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Human Molecular Genetics

Dyskeratosis congenita mutations in dyskerin SUMOylation consensus sites lead to impaired telomerase RNA accumulation and telomere defects

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Mutations in the dyskerin gene (DKC1) cause X-linked dyskeratosis congenita (DC), a rare and fatal premature aging syndrome characterized by defective telomere maintenance. Dyskerin is a highly conserved nucleolar protein, and a component of the human telomerase complex that is essential for human telomerase RNA (hTR) stability. However, its regulation remains poorly understood. Here, we report that dyskerin can be modified by small ubiquitin-like modifiers (SUMOs). We find that human DC-causing mutations in highly conserved dyskerin SUMOylation consensus sites lead to impaired hTR accumulation, telomerase activity and telomere maintenance. Finally, we show that modification of dyskerin by SUMOylation is required for its stability. Our findings provide the first evidence that dyskerin stability is regulated by SUMOylation and that mutations altering dyskerin SUMOylation can lead to defects in telomere maintenance that are characteristics of DC.

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