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Proteolysis of a Human Host-Defense Peptide Unmasks Innate Immune Function

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Defensins are small, cysteine-rich, ribosomal peptides produced by eukaryotes. These hostdefense peptides participate in the human innate immune response. Human α - defensin 6 (HD6) is synthesized and stored in small intestinal Paneth cell granules. Its biophysical properties and physiological function are both remarkable and warrant extensive investigation. Whereas other human α -defensins exhibits broad-spectrum antimicrobial activity, HD6 exerts negligible antibacterial activity in vitro and provides host-defense by an alternative mechanism. In the small intestinal lumen, this 32-residue peptide self-assembles into higher-order oligomers or "nanonets" that entrap bacteria and thereby prevent bacterial invasion into host cells.¹ The distribution of hydrophobic residues in the HD6 primary sequence differs from that of other human α -defensins, and our recent biochemical and biophysical investigations revealed that hydrophobic residues are essential for HD6 self-assembly and innate immune function.² Here, we present the results from investigations designed to elucidate how the Paneth cell stores HD6 as well as how and where the HD6 nanonet forms. Analysis of human mRNA indicates that HD6 is biosynthesized as prodefensin 6 (proHD6) exhibiting a 49-residue N-terminal region.³ Our studies reveal that proHD6 neither self-assembles into higher-order oligomers nor prevents the human gastrointestinal pathogen Listeria monocytogenes from invading epithelial cells. Moreover, trypsin-catalyzed proteolysis of proHD6 unleashes mature HD6, unmasking immune function. In analogy to zymogen activation, these insights provide a working model whereby the Paneth cell synthesizes, packages and stores inactive proHD6. Proteolytic processing of the propeptide occurs during or following vesicular release, which triggers HD6 self-assembly and allows for nanonet formation in the intestinal lumen.

References

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- (3) Yang, D. et. al. Annu. Rev. Immunol. 2004, 22, 181-215.