Inactivation of DNase1L2 and DNase2 in keratinocytes suppresses DNA degradation during epidermal cornification and results in constitutive parakeratosis

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Abstract

Nuclear DNA of keratinocytes is degraded during the formation of the stratum corneum. Here, we investigated the mechanism of cornification-associated DNA degradation by generating mouse models deficient of candidate DNA-degrading enzymes and characterizing their epidermal phenotypes. In contrast to DNase1L2 knockout mice and keratinocyte-specific DNase2 knockout mice, DNase1L2/DNase2 double knockout mice aberrantly retained nuclear DNA in the stratum corneum, a phenomenon commonly referred to as parakeratosis. The DNA within DNase1L2/DNase2-deficient corneocytes was partially degraded, indicating that an additional, though insufficient mechanism of DNA fragmentation operates beside DNase1L2 and DNase2. Isolation of corneocytes and *in situ* DNA labelling demonstrated that corneocytes of DNase1L2/DNase2 double knockout mice contained DNA in a nucleus-like compartment that also contained nucleosomal histones but lacked the nuclear intermediate filament protein lamin A/C. Parakeratosis was not associated with altered corneocyte resistance to mechanical stress, changes in transepidermal water loss, or inflammatory infiltrates in DNase1L2/DNase2 double knockout mice. The results of this study suggest that cornification of epidermal keratinocytes depends on the cooperation of DNase1L2 and DNase2 and indicate that parakeratosis *per se* does not suffice to cause skin pathologies.

Generation of DNase knockout mice

DNase1L2 knockout: Fischer et al., JID 2011
- parakeratosis in hair and nails

DNase2 knockout: Fischer et al., JID 2017
DNase2^{f/f} K14-Cre, deletion in K14 epithelia
- suppression of DNA degradation in sebaceous glands

Double knockout: DNase1L2/DNase2 DKO by crossing single-KO mice

Results

Double knockout of DNase1L2 and DNase2 causes parakeratosis: retention of DNA and histone H3

Thin section through the sole skin of DNase1L2 KO mice and DNase1L2/DNase2 double knockout (DKO) mice were labeled for DNA, TUNEL, histone H3 and lamin A/C. Results for wildtype and DNase2 KO mice (not shown) were similar to those of DNase1L2 KO mice, that is, normal orthokeratosis.

Tape-stripped corneocytes of DNase1L2/DNase2 double knockout mice contain DNA

Corneocytes of DNase1L2/DNase2 are stress-resistant

DNase knockout does not lead to skin inflammation

Summary and conclusions

- DNase1L2 and DNase2 cooperate in DNA degradation during cornification.
- The contribution of DNase2 suggests a role of lysosomes in this process.
- DNA retention in cornifying keratinocytes does not cause skin inflammation.