-associated macrophages as treatment targets in oncology. Nat. Rev. Clin. Oncol. *14*, 399–416. https://doi.org/10.1038/nrclinonc.2016.217.
3. Fridman, W.H., Zitvogel, L., Sautès-Fridman, C., and Kroemer, G. (2017). The immune contexture in cancer prognosis and treatment. Nat. Rev. Clin. Oncol. *14*, 717–734. https://doi.org/10.1038/nrclinonc.2017.101.
4. Mantovani, A., Marchesi, F., Jaillon, S., Garlanda, C., and Allavena, P. (2021). Tumor-associated myeloid cells: diversity and therapeutic targeting. Cell. Mol. Immunol. *18*, 566–578.
5. Bassler, K., Schulte-Schrepping, J., Warnat-Herresthal, S., Aschenbrenner, A.C., and Schultze, J.L. (2019). The myeloid cell compartment-cell by cell. Annu. Rev. Immunol. *37*, 269–293. https://doi.org/10.1146/annurev-immunol-042718-041728.
6. Donadon, M., Torzilli, G., Cortese, N., Soldani, C., Di Tommaso, L., Franceschini, B., Carriero, R., Barbagallo, M., Rigamonti, A., Anselmo, A., et al. (2020). Macrophage morphology correlates with single-cell diversity and prognosis in colorectal liver metastasis. J. Exp. Med. *217*, e20191847 https://doi.org/10.1084/jem.20191847.
7. Cheng, S., Li, Z., Gao, R., Xing, B., Gao, Y., Yang, Y., Qin, S., Zhang, L., Ouyang, H., Du, P., et al. (2021). A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell *184*, 792–809.e23. https://doi.org/10.1016/j.cell.2021.01.010.e23.
8. Palucka, K.A., Taquet, N., Sanchez-Chapuis, F., and Gluckman, J.C. (1998). Dendritic cells as the terminal stage of monocyte differentiation. J. Immunol. *160*, 4587–4595.
9. Ginhoux, F., Yalin, A., Dutertre, C.A., and Amit, I. (2022). Single-cell immunology: Past, present, and future. Immunity *55*, 393–404. https://doi.org/10.1016/j.immuni.2022.02.006.
10. DeNardo, D.G., and Ruffell, B. (2019). Macrophages as regulators of tumour immunity and immunotherapy. Nat. Rev. Immunol. *19*, 369–382. https://doi.org/10.1038/s41577-019-0127-6.