

Ex Vivo Improvement of a von Willebrand Disease Type 2A Phenotype Using an Allele-Specific Small Interfering RNA

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von Willebrand disease (VWD), the most common inherited bleeding disorder, is frequently caused by dominant-negative mutations in the gene coding for the multimeric protein von Willebrand factor (VWF).^{1,2} VWF is synthesized in endothelial cells and megakaryocytes and is coded by a 175-kb gene located on the short arm of chromosome 12. The gene carries several frequent single nucleotide polymorphisms (SNPs).³ In patients, different mutations in the gene have been reported, which can cause quantitative (type 1 and 3) or qualitative (type 2) defects.⁴ Treatment mostly relies on desmopressin, but substitution therapy with VWF is sometimes required. These therapies do not prevent mutant VWF being produced, and subsequent thrombocytopenia in the case of VWD type 2B or competition with normal VWF for platelet receptors can occur. In this issue of *Thrombosis and Haemostasis*, de Jong and coauthors⁵ present an ex vivo study in endothelial colony-forming cell clones (ECFCs) using allele-specific small interfering RNAs (siRNAs). In an earlier proof-of-principle study, the authors identified a siRNA, which targeted a heterozygous SNP located on the same allele as a type 2 mutation, which could successfully inhibit VWF expression in human embryonic kidney cells.⁶ Now they showed, in ECFCs isolated from a VWD type 2A patient, that this siRNA could knock down this mutant allele and improved the cellular phenotype in the patient's ECFCs. The results are very promising and should encourage future research to evaluate the efficiency and

specificity of allele-specific siRNAs, notably that allele-specific siRNAs can correct the bleeding phenotype in vivo and ultimately in patients.

Conflict of Interest

None declared.

References

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