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preventing damage to protein products, cells or the venom gland tissue. It is therefore expected that the extreme demands placed on venom gland tissue during venom production are associated with similarly extreme cellular physiology to accommodate extreme cellular and physiological performance, yet this has not been examined in previous studies.

In addition to unique physiology and functionality associated with the upregulation of venom production following venom depletion, the steady-state venom gland is tasked with housing an abundance of highly toxic venom components in a manner that protects the venom gland and surrounding tissue from the biological

unfolded protein response (Fig 3c). Overrepresented GO terms include “response to endoplasmic reticulum stress” and other terms related to responses to misfolded proteins (Fig 3d), indicating a relatively high degree of endoplasmic reticulum stress in the unextracted venom gland relative to other secretory tissues.

Several pathways and URMs involved in tumor suppression, cell cycle regulation, and regulation of cellular growth and proliferation are relatively highly active in the unextracted venom gland, and these are largely exclusive of regulatory mechanisms implicated in venom production. For example, while PTEN is inferred to be upregulated both in this analysis and during venom production, pathways including protein kinase A signaling, PPAR signaling and Wnt/ -catenin signaling pathways are uniquely activated in the unextracted venom

unextracted venom gland and instead two broblast growth factor (FGF) transcription factors show evidence of activation. Additional URMs with inferred activation in the unextracted venom gland include Ras-related protein Rab-1B (RAB1B), a regulator of intracellular vesicle transport between the ER and Golgi, which is also activated during venom production (Fig. 3c).

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complexity of this process. Our inferences provide the rst detailed molecular characterization of this response, including regulatory mechanisms driving secretory function and epithelial maintenance, and highlight a role of cellular stress response activation during venom production. Characterization of the unextracted venom gland gene expression programs compared to other secretory tissues suggests unique activation of additional signalin

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