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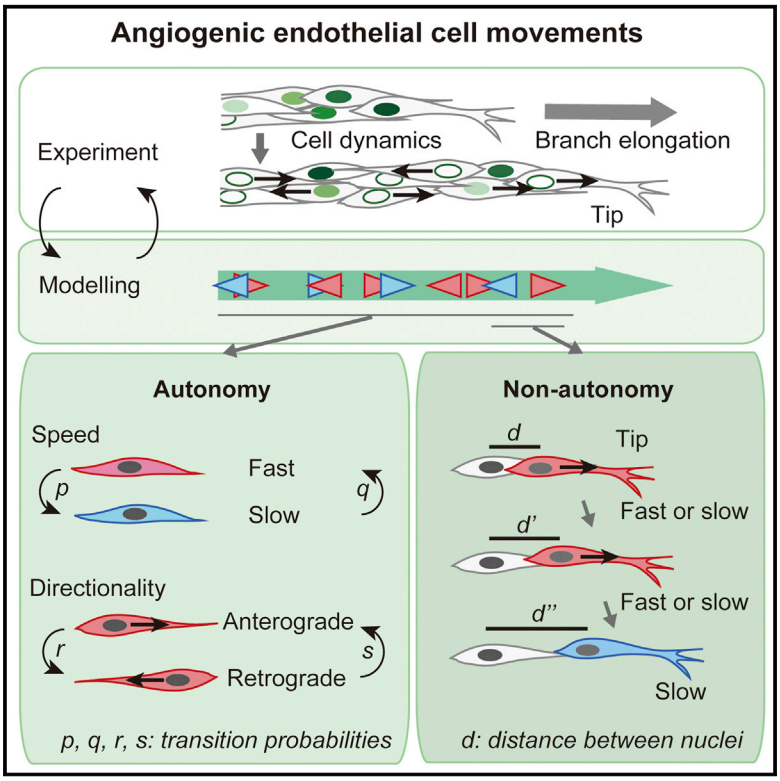
Autonomy and Non-autonomy of Angiogenic Cell Movements Revealed by Experiment-Driven Mathematical Modeling

Graphical Abstract



Authors

Kei Sugihara, Koichi Nishiyama, Shigetomo Fukuhara, ..., Toshio Suda, Hisao Ogawa, Hiroki Kurihara

Correspondence

nkanako@kumamoto-u.ac.jp

In Brief

Angiogenesis is a multicellular phenomenon driven by morphogenetic cell movements. By combining experimental and modeling assays, Sugihara et al. demonstrate cell-autonomous and coordinated aspects of morphogenesis to be governed by multicellular behaviors, which provides insights allowing angiogenic morphogenesis to be understood systematically.

Highlights

- A mathematical model is developed to simulate angiogenic multi-EC movements
- Cell-autonomous processes sufficiently illustrate core features of morphogenetic ECs
- A regulatory mechanism governed by the follower EC restricts tip EC motility

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Autonomy and Non-autonomy of Angiogenic Cell Movements Revealed by Experiment-Driven Mathematical Modeling

Kei Sugihara,[1,11] Koichi Nishiyama,[1,2,3,4,11,*] Shigetomo Fukuhara,[5] Akiyoshi Uemura,[6] Satoshi Arima,[1] Ryo Kobayashi,[7] Alvaro Köhn-Luque,[8] Naoki Mochizuki,[5] Toshio Suda,[3,9] Hisao Ogawa,[2] and Hiroki Kurihara[1,4,10]

[1]Department of Physiological Chemistry and Metabolism, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[2]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan

[3]International Research Center for Medical Sciences, Kumamoto University, 2-2-1 Honjo, Chuo-ku, Kumamoto 860-0811, Japan

[4]Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency (JST), Chiyoda-ku, Tokyo 102-0076, Japan

[5]Department of Cell Biology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

[6]Department of Retinal Vascular Biology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

[7]Department of Mathematical and Life Sciences, Graduate School of Science, Hiroshima University, Higashi-Hiroshima, Hiroshima 739-8526, Japan

[8]Department for Innovative Methods of Computing, Center for Information Services and High Performance Computing (ZIH), Technische Universität Dresden, 01062 Dresden, Germany

[9]Cancer Institute of Singapore, National University of Singapore Centre for Translational Medicine, 14 Medical Drive, 12-01, Singapore 117599, Singapore

[10]Institute for Biology and Mathematics of Dynamical Cell Processes (iBMath), the University of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo 153-8914, Japan

[11]Co-first author

*Correspondence: nkanako@kumamoto-u.ac.jp

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SUMMARY

Angiogenesis is a multicellular phenomenon driven by morphogenetic cell movements. We recently reported morphogenetic vascular endothelial cell (EC) behaviors to be dynamic and complex. However, the principal mechanisms orchestrating individual EC movements in angiogenic morphogenesis remain largely unknown. Here we present an experiment-driven mathematical model that enables us to systematically dissect cellular mechanisms in branch elongation. We found that cell-autonomous and coordinated actions governed these multicellular behaviors, and a cell-autonomous process sufficiently illustrated essential features of the morphogenetic EC dynamics at both the single-cell and cell-population levels. Through refining our model and experimental verification, we further identified a coordinated mode of tip EC behaviors regulated via a spatial relationship between tip and follower ECs, which facilitates the forward motility of tip ECs. These findings provide insights that enhance our mechanistic understanding of not only angiogenic morphogenesis, but also other types of multicellular phenomenon.

INTRODUCTION

Morphogenetic cell movements give rise to various tissue and organ shapes. The modes of these cell movements are diverse and context dependent: clusters, strands, sheets, tubes, and so on (Montell, 2008; Friedl and Gilmour, 2009). This raises fundamental questions, including whether these diverse movements share common principles and how individual cells spatiotemporally coordinate their behaviors with each other and their surroundings.

Angiogenesis is a type of morphogenetic cell movement, wherein a new vascular network emerges from pre-existing vessels in physiological and pathological contexts. Vascular endothelial cells (ECs) collectively behave in consort with mural cells in an orderly fashion to form dendrite structures through sprouting, elongating, branching, and lumenization processes. To date, a number of angiogenesis-related molecular players and signaling pathways have been identified, the first being vascular endothelial growth factor (VEGF) (Armulik et al., 2005; Holderfield and Hughes, 2008; Gaengel et al., 2009), and their angiogenic functions have been explored extensively even at the single-cell level. However, the underlying cellular