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EDITORIAL

Novel paradigms of macrophage biology and function: identification of disease biomarkers and therapeutic targets

Diane Catherine Wang · Xuanqi Liu · Charles A. Powell · Xiangdong Wang

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With the rapid development of biotechnology, the understanding of macrophage biology has been extended from phagocytosis, digestion, and production of inflammatory mediators into control of microenvironmental homeostasis, regulation of cancer metastasis, and orientation of tissue remodeling. Spatiotemporal dynamics and distributions of tumor-, inflammation-, regeneration-, metabolism-, and cell death-associated macrophages represent key components of spatiotemporal molecular medicine (Wang and Fan 2021a, b). Spatial multi-omic profiles of tissue macrophages show the location and population of function-specific macrophages and the formation of macrophage-based niches and macrophage-driven microenvironment, in which macrophages develop and function to contribute to homeostatic metabolisms and intercellular communication (Guilliams et al. 2022). The specificity and function of macrophage subtypes and phenomes are dependent upon dynamic changes in intercellular and intracellular homeostasis and are associated with organ/tissue function and patient survival. The population and activation of $FOLR2^{+}$ tissue-resident macrophages were found to have close communications with $CD8^{+}$ T cells in perivascular areas in the tumor stroma and were positively correlated with better survival rate of patient with breast cancer (Nalio Ramos et al. 2022). Macrophage-driven molecules, signal pathways, transits, subsets, and interactions can be an important source of biomarkers and therapeutic targets. The interaction between macrophage and other cells plays critical roles in the transit between macrophage subsets, promotion of cell proliferation and migration, activation of intracellular signaling, and spatial reconstruction of the tissue (Yan et al. 2021). The present issue focuses on macrophage biology and toxicology that advance our understanding of molecular mechanisms and biological functions of macrophage-oriented organoids, macrophage-derived extracellular vesicles, macrophage-delivered inflammatory mediators, and macrophage-dominated intercellular communication, as well as macrophage-specific transit and polarization.

Human multicellular organoid resources have potential to provide breakthroughs in cell biology and toxicology. There is growing evidence that

D. C. Wang
Emergency Medicine, Sunshine Coast University Hospital, Birtinya, Sunshine Coast, Australia

X. Liu · X. Wang (✉)
Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Institute for Clinical Science, Shanghai Institute of Clinical Bioinformatics, Shanghai Engineering Research for AI Technology for Cardiopulmonary Diseases, Fudan University Shanghai Medical College, Shanghai, China
e-mail: xdwang@fuccb.com

C. A. Powell
Division of Pulmonary, Critical Care and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: charles.powell@mssm.edu

demonstrate organoids as an important model for investigating cell–cell communication and interaction in three-dimensional microenvironment, for understanding molecular mechanisms of human diseases, and for discovering biomarkers and screening drug efficacy, especially in patient-derived organoids. One of the challenges in the establishment of human organoids is to establish reproducibility and high specificity in target cells that lack cell pluripotency. In the present issue, Choi et al. (2022) developed a model of human lung organoids containing alveolar macrophage-like cells derived from pluripotent stem cells, to make it possible for organoids to contain inflammatory cells and to mimic the reality of lung tissue microenvironment. The differentiated macrophages were characterized by lung epithelia- and macrophage-specific markers and were spatially allocated around the alveolar epithelial surface with human lung organoids. Bleomycin-oriented human lung organoids were shown to have lung fibrotic phenomes for drug screening and optimization (Choi et al. 2022). Using single-cell sequencing, human lung organoids were used to trace the trajectories of alveolar-lineage cells during injury repair and lung regeneration, by defining the alveolar type II cell-lineage population and their transient progenitors (Choi et al. 2020). The molecular mechanisms by which alveolar cells with Il1r1 were differentiated into the progenitors were further investigated in lung organoids; e.g., macrophage-derived IL-1β primed a subset of alveolar type II cells for the differentiation via a HIF1α-mediated glycolysis pathway. In addition to drug screening, this model of human organoids was used to optimize therapeutic strategies, to define evolutional development of cell subtypes/subsets, and to explore molecular communications between cells (Pan et al. 2021).

Extracellular vesicles (EVs) play important roles in the maintenance of macrophage communication with other cells. Macrophage-derived EVs deliver molecules that contribute to microenvironment heterogeneity, to regulation of cell phenomics, and to reprogramming and processing of cell metabolism. On the other hand, EVs from bacteria and other cells or cells can activate macrophages to produce EVs. The present issue highlights molecular mechanisms by which macrophage with or without cancer association communicate with stem cells with or without cancer origins as well as the biological and toxicological effects of EVs. Chang et al. (2022) show that polarized M2 macrophages interact with pancreatic cancer stem cells and altered cell bio-behaviors and capacities by the intercommunication between stem cell Krüppel-like factor 3 and miR-21-5p from macrophage-derived EVs. In addition, Liu et al. (2022) show that mesenchymal stem cells downregulated TGFB1 expression and M2 polarization of macrophages by miR-744-5p from stem cell-derived EVs, weakening malignant phenotypes and degrees of glioma cells. In addition, the interaction between cancer cells and cancer-associated macrophages in the microenvironment can be facilitated by exosomes derived from each source. It was found that lung cancer cells promoted M2 polarization of cancer-origin macrophages by delivering cancer cell EVs and miR-19b-3p, targeting protein tyrosine phosphatase receptor type D, and dephosphorylating STAT3, while M2-polarized macrophages facilitated the lung cancer cell malignancy by producing EVs and LINC00273, recruiting E3 ubiquitin protein ligase NEDD4 for LATS2 ubiquitination, and inactivation of the Hippo pathway (Chen et al. 2021).

The present issue presents new insights into understanding the molecular mechanisms of inflammation- and infection-associated macrophages. Cinquegrani et al. (2022) provided evidence that inflammation-activated human macrophages were more active and protective than silent or non-triggered macrophages against glycosylated Spike, of SARS-CoV-2 Spike S1. This may explain poor outcomes in patients with COVID-19 infection and concurrent bacterial infections (Yu et al. 2021). Jiang et al. (2022) found that macrophages could contribute to renal tubular epithelial cell injury and dysfunction by leucine-rich α-2-glycoprotein 1-enriched EVs from inflammation-associated macrophages in a TGFβR1-dependent process. Nie et al. (2022) demonstrated that crystalline silica induced pulmonary neutrophilic inflammation by a macrophage-dominated mechanism, where necrotic alveolar macrophages had mitochondrial damage, edema, and leakage of DNA to recruit and activate neutrophils through the TLR9 signaling pathway. The switch between M1 and M2 macrophages and interaction between macrophages and trophoblasts were defined as an important mechanism of chemerin-induced preeclampsia by activating CMKLR1/Akt/CEBPα axis and as a potential target pathway for prevention and therapy (Ji et al. 2022). Inhibition of M2

macrophage polarization and infiltration as well as interaction between macrophages and cancer cells in microenvironment could reduce the capacities of cancer cell growth and metastasis, demonstrating potential therapeutic impact (Gu et al. 2022).

In conclusion, this special issue has a clear focus on macrophage biology and toxicology and attracts a special attention to the roles of macrophages in the microenvironment. The current issue presents a new model of human cell organoids with stem cell origin macrophages, which is well-controlled, reproducible, and target-specific. For multiple mediators, exciting reports highlight the regulatory roles of macrophage-derived extracellular vesicles and enriched molecules in the intercellular communication. Understanding the complexity of the interaction between macrophages and cancer cells and other cells provides opportunities to discover and identify biology-, toxicity-, and disease-specific biomarkers and to define molecular mechanisms. This special issue brings attention to the possibilities within targeting the processes and regulations of cancer- and inflammation-activated/associated macrophage activation, polarization, subset transit, infiltration, and production. Macrophages and macrophage-dominated interaction with other cells show promise as targets for the development of new therapies, although the complex biological dynamics and stability of macrophages present challenges to these efforts. Thus, the new visions for understanding the homeostasis and heterogeneity of tissue microenvironment advances driven by the models and reports in this issue that advance our understanding of spatialization and temporization of macrophages be important for translation macrophage biology research.

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