先端医療講習セミナー

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会場：臨床教育開発棟（スキルスラボ2F）カンファレンス室

演題タイトル

Regulation of the Chemotactic Migration of Mesenchymal Stem Cells and the Implications for the Cell-Based Therapy Strategies

演 者 Prof.Huanxiang Zhang

Department of Cell Biology, Medical College of Soochow University, Suzhou 215123, China

概 要

Precise migration of stem cells is crucially important for embryonic development, homeostasis in adults, and tissue repair after injury. However, the detailed mechanisms of the directed migration of these cells are not clear. Given the fact that only a very limited number of transplanted cells successfully reach the injured tissues, which severely restricts their clinical applications, further understanding of the cellular and molecular events underlying the directed migration of these cells will help to improve the application of stem cells as therapeutic vehicles.

The multipotent mesenchymal stem cells (MSCs) with the ability to self-renew and differentiate into a variety of tissue cells have emerged as a promising source for cell-based therapies. In an effort to find a population of MSCs with strong migratory capacity, especially in response to growth factors or cytokines that are released from the injury sites and that act as chemoattractants to stimulate the directed migration of MSCs, our work has been focusing on the relationship between the chemotactic responses of MSCs and their differentiation status, as well as the delineation of the underlying regulatory mechanisms. Results showed that MSCs in varying differentiation states display different chemotactic responses to a variety of chemoattractants, such as hepatocyte growth factor (HGF): first, the number of chemotaxing MSCs and the optimal concentrations of HGF that induced the peak migration varied greatly; second, time-lapse video analysis showed that MSCs in certain differentiation state migrated more efficiently toward HGF; third, the phosphorylation levels of Akt, ERK1/2, SAPK/JNK, and p38MAPK were closely related to the differentiation levels of MSCs subjected to HGF; and finally, although inhibition of ERK1/2 signaling significantly attenuated HGF-stimulated transfilter migration of both undifferentiated and differentiating MSCs, abolishment of PI3K/Akt, p38MAPK or SAPK/JNK signaling only decreased the number of migrated cells in certain differentiation state(s). Blocking of PI3K/Akt or MAPK signaling impaired the migration efficiency and/or speed, the extent of which depends on the cell differentiation states. Meanwhile, F-actin rearrangement, which is essential for MSCs chemotaxis, was induced by HGF, and the time points of cytoskeletal reorganization were different among these cells. Accordingly, the formation and the asymmetrical distribution of focal adhesions (FAs) between the leading lamella and the cell rear, the phosphorylation of focal adhesion kinase (FAK) and paxillin, as well as the turnover of FAs varies greatly in differentiating MSCs, leading to the most effective chemotactic responses of MSCs in certain differentiation states. Further, we demonstrated the participation of several microRNAs and Wnt/beta-catenin signaling in regulating the chemotactic responses of MSCs. More importantly, we found that beta-catenin signaling is likely to be prerequisite for the chemotactic migration of MSCs. Collectively, these results demonstrate that the differentiation of MSCs influences their chemotactic responses to HGF: MSCs in varying differentiation states possess different migratory capacities, thereby shedding light on optimization of the therapeutic potential of these cells to be employed for tissue regeneration after injury. In this talk, I will summarize our data regarding the regulatory effects of PI3K/Akt, MAPKs, microRNAs, and beta-catenin signaling on the differentiating MSCs that undergo chemotaxis.

多くの方のご参加をお待ちしています。問い合わせ：内分泌代謝・先端医療・臨床検査医学講座