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雑誌

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Oie Y, Nozaki T, Takayanagi H, Hara S, Hayashi R, Takeda S, Mori K, Moriya N, Soma T, Tsujikawa M, Saito K, Nishida K.	Development of a cell sheet transportation technique for regenerative medicine.	Tissue Eng Part C	20	373-82	2014
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Oie Y, Nishida K.	Translational research on ocular surface reconstruction using oral mucosal epithelial cell sheets.	Cornea	33	S47-52	2014

IV. 研究成果の刊行物・別刷

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Computational Promoter Modeling Identifies the Modes of Transcriptional Regulation in Hematopoietic Stem Cells

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Abstract

Extrinsic and intrinsic regulators are responsible for the tight control of hematopoietic stem cells (HSCs), which differentiate into all blood cell lineages. To understand the fundamental basis of HSC biology, we focused on differentially expressed genes (DEGs) in long-term and short-term HSCs, which are closely related in terms of cell development but substantially differ in their stem cell capacity. To analyze the transcriptional regulation of the DEGs identified in the novel transcriptome profiles obtained by our RNA-seq analysis, we developed a computational method to model the linear relationship between gene expression and the features of putative regulatory elements. The transcriptional regulation modes characterized here suggest the importance of transcription factors (TFs) that are expressed at steady state or at low levels. Remarkably, we found that 24 differentially expressed TFs targeting 21 putative TF-binding sites contributed significantly to transcriptional regulation. These TFs tended to be modulated by other nondifferentially expressed TFs, suggesting that HSCs can achieve flexible and rapid responses via the control of nondifferentially expressed TFs through a highly complex regulatory network. Our novel transcriptome profiles and new method are powerful tools for studying the mechanistic basis of cell fate decisions.

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Introduction

Hematopoiesis is a complex and dynamic process, which generates mature blood cells throughout the life of organisms. In the adult bone marrow, long-term hematopoietic stem cells (LT-HSCs) maintain a balanced pool of stem cells, which also differentiates into more mature short-term hematopoietic stem cells (ST-HSCs), multipotent progenitors with a lower self-renewal capacity. It is believed that the blood lineage choice of HSCs is governed by a stepwise cell fate decision [1,2]. However, recent studies have raised questions about the hierarchical hematopoietic system [3,4]. Many studies based on genome-wide gene expression profiling [5–9] have demonstrated that specific extrinsic and intrinsic regulators play key roles in hematopoiesis [10–12]. Recently, high-throughput sequencing techniques have been applied widely [13–15], which have provided new insights into *in vivo* transcription factor (TF) binding and epigenetic modifications [16–18]. Systems biology approaches are also enhancing our understanding of the regulatory dynamics of hematopoiesis [19].

Despite the biological importance of the formation of all blood cells via a transition from LT-HSC to ST-HSC, little is known about the mechanism that underlies this early differentiation. A major explanation for this deficiency is a lack of comprehensive genome-wide identification studies and characterizations of the regulatory elements that govern gene expression in HSCs. The profiling of potential key regulators [8,17,20] and the large-scale integration of datasets [21,22] have improved our understanding greatly. However, these studies are limited to a small number of factors that function in heterogeneous HSCs, which were isolated using different combinations of monoclonal antibodies. Therefore, unconsidered key regulators may exist at this early stage of hematopoiesis. Indeed, novel key factors [23,24] and new multipotent progenitors [3,4,25] have been identified recently.

To address these deficiencies, we developed a computational method on the basis of novel transcriptome data from adult mouse bone marrow HSCs; $CD34^{-}KSL$ ($c\text{-}kit^{+}Sca1^{+}Lin^{-}$) LT-HSCs and $CD34^{+}KSL$ ST-HSCs, a widely used strategy to isolate HSCs at high purity [26,27]. Our method uses a regression-based approach [28–30] to model the linear relationships between gene expression and the characteristics of regulatory elements compiled from a database. In the present study, we extended this regression modeling-based approach using large-scale log-linear modeling (LLM) [31], which considered the combinatorial nature of TFs. Thus, our method can systematically infer the regulation modes exerted by TFs that are probably necessary for gene expression, as well as suggesting synergistic TF modules. Using our transcriptome profiles and this novel method, we characterized transcriptional regulatory modes related to HSCs, which suggested the