Transcriptional Regulation of Vascular Development

Thomas N. Sato

The problem of cell type differentiation has been a classic subject and extensively studied in other fields of biology such as immunology and neurobiology. In these fields, varieties of cell types are defined by their combinatorial expression of the specific markers. Identification and the systematic classification of such specific markers have led to significant advances in our understanding of the molecular mechanisms underlying the origin of cell type heterogeneity in immune and neural systems. However, the origin of endothelial cells and the generation of the diverse endothelial types have been the subject of molecular studies during only the last few years. One of the bottlenecks in this area has been the lack of systematic dissection of the expression patterns of specific markers in the various endothelial cell populations. Classification of endothelial cell types based on specific expression of such markers could be expected to lead directly to analysis of mechanisms underlying their origin and subtype differentiation.

The study of Dube et al5 in this issue of Circulation Research is an example of this type of investigative approach. The authors are trying to assess whether the problem of endothelial origin can be determined by transcriptional regulation. Tie2/Tek is one of the markers expressed primarily in endothelial lineages.6−9 It is undetectable in this hemangioblast population, but it is expressed in further differentiated endothelial cells. Therefore, authors have studied the transcriptional regulation of the Tie2 gene in an effort to understand transcriptional mechanisms underlying the specification of endothelial cells. Previously, cis-acting elements in both promoter and enhancer regions of the Tie2 gene that are critical for its endothelial-specific expression were defined.10,11 ELF-1 was identified as one of the Ets transcription factors that shows expression in endothelial cells. Furthermore, ELF-1 binds to one of the cis-acting sequences in the Tie2 promoter that is essential for its endothelial-specific expression. It was also shown that the endothelial nuclear extract contains ELF-1 that binds to the same cis-acting sequences in vitro. In addition, ELF-1 can transactivate the endothelial-specific promoter derived from another endothelial-specific gene, Tie1. On the basis of this evidence, Dube et al5 suggest that ELF-1 controls the expression of endothelial-specific marker genes such as Tie1 and Tie2. Although the data presented are correlative, ELF-1 should be added to the list of potentially important transcription factors in vascular development. Some key future investigations could include (1) specific perturbation of ELF-1 function in developing embryos to show that ELF-1, in fact, is directly involved in the regulation of Tie1 and Tie2 gene expression during vascular development; (2) precise determination of the temporal and spatial ELF-1 expression pattern during endo-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Circ Res. 2001;88:127-128.)

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Overview of the endothelial cell specification during development. See text for details.

As suggested based on the presence of multiple cis-acting sequences within the Tie2 gene mediating endothelial-specific expression, it is likely that the combinatorial functions of many transcription factors present in developing endothelial cells are required for Tie2 gene expression.10–12 The clever use of increasing genomic information and further characterization of ELF-1 and other known and novel transcription factors could be expected to contribute to new understanding of how endothelial specification is regulated at the transcriptional level. Further identification and systematic classification of markers in endothelial cell subtypes should help discern the molecular mechanisms underlying the generation of these diverse classes of endothelial cells during vascular development.

References


Key Words: vascular development ■ angiogenesis ■ Tie2 gene ■ gene expression
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_Circ Res._ 2001;88:127-128
doi: 10.1161/01.RES.88.2.127

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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