BDR SEMINAR (Kobe & online hybrid)

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Tuesday, February 4, 2025

15:00-16:00

1F Auditorium, DB Building C, Kobe / Broadcast online via Zoom

Zoom meeting URL will be announced on the event day by e-mail

※This seminar is open only to BDR members.

Propranolol rescues an NR2F2-driven orphan syndrome via SOX18 inhibition

Summary

Genomic advancements have significantly enhanced our capacity to identify disease-causing mutations; however, translating these discoveries into effective treatments continues to present substantial challenges, particularly for rare genetic disorders. Hurdles include revealing the mechanisms by which variants of uncertain significance (VUS) impact molecular and cellular functions and devising therapeutic strategies to address the resulting physiological disorders. Here, we identify a de novo heterozygous mutation in the nuclear receptor subfamily 2 group F member 2 (COUPTFII/NR2F2) gene, a marker of venous identity, which causes an orphan paediatric syndrome, characterized by leaky, aberrant vascular development. Functional validation in human embryonic stem cells (hESCs) carrying the proband's mutation displays venous differentiation defects. Through in silico modelling and live-cell molecular imaging, we demonstrate that the NR2F2 variant protein is hypermobile, incapable of forming homodimers, and fails to recruit a critical transcription factor partner, SOX18, thereby disrupting transcriptional regulation. Multi-omics analysis further identifies an antagonistic coordinated regulation of target genes by NR2F2 and SOX18. Here, we posit that inhibiting SOX18 activity could mitigate NR2F2 dysfunction. Remarkably, pharmacological blockade of SOX18 shows a rescue of the NR2F2 variant in hESC-derived venous endothelial cells. Further, treatment with an FDA-approved drug known for its off-target SOX18 inhibition, led to significant reduction in haemorrhaging resulting in a significant increase in quality of life. This study showcases a personalized medicine approach, leveraging molecular insights to repurpose existing drugs for rare vascular diseases.

Keywords: transcription factor, transcription inhibitor, stem cell, vascular anomalies, endothelial cells, live cell imaging, quantitative molecular imaging, single molecule tracking

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