Chinese Medical Journal®

Prospect of using deep learning for predicting differentiation of myeloid progenitor cells after sepsis

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Emergency departments often encounter many severe illnesses.[1-3] Sepsis, a major cause of death in the emergency room, is a syndrome involving physiologic, pathologic, and biochemical abnormalities, induced by a life-threatening infection.[4] Sepsis directly or indirectly impairs the function of virtually all types of immune cells,[5,6] and initiates a complex immune response that varies over time, which results in profound immunosuppression, including metabolic failure, epigenetic reprogramming, and myeloid-derived suppressor cells.[7,8]

Granulocytes and monocytes, collectively called myeloid cells, are differentiated descendants of the common myeloid progenitors derived from the hematopoietic stem cells in the bone marrow.[9] Proper orchestration of myeloid progenitor cell differentiation is of vital significance to human health.[10] Some researchers have shown that patients who survive early sepsis, but remain dependent on intensive care, develop immunosuppression, which is evidenced by reduced expression of human leukocyte antigen-DR isotype (HLA-DR) on myeloid cells.[11] HLA-DR is a marker of mature myeloid cells. It has been reported that an immature myeloid cell population with immunosuppressive function is generated after sepsis; this population is now recognized as myeloid-derived suppressor cells (MDSCs).

MDSCs can be delineated into two types: polymorphonuclear-MDSCs (PMN-MDSCs), which are phenotypically and morphologically similar to neutrophils, and monocytic-MDSCs (M-MDSCs), phenotypically and morphologically similar to monocytes. Nevertheless, MDSCs have different genomic and biochemical profiles and functional activity.[12]Figure 1 provides a schematic illustration of myeloid progenitor cell differentiation.

MDSCs expand after sepsis because of the upregulation of specific colony-stimulating factors (CSFs).[13,14] Despite the fact that cells of myeloid lineage play vital roles in the body, much is still unknown about the dynamics of their differentiation.

Although it is difficult to differentiate MDSCs from neutrophils and monocytes phenotypically and morphologically, researchers have made extensive progress. Human neutrophils can be isolated in the high-density Ficoll-Hypaque gradient fraction, whereas PMN-MDSCs can be isolated in the low-density fraction. Monocytes and M-MDSCs can be separated based on the expression of HLA-DR. However, in mice, such distinction is much more challenging.[15] Human PMN-MDSCs have a unique genomic profile, distinguishing them from neutrophils in the same patient, which led researchers to identify the expression of lectin-type oxidized low-density lipoprotein receptor-1 on the two cell types.[16] Mouse MDSCs are also characterized by specific proteome[17] and transcriptome profiles in case of malignancy.[18] These outcomes help better identify mature myeloid cells and MDSCs; however, it is still unknown how sepsis induces myeloid progenitor cells into MDSCs.

Recently, a study made novel predictions about myeloid cell differentiation by mathematical analysis of numerous experimental observations of myeloid progenitor cell differentiation in response to varying dosages of three types of CSFs, namely, granulocyte-CSF (G-CSF), macrophage-CSF (M-CSF), and granulocyte/macrophage-CSF (GM-CSF). According to the findings of that study, G-CSF, M-CSF, and GM-CSF may all favor the development of M-MDSCs under different combinations and concentrations.[19] This research provided new insight about the

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000349

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Chinese Medical Journal 2019;132(15)

Received: 15-02-2019 **Edited by:** Yi Cui

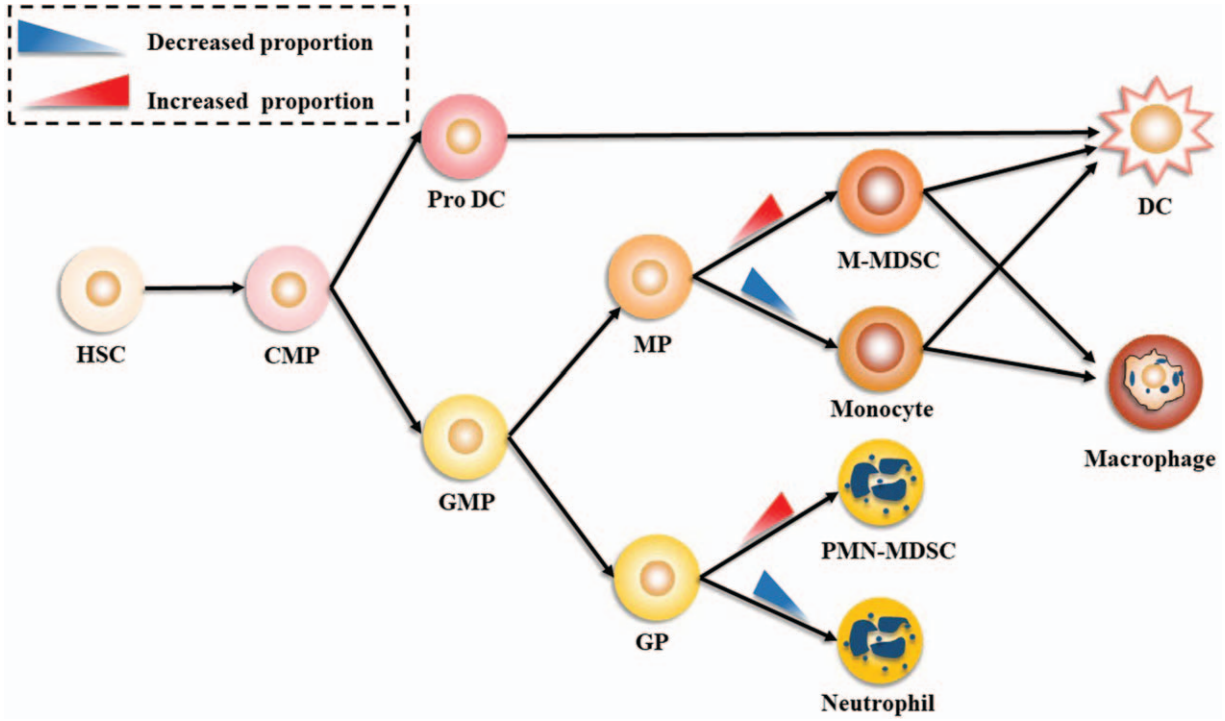

Figure 1: Myeloid branch of hematopoiesis after sepsis. Hematopoietic stem cells (HSC) can give rise to the common myeloid progenitors (CMP). CMPs can give rise to all myeloid cells. Granulocyte-monocyte progenitor (GMP) cells differentiate into monocyte progenitors (MPs) or granulocyte progenitors (GP). MPs and GPs differentiate into monocytic-myeloid-derived suppressor cells (M-MDSCs) and polymorphonuclear-myeloid-derived suppressor cells (PMN-MDSC) after sepsis.

prediction of cell dynamic processes, in addition to available data about sepsis. However, the model still has limitations and potential sources of inaccuracy. Owing to advances in high-throughput technologies, a deluge of biologic and medical data has been obtained in recent decades, including data related to medical images, biologic sequences, and protein structures.[20,21] Learning from these data facilitates the understanding of human health and disease. Deep learning allows computational models that are composed of multiple processing layers to learn different representations of data with multiple levels of abstraction, and shows great promise in extracting features and learning patterns from complex data.[22] The term "deep" is derived from the numerous hidden layers in the Artificial Neural Network structure.

Deep learning methods have attained success in a variety of computer vision tasks such as object recognition, localization, and segmentation in images like computed tomography images, magnetic resonance images, histopathology images, etc.[23] Recently, researchers have identified hematopoietic lineage by using deep learning. They collected images of moving single cells and cell divisions by long-term high-throughput time-lapse microscopy for the construction of cellular genealogies. Additionally, quantification of molecular lineage markers was made possible by fluorescent imaging. Then, a convolutional neural network was developed for automatically extracting shape-based features with a recurrent neural network architecture, modeling the dynamics of the cells, and predicting lineage choice in the differentiation of primary hematopoietic progenitors.[24] This impressive research points out a new way of using deep learning to observe and predict the differentiation of myeloid branch after sepsis, provided we construct a relevant model.

Moreover, deep learning plays an important role in genomic sequencing and gene expression analyses. To decode the mechanism of alternative splicing, a genetically and epigenetically regulated pre-mRNA processing method to increase transcriptome and proteome diversity, Xu *et al*[25] integrated multi-omics data (e.g., genomics, epigenomics, and transcriptomics) of human embryonic stem cells (hESCs), with a newly implemented deep neural network, DeepCode, to decipher an extended splicing code for ESC fate decision. With the advantages of epigenetic features, DeepCode significantly improves the performance of predicting splicing patterns during hESC differentiation. They also found a novel candidate mechanism linking histone modifications to hESC fate decision by DeepCode.[25] Such innovative research methods can be applied to predict the myeloid progenitor cell fate after sepsis, provided the multi-omics data of the cell affected by sepsis are available.

In the era of big data, transformation of biomedical big data into valuable knowledge has been one of the most important challenges. Deep learning, a branch of machine learning, has recently emerged based on big data. This popular technique has been widely used in clinical medicine for diagnosing diseases and predicting prognosis through labeled literal and image data. However, this is inadequate. Precision medicine requires biomedical data such as those from genomic sequencing and other -omics methods. Combination of electronic health records and biomedical data presents an inevitable tendency to

charting personalized treatment plans, especially for diseases with time-dependent pathologic process, such as sepsis. However, the complexity of data asks for more advancement in the processing method. Deep learning will be the most ideal computing technique to study clinical and molecular data; to predict the exact diagnosis, from both macro and micro aspects; and help physicians treat effectively and individually.

With the aid of deep learning and detection methods (e.g., high-throughput imaging and sequencing), the scientific community is looking forward to elucidating the post-sepsis fate of myeloid progenitor cells, and to making precision medicine a reality to subsequently improve the prognosis of patients with sepsis.

Acknowledgements

The authors thank Jiao-Jiao Yang, from the First Affiliated Hospital, School of Medicine, Zhejiang University, for providing assistance with language editing.

Funding

This work was supported by the grants from National Natural Science Foundation of China (No. 81272075), the Foundation of Key Discipline Construction of Zhejiang Province for Traditional Chinese Medicine (No. 2017-XK-A36), the National Natural Science Foundation of China (No. 81801572), the General Research Program of Zhejiang Provincial Department of Medical and Health (No. 2013KYA066), the Key Research and Development Program of Zhejiang Province (No. 2019C03076), and the Opening Foundation of State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases (No. 2018KF02).

Conflicts of interest

None.

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How to cite this article: Ruan WS, Xu J, Lu YQ. Prospect of using deep learning for predicting differentiation of myeloid progenitor cells after sepsis. Chin Med J 2019;132:1862–1864. doi: 10.1097/CM9.0000000000000349