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RNase L represses hair follicle regeneration through altered innate immune signaling

Injury responses in mammals typically induce fibrosis and scarring rather than functional regeneration. This limited regenerative capacity in mammals could reflect a loss of proregeneration programs or active suppression by genes functioning akin to tumor suppressors. To uncover programs governing regeneration in mammals, we screened transcripts in human participants following laser rejuvenation treatment and compared them with mice with enhanced wound-induced hair neogenesis (WIHN), a rare example of epimorphic regeneration in mammals. We found that Rnasel-/- mice exhibit an increased regenerative capacity, with elevated WIHN through enhanced IL-36α. Consistent with RNase L's known role in activating caspase-1, we found pharmacologic inhibition of caspases promoted regeneration in an IL-36-dependent manner in multiple epithelial tissues. We identified a negative feedback loop, where RNase L-activated caspase-1 restrains the proregenerative dsRNA-TLR3 signaling cascade through the cleavage of toll-like adaptor protein TRIF. Through integrated single-cell RNA-seq and spatial transcriptomic profiling, we confirmed OAS & IL-36 genes to be highly expressed at the site of wounding and elevated in Rnasel-/- mouse wounds. This work suggests that RNase L functions as a regeneration repressor gene, in a functional trade off that tempers immune hyperactivation during viral infection at the cost of inhibiting regeneration.

Keywords
regeneration, skin, hair follicles, innate immunity

Biography
Sashank Reddy received his MD and PhD from Harvard Medical School and completed plastic surgery residency and craniofacial fellowship at Johns Hopkins University prior to joining the university faculty. He currently serves as Associate Professor in the Department of Plastic and Reconstructive Surgery with secondary appointment in Biomedical Engineering. Dr. Reddy is also the Associate Director of the university's Institute for NanoBioTechnology and Senior Medical Director of Johns Hopkins Technology Ventures. Dr. Reddy's clinical practice spans facial skin cancer reconstruction, headache surgery, and craniofacial trauma. His research interests span regeneration and aging.

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