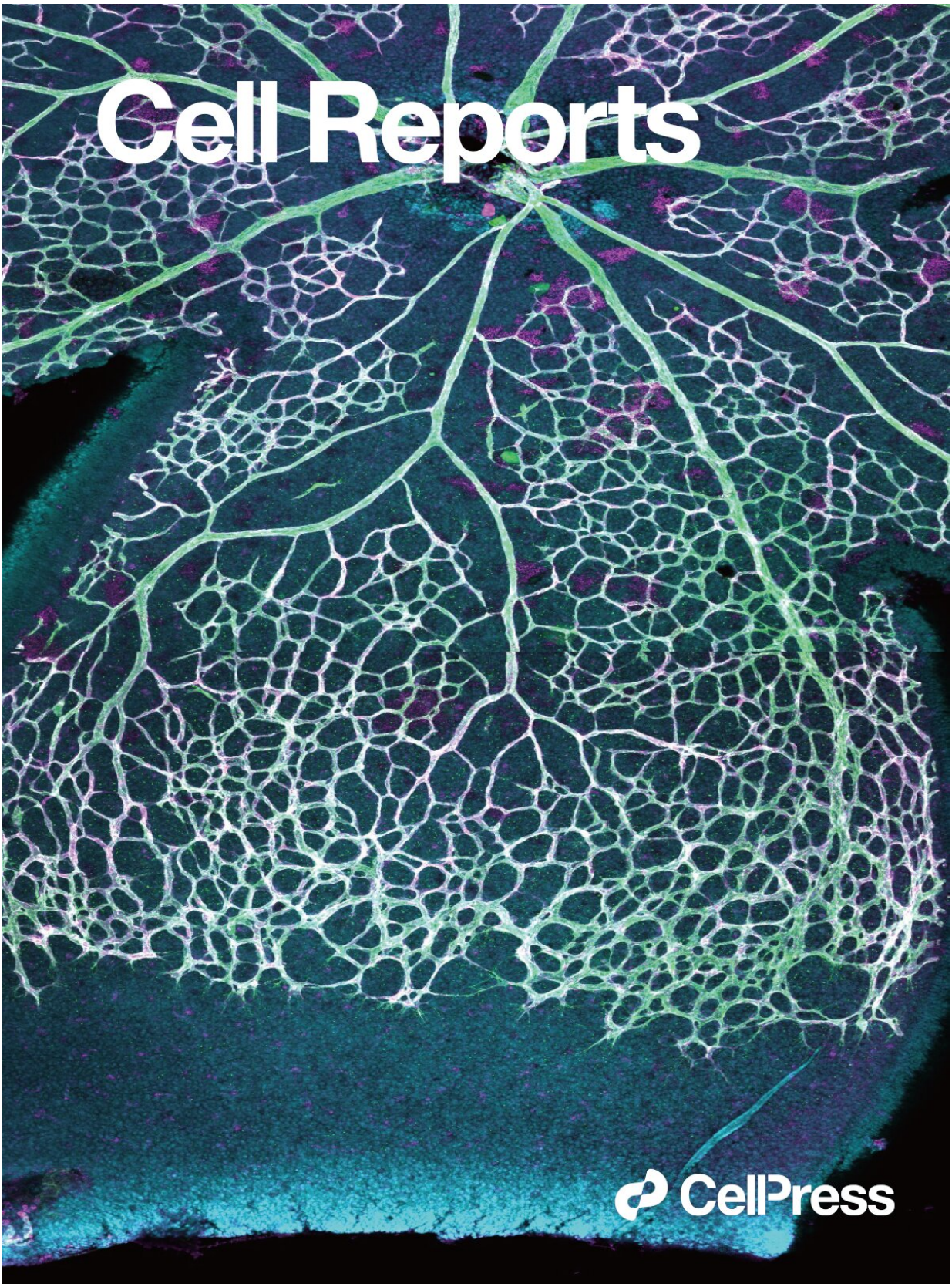
Identification of a unique 'switch' for blood vessel generation

February 8 2022


Cell Reports
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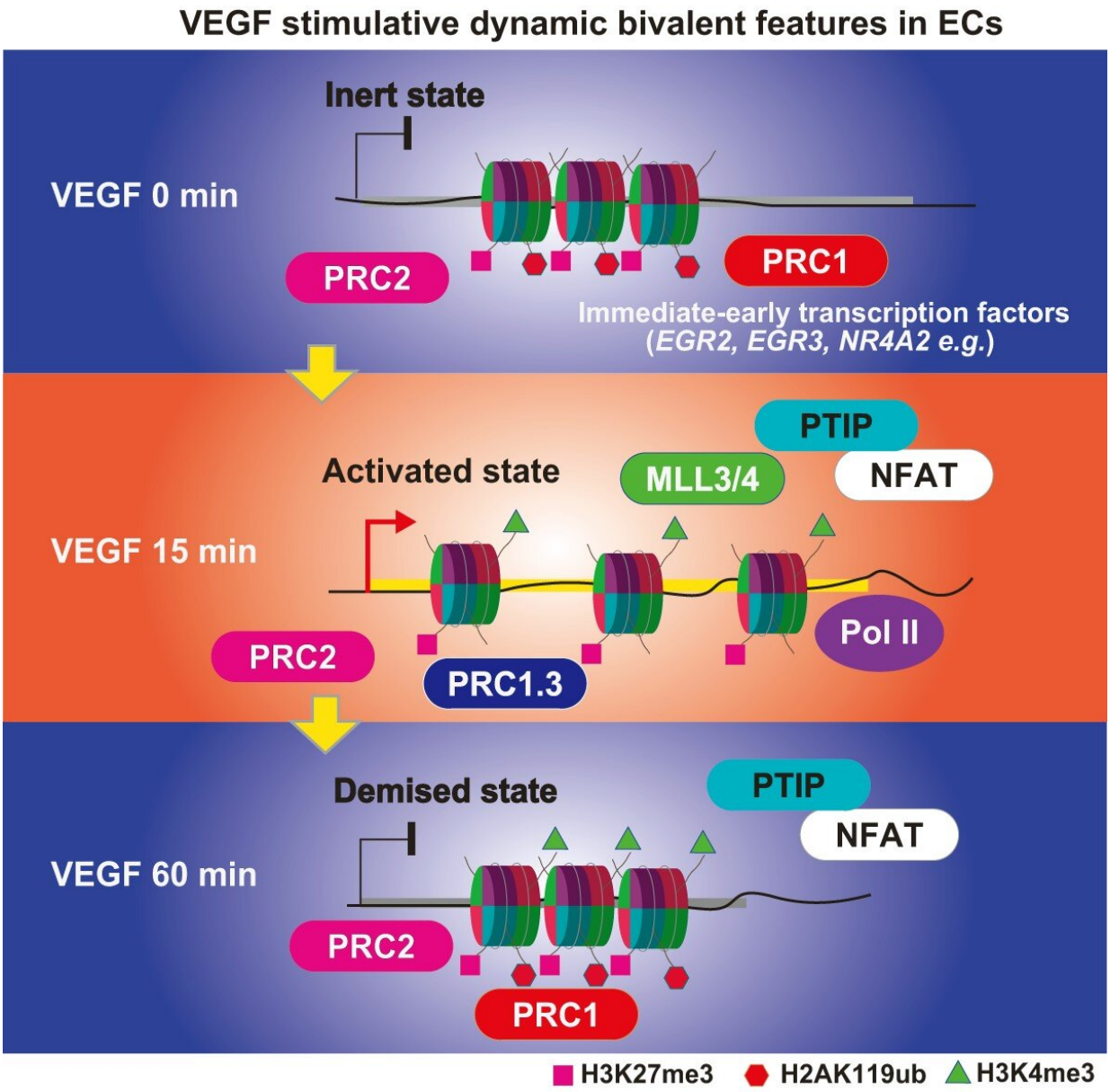
On the cover: Kanki and Minami et al. present a global mapping of VEGF-mediated dynamic transcriptional events, focusing on major histone-code profiles using ChIP-seq. They identify a bivalent histone-marked immediate-early transcription factor essential for VEGF-responsive angiogenesis. The cover highlights the retina's non-canonical polycomb 1 (PRC1.3)-mediated proper postnatal vascular network. Colors indicate green, CD31; magenta, isolectin B4. Credit: Dr. Takashi Minami

By systematically analyzing epigenetic changes in angiogenesis-stimulated vascular endothelial cells, Professor Takashi Minami (Kumamoto University, Japan) and his team have found a unique epigenetic modification (bivalent histone-mark switch) specific to critical transcription factors that induce genes essential for angiogenesis and revealed that the histone modifiers responsible for this modification are vital for postnatal angiogenesis.

Although comprehensive epigenetic datasets, especially in cancer cells or stem (ES/iPS) cells, have been constructed, the changes in epigenome dynamics in normal vascular endothelial cells upon angiogenesis stimulation are still not completely understood. New research from Dr. Minami is expected to lead to the compilation of an epigenomic database for normal endothelial cells and selective epigenomic drug discovery to protect against age-related vascular diseases.

The vascular network that extends throughout the body is the foundation of the biological homeostasis that keeps the body in a steady state. Endothelial cells form the basis of these blood vessels, and their proper functioning is necessary for human health. If the vascular system is over-activated or activated at misplaced regions, it may lead to cancer, heart disease, or cerebrovascular disease. However, revealing the detailed mechanisms of endothelial cell activation-mediated postnatal angiogenesis and epigenomic changes has proven to be challenging

research.



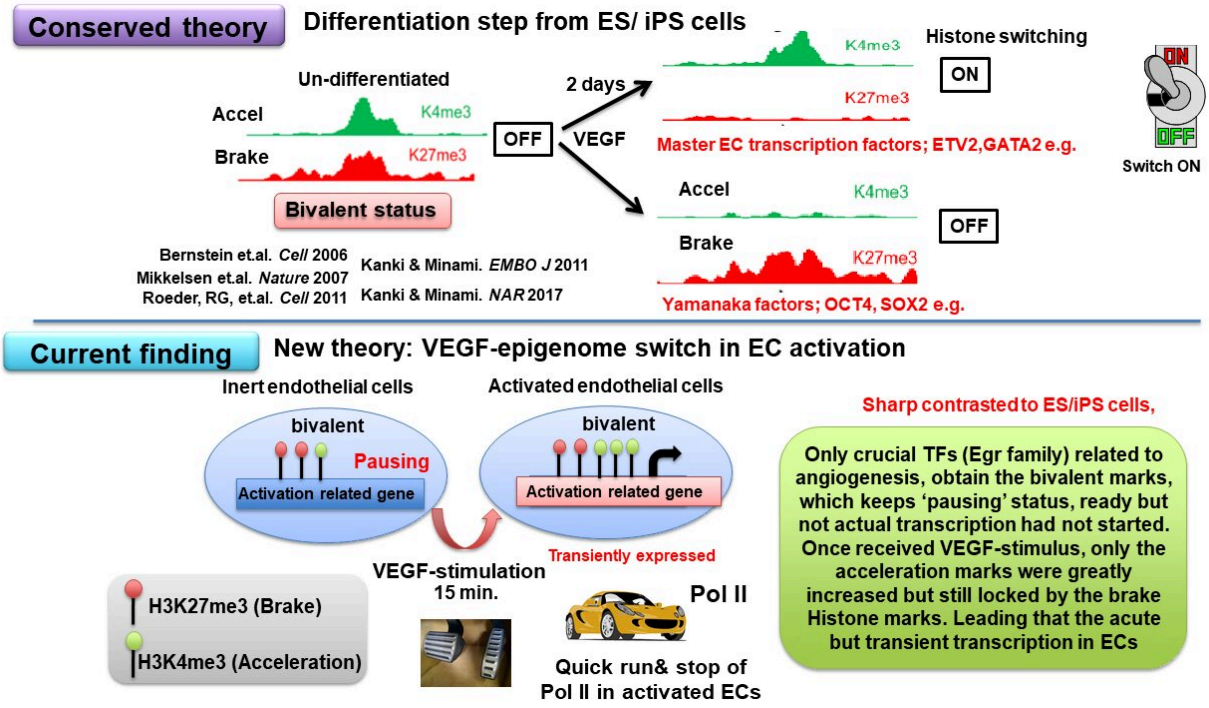
Kanki, et.al. demonstrate that angiogenesis essential immediate-early genes are silent with canonical PRC-brake in inert endothelium. In a short time, VEGF unlocks the transcription of these genes through bivalent status on the gene loci with PTIP/NFAT, MLL3/4 and noncanonical PRC1.3 accumulation. Credit: Dr. Takashi Minami

To tackle this problem, Dr. Minami and his team conducted a genome-wide analysis of epigenetic changes (mRNAs and histone modification changes) in VEGF (vascular endothelial growth factor essential for angiogenesis) signaling over a minute-by-minute basis. They then cataloged and mapped the changes to understand where changes occurred. In addition, they used a mouse model to evaluate whether the histone-mark changes from their comprehensive database are critical for postnatal angiogenesis.

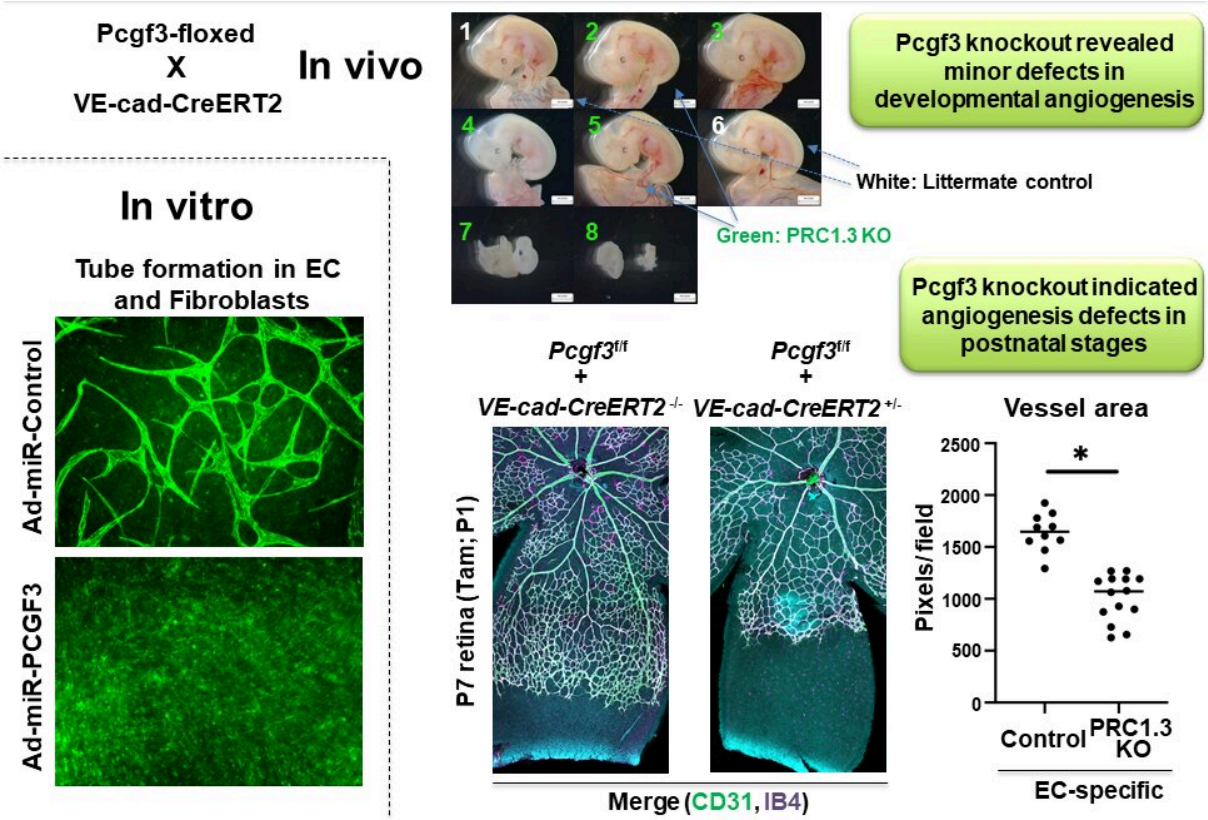
They found that when vascular endothelial cells receive VEGF signaling, a unique "bivalent histone switch" that is limited to immediate-early type transcription factors essential for angiogenesis is triggered, coinciding with the timing of the transfer of the transcription factor NFAT (which is involved in, among other things, the immune response and cardiac muscle development) into the nucleus.

The term "bivalent" refers to the fact that H3K27me3 (a transcriptional brake) and H3K4me3 (a transcriptional accelerator), which mark epigenetic histone modifications, coexist in the region where transcription factors are expressed. The two marks (H3K27me3 and H3K4me3) are known to occur in the regulatory region of transcription factor expression during the differentiation of stem (ES/iPS) cells. However, the bivalent switch in endothelial cells is highly dynamic and specific, occurring in the gene region of a group of angiogenesis-inducing/-essential transcription factors fully enriched in H3K27me3 brake marks. The non-canonical PRC1 is considered to be functionally different from the canonical PRC1. In the endothelium, non-canonical PRC1.3 binds to this genomic region 15 minutes after VEGF stimulation and disables brakes until the canonical PRC1-brake returns to the endothelium at 60 minutes. After 15 minutes of VEGF treatment, and at the same time as NFAT nuclear localization, NFAT interacts with PTIP-

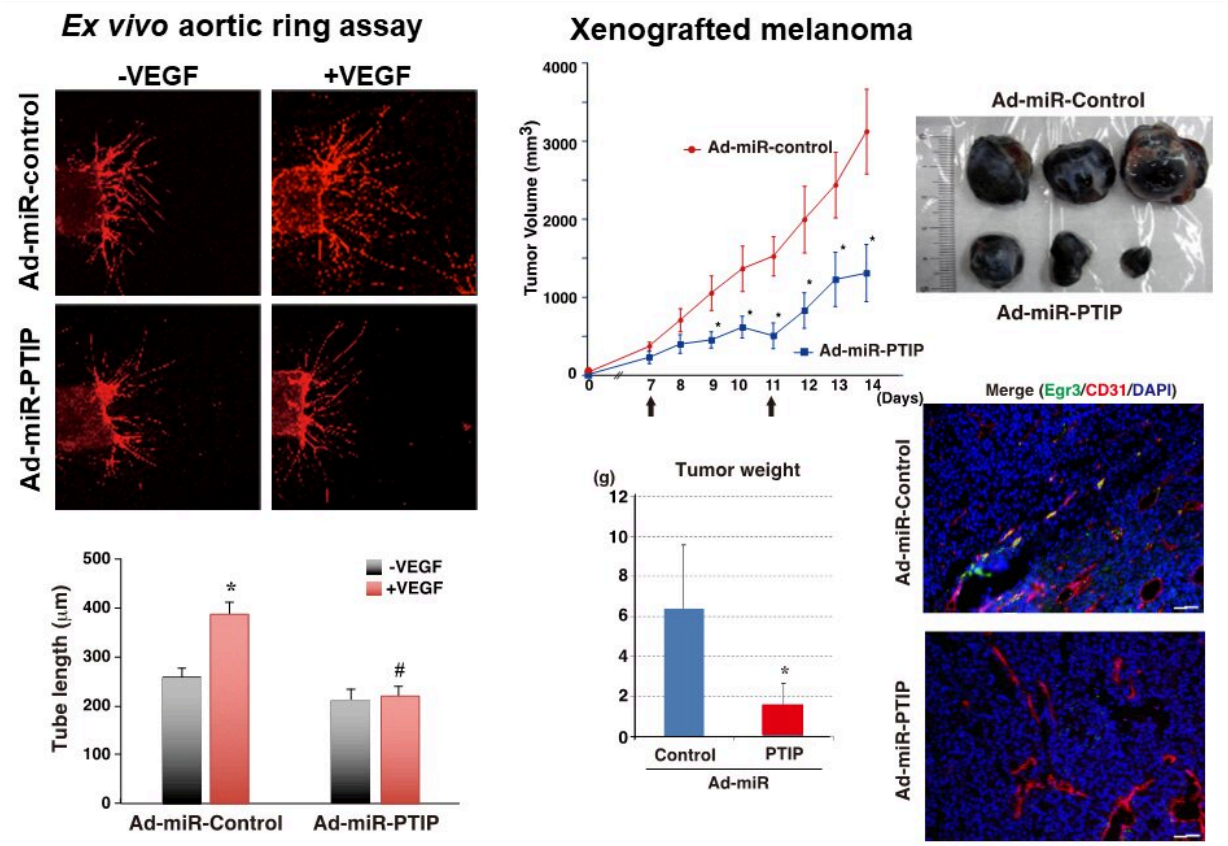
triggered H3K4me3 markers at the region of immediate-early type transcription factors, resulting in an angiogenesis-specific bivalent switch. PTIP is a component (guidance factor) of the MLL3/4, H3K4me3 marking enzyme.



Concept of the endothelial-activated Bivalent switch (bottom row); unlike existing stem cell differentiation switches (top row), the gas pedal for Pol II running on the gene is applied with the brake on, resulting in transient transcription. Credit: Dr. Takashi Minami



Loss of PRC1.3 abolished VEGF-mediated tube-formation. Credit: Dr. Takashi Minami

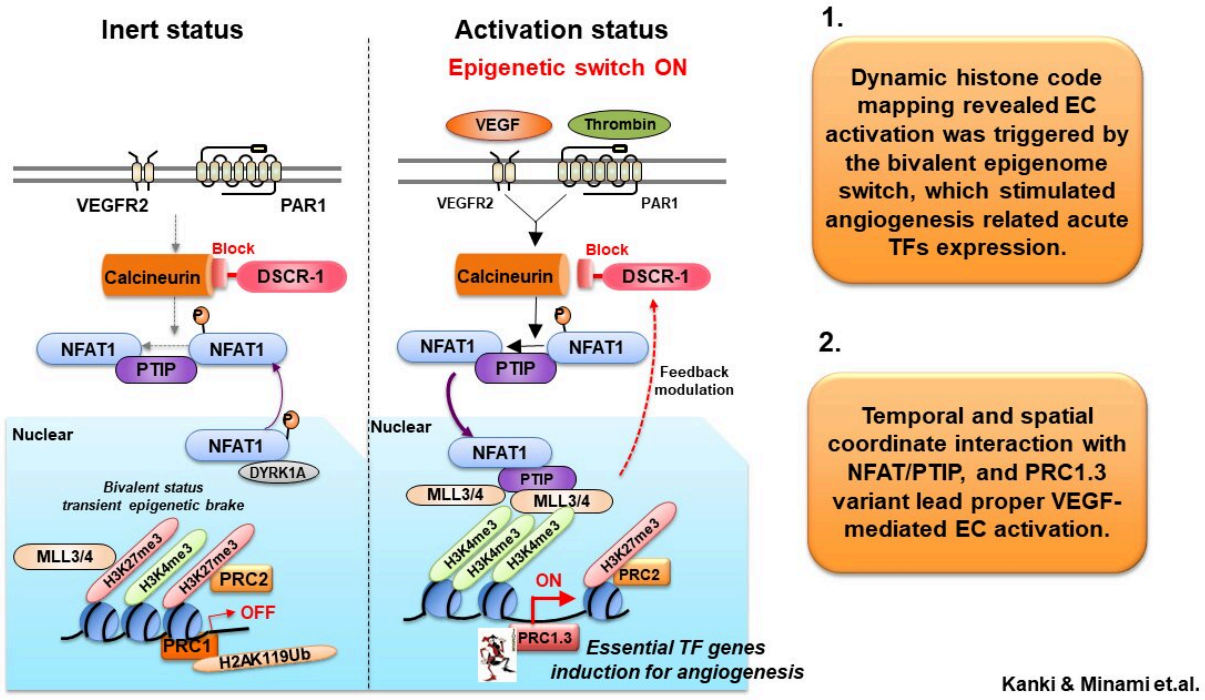


Loss of PTIP lead abrogation of VEGF-mediated tumor angiogenesis. Credit: Dr. Takashi Minami

The researchers also found endothelial cell-specific removal of PRC1.3 and PTIP suppressed only postnatal VEGF-induced angiogenesis without affecting developmental blood vessels, thereby delaying cancer growth and suppressing pathological inflammation.

Recently, the epigenome has come to be regarded as "chromatin biology" and includes histone modifications and nuclear structures. It has been mainly studied in ES/iPS cells and cancer cells. This is the first time an epigenetic database of normal endothelial cells has been established. The researchers expect that it will lay the foundation for

endothelial activation analyses, which will lead to the future of angiogenesis research.



Dynamic histone code mapping revealed that endothelial cell (EC) activation was triggered by the bivalent epigenome switch which stimulated angiogenesis related acute transferrin (TF) expression. Then, temporal and special coordinate interaction with NFAT/PTIP and the PRC1.3 variant lead proper VEGF-mediated EC activation. Credit: Dr. Takashi Minami

Dr. Minami commented that, "We believe that the development of drugs that specifically inhibit PTIP-NFAT interaction, as well as epigenomic drugs focused on non-canonical PRC1.3, are expected to lead the way to selective drug discovery that will protect against the vascular diseases found in aging."

More information: Takashi Minami, Bivalent histoneÂ marked immediate-early gene regulation is vital forÂ VEGF-responsive angiogenesis, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.110332. www.cell.com/cell-reports/full … 2211-1247(22)00048-1

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