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Kindlin-1 protects cells from oxidative damage through activation of ERK signalling

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Abstract:

Kindlin-1 is a FERM domain containing adaptor protein that is found predominantly at cell-extracellular matrix adhesions where it binds to β-integrin subunits and is required for integrin activation. Loss of function mutations in the *FERMT1* gene which encodes Kindlin-1 leads to the development of Kindler Syndrome (KS) an autosomal recessive skin disorder characterized by skin blistering, photosensitivity, and predisposition to aggressive squamous cell carcinoma (SCC). Here we show that loss of Kindlin-1 sensitizes both SCC cells and keratinocytes to oxidative stress: Kindlin-1 deficient cells have higher levels of reactive oxygen species, decreased viability and increased DNA damage after treatment with either hydrogen peroxide (H_2O_2) or irradiation with UVA. We show that Kindlin-1 is required to fully activate ERK signalling after oxidative damage, and that activation of ERK protects cells from DNA damage following oxidative stress: inhibition of ERK activation sensitizes Kindlin-1 expressing cells, but not Kindlin-1 deficient cells to oxidative stress. Finally we demonstrate that the Kindlin-1 dependent activation of ERK and protection from DNA damage following oxidative stress depends on the ability of Kindlin-1 to bind integrins. Thus loss of Kindlin-1 leads to an imbalance in the cellular oxidative state, which renders Kindlin-1 deficient cells more prone to the effects of ROS generated in response to oxidative stress. We propose that Kindlin-1 dependent activation of ERK signalling is a key molecular mechanism that renders KS keratinocytes more sensitive to oxidative damage and contributes to the increased photosensitivity in KS patients.

Full text:

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