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Impact of transcription factors on dendritic cell development

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Abstract

Dendritic cells (DC) are critical immune modulators. In the presented work, the author investigated the roles of genes, which might be involved in the development of classical DC (cDCs) and plasmacytoid DC (pDCs), using an immortalized hematopoietic stem and progenitor cell (iHSPC) line. The iHSPCs were first subjected to transduction with a lentivirus carrying shRNA in order to knockdown the following genes: IRF7, ETS1, PHF17 and Zfp719. The stable knockdown iHSPC cell lines were then cultured in vitro for 5 days with Flt3 ligand, a cytokine required for DC development, and analyzed with flow cytometry. The flow cytometry results and cell counts showed a strong impact of each of the genes on the survival and development of cDCs and pDCs, compared to shLacZ, a knockdown control. Normally highly expressed in pDCs, the genes proved to be crucial for their development – with the strongest effect observed for IRF7 knockdown. These results give a new insight into the DC biology and shows possible footholds for influencing their functions. This approach may prove useful in designing vaccines, fighting infections and paving the way for new strategies for immunotherapy in cancer.

Introduction

The immune system comprises a large number of highly differentiated cell types whose functions emerge from coordinated interactions among developmentally heterogeneous cells, and are rarely observed in complete isolation. For example, phagocytic cells such as neutrophils or macrophages best exert their function through interactions with soluble components of the immune system such as antibodies secreted by B cells, or in their absence, mannose-binding lectins or deposition of complement protein C3. Perhaps the most elegant example of coordinated immunity is the generation of high affinity, isotype-switched antibodies capable of neutralizing a pathogen. Such a response requires not only the cell-intrinsic capacity of the B cell, but also linked recognition and activity of a differentiated form of the CD4+ T cell, the T follicular helper cell (Tfh), as well as contributions to T cell priming produced by cells of the phagocyte system called dendritic cells (DC). This three way interaction represents a highly organized system with each cell presenting checkpoints and barriers to improper activation as a means of guarding against autoimmunity. While the molecular mechanisms responsible for the development and diversification of T and B cells are well studied, those responsible for DCs are only beginning to be defined. This review will provide a synopsis of the known cellular and molecular events required for the development of DCs at steady-state.

The transcriptional networks regulating the diversification of myeloid lineages are currently being elucidated. Arguably, DCs remain the most enigmatic and developmentally uncharacterized cell type within this system. However, recent studies have defined key steps in the DC differentiation pathway by identifying restricted bone marrow precursors. We hope that these advances will encourage the current transition of the field from a relatively descriptive state to one in which molecular mechanisms are emphasized. This shift in approach is needed to clarify confusion regarding the precise role of the DC lineage, and particularly specific DC subsets, in settings of infection and tolerance. For example, our understanding of the functional differences between pDCs and cDC subsets has greatly improved since the identification of transcription factors which are required for their development, such as E2-2 and Batf3, respectively. The deletion of either gene leads to a model in which the exact function of the relevant cell can be interrogated.

Biography

Krzysztof Olesiejuk is a Medical Student from Medical University of Lodz, Poland. Having already taken part in research on three continents, he is engaged in scientific fields such as immunology, cancer biology and multi-drug-resistance of bacteria. Apart from this, his interests include wound healing processes and neural interfaces.

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