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Endothelial cells: The heart attack of the Clones

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Abstract

Neovascularization induced by acute myocardial infarction is mediated by clonal expansion of mature endothelial cells, which is triggered by VEGFR-2 signaling.

The exact source of cells underlying new blood vessel formation after ischemia has not been fully elucidated. Using models of neovascularization, such as zebrafish vascular development, three-dimensional sprouting assays, and chimeric murine retinas, endothelial cells have been shown to randomly integrate into blood vessels during physiological vascular growth. Nevertheless, the precise processes leading to neovascularization following organ injury in mammals remained hitherto undetermined.

Manavski and collaborators traced the genetic lineage of clonally expanding endothelial cells using multicolor fluorescent reporter mice (confetti mice), which allowed them to label and distinguish individual cells with nuclear localized, membrane-targeted, or cytoplasmic fluorescent proteins. They found that mature endothelial cells, identified via the *VE-cadherin* marker, clonally expand in the heart after acute myocardial infarction (heart attack). Using laser capture microdissection in different tissue sections (the border, infarct, and the remote zones of ischemic heart tissue) from mice after acute myocardial infarction, the authors isolated clonally expanded endothelial cells. They compared the transcriptome with nonclonally expanded cells of the same regions and endothelial cells that were isolated from the remote zone of the myocardium. Interestingly, they found that clonally expanded endothelial cells exhibited an enrichment of genes involved in endothelial-to-mesenchymal transition. Clonal expansion of endothelial cells was essentially dependent on vascular endothelial growth factor receptor 2 (VEGF-2) signaling, which is known to be induced by hypoxia. Clonal outgrowth of endothelial cells was also verified in other vascular beds, including the retina (retinopathy of prematurity) and skeletal muscle after hypoxia or ischemia. Of note, the same group has recently demonstrated that a long noncoding antisense transcript of GATA6 is up-regulated in endothelial cells during hypoxia and interacts with the epigenetic regulator LOXL2 to regulate endothelial gene expression via changes in histone methylation.

Highlighted Article

Y. Manavski, T. Lucas, S. F. Glaser, L. Dorsheimer, S. Günther, T. Braun, M. A. Rieger, A. M. Zeiher, R. A. Boon, S. Dimmeler, Clonal expansion of endothelial cells contributes to ischemia-induced neovascularization. *Circ. Res.* 10.1161/CIRCRESAHA.117.312310 (2018).

The current discovery has translational potential spanning from tissue regeneration following acute myocardial infarction to peripheral artery disease — two of the most frequent and disabling cardiovascular disorders. Indeed, the knowledge that the clonal expansion of endothelial cells is a crucial determinant of post-ischemic injuries could be exploited therapeutically to promote neovascularization.

Acknowledgments

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