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Structural biology of peptidylarginine deiminases and their substrate S100A3 protein in human hair cuticle

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Mature hair cuticles form the outermost protective tissue of the hair fiber. Hair cuticle constitutes the cornified envelope thicker than that of skin corneocytes; however, its terminal differentiation process remains unclear. In human hair cuticular cells, a hair dominant type of Ca^{2+}-dependent peptidylargine deiminase (*PADI3*) catalyze the conversion of specific arginines on the homodimer interface of S100A3 into citrullines. This irreversible modification causes assembly of an S100A3 homotetramer in the presence of Ca^{2+} and Zn^{2+}. Phylogenetic analysis suggests that divergence of the S100A3 gene coincided with the emergence of hair, a defining feature of mammals. Amino acid sequences deduced from therian S100A3 genes conserve the $(Cys)_3$His-type Zn^{2+}-binding site in the C-terminus in addition to two EF-hand-type Ca^{2+}-binding motifs. To elucidate functional significances of Ca^{2+}- and Zn^{2+}-homeostatic regulation underlying in the superficial epithelium, the structural and functional role of the C-terminal Zn^{2+}-binding domain in the S100A3 tetramrerization were investigated. The binding of either Ca^{2+} to two EF-hand-type Ca^{2+}-binding motifs or Zn^{2+} to the $(Cys)_3$His-type Zn^{2+}-binding site reduced the α-helix content of S100A3 and modulated its affinity for the other cation. The binding of a single Zn^{2+} cation promoted Ca^{2+}-dependent tetramerization of S100A3 and induced extensive unfolding of helix IV. The Ca^{2+} and Zn^{2+} binding affinities of S100A3 were enhanced by binding of the other cation in conjunction with the tetramerization. Binding of Ca^{2+} or Zn^{2+} to each S100A3 subunit within the homotetramer is induced by repositioning of helix III and rearrangement of the C-terminal tail domain. The heterotrophic allosteric modulation of S100A3 by binding of Ca^{2+}/Zn^{2+} suggests that S100A3 is involved in Ca^{2+}- and Zn^{2+}-homeostasis in the superficial epithelium. We also determined structures of two peptidlyarginin deiminases (PAD1 and PAD3) to understand the substrate recognition mechanism.

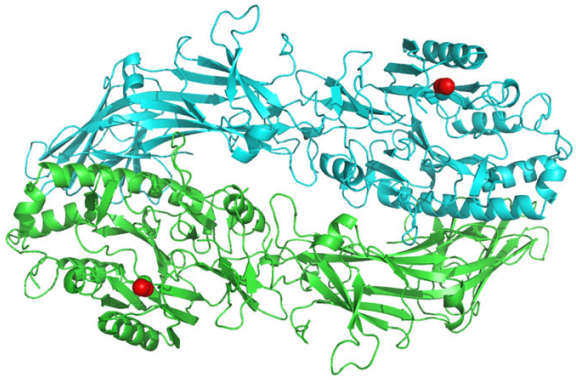

Figure 1: Overall structure of peptidylarginine deiminase type III, PAD3

References

[1] M. Unno, et al., Acta F., 68 (2012), 668-670

1

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