Gentamicin-Induced Readthrough and Nonsense-Mediated mRNA Decay of SERPINB7 Nonsense Mutant Transcripts

Yuka Ohguchi1,5, Toshifumi Nomura1,5, Shotaro Suzuki1,5, Masae Takeda1, Toshinari Miyauchi1, Osamu Mizuno1, Satoru Shinkuma1, Yasuyuki Fujita1, Osamu Nemoto2, Kota Ono3, W.H. Irwin McLean4 and Hiroshi Shimizu1

Nagashima-type palmoplantar keratosis (NPPK) is an autosomal recessive skin disorder with a high, unmet medical need that is caused by mutations in SERPINB7. Almost all NPPK patients carry the founder nonsense mutation c.796C>T (p.Arg266Ter) in the last exon of SERPINB7. Here we sought to determine whether topical nonsense-suppression (readthrough) therapy using gentamicin is applicable to NPPK. First, we demonstrated that gentamicin enhanced readthrough activity in cells transfected with SERPINB7 cDNA carrying the mutation and promoted full-length SERPINB7 protein synthesis in NPPK keratinocytes. We next conducted an investigator-blinded, randomized, bilaterally controlled compassionate use study of topical gentamicin in which five NPPK patients with c.796C>T were enrolled. Patients’ self-reported improvement of hyperkeratosis was significantly greater on the gentamicin side than the control side (P = 0.0349). In two patients, hyperkeratosis was improved on the gentamicin side, as determined by a blinded-investigator assessment. These results indicate the therapeutic potential of topical gentamicin for NPPK. Unexpectedly, we also found that mutant SERPINB7 mRNAs harboring c.796C>T were degraded by nonsense-mediated mRNA decay. Furthermore, the truncated SERPINB7 protein was degraded via a proteasome-mediated pathway. These findings provide important insights into the mRNA/protein quality-control system in humans, which could be a potential therapeutic target for genetic diseases.


In the read-through phenomenon, a nonsense mutation is read through during translation by the ribosome. However, not all nonsense mutations are always read through, and the most important part of clinically applying read-through treatments is to determine whether the nonsense mutation and disorder can be easily read through. In this paper, we hypothesized that Nagashima-type palmoplantar keratosis is an ideal target for read-through treatments, and we proved this to be true. I owe it to Dr. Nomura, Professor Shimizu and all the other members in the laboratory and the department that I was able to research such a clear story and sum it up in the paper. I have great appreciation for them. I sincerely hope our paper will contribute to the treatment of hereditary skin disorders.

リードスルーとは、リボソームによる翻訳時にナンセンス変異が「読み飛ばされる（readthrough）」現象のことで、この現象を用いて遺伝性疾患を治療することが期待されています（リードスルー治療）。しかしながら、全てのナンセンス変異が等しくリードスルーされるわけではないため、リードスルー治療の臨床応用には、リードスルーされやすいナンセンス変異・疾患を見極めることが最も重要です。我々は、様々な理由から長島型掌蹠角化症がリードスルー治療の最適なターゲットであるとの仮説を立て、本論文でこれを実証しました。非常に明確なストーリーで研究を行い、論文にまとめることができたのも、乃村先生、清水教授を始め、研究室のメンバー、医局の皆様のご指導のおかげと大変感謝しております。我々の論文が遺伝性皮膚疾患の治療に寄与することを願っております。