

Abstract

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Accelerated hematopoietic stem cell aging in a mouse model of dyskeratosis congenita responds to antioxidant treatment.

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BACKGROUND: Mutations in DKC1, encoding telomerase associated protein dyskerin, cause X-linked dyskeratosis congenita (DC), a bone marrow (BM) failure, and cancer susceptibility syndrome. Decreased accumulation of telomerase RNA resulting in excessive telomere shortening and premature cellular senescence is thought to be the primary cause of disease in X-linked DC. Affected tissues are those that require constant renewal by stem cell activity.

OBJECTIVE AND METHODS: We previously showed that in *Dkc1*(Δ 15) mice, which contain a mutation that is a copy of a human mutation causing DC, mutant cells have a telomerase-dependent proliferative defect and increased accumulation of DNA damage in the first generation before the telomeres are short. We now demonstrate the presence of the growth defect in *Dkc1*(Δ 15) mouse embryonic fibroblasts in vitro and show that accumulation of DNA damage and levels of reactive oxygen species increase with increasing population doublings.

RESULTS: Treatment with the antioxidant, N-acetyl cysteine (NAC), partially rescued the growth disadvantage of mutant cells in vitro and in vivo. Competitive BM repopulation experiments showed that the *Dkc1*(Δ 15) mutation is associated with a functional stem cell defect that becomes more severe with increasing age, consistent with accelerated senescence, a hallmark of DC hematopoiesis. This stem cell phenotype was partially corrected by NAC treatment.

CONCLUSION: These results suggest that a pathogenic *Dkc1* mutation accelerates stem cell aging, that increased oxidative stress might play a role in the pathogenesis of X-linked DC, and that some manifestations of DC may be prevented or delayed by antioxidant treatment.

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