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586 New class of mTOR inhibitor stabilizes intermediate filament networks in severe epidermolysis bullosa simplex keratinocytes

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Epidermolysis Bullosa Simplex (EBS) is a rare genodermatosis caused by mutations in either KRT5 or KRT14. Severe EBS (i.e., EBS Dowling-Meara) is characterized by extremely fragile skin with frequent and severe herpetiform blistering. Genetic mutations cause poor keratin 5/14 dimerization resulting in mechanically weakened intermediate filament (IF) networks that collapse into intracellular aggregates upon stress (e.g., scratching, UV). Enhanced cellular removal and degradation of mutant keratins through stimulation of autophagy and the UPS system has the potential to strengthen the IF networks, reducing blistering and erosions. Previously, UPS cochaperones (e.g., 4-phenylbuterate) were shown to decreased keratin aggregation but also decreased keratinocyte adhesion and migration. The purpose of this research was to evaluate if BM-3103, (4-Hydroxy 4'-methyoxytolan), a known wound healing promoter, anti-inflammatory, and autophagy inducer, could remove mutant keratins/aggregates thereby strengthening the IF network without adversely affecting cell survival, adhesion, or migration. Assays tested on patient derived EBS keratinocytes included: (1) Assessment of cytotoxicity, adhesion, and migration effects of BM-3103 using MTT, LDH, and scratch assays. (2) Autophagy induction (LC3-II conversion) and keratin aggregation (heat stress assay). There were no signs of cytotoxicity, loss of cell adhesion or slowed migration. Cells were exposed to escalating concentrations of BM-3103 for 24 hrs then heat shocked (43°C for 30min) generating an abundance of aggregates visualized by immunofluorescent microscopy. Untreated keratinocytes displayed keratin aggregate formation in 72% of KRT5 and 87% of KRT14 mutant cells. Treatment with BM-3103 reduced the incidence of keratin aggregates to 16% ($p<0.01$) of KRT5 and 24% ($p<0.01$) KRT14 mutant cells. BM-3103 is the first compound identified that is capable of stabilizing IF networks in keratinocytes from severe EBS patients. A clinical trial is ongoing to assess if BM-3103, can heal blistering areas and strengthen EBS patient skin.

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