Structural basis for Ca^{2+}-induced Activation of Human PAD4

Kyouhei Arita[a], Toshiyuki Shimizu[a], Hiroshi Hashimoto[a], Michiyuki Yamada[a], Yuji Hidaka[b], Mamoru Sato[a], *[a]Graduate School of Integrated Science, Yokohama City University of Japan. [b]Department of Life Science, Faculty of Science and Engineering, Kinki University of Japan.* E-mail: kyouhei@tsurumi.yokohama-cu.ac.jp

Peptidylarginine deiminase 4 (PAD4) is a Ca^{2+}-dependent enzyme that catalyzes the conversion of protein arginine residues to citrulline residues. PAD4 is expressed mainly in bloodstream granulocytes and present in the cell nucleus. The recent experimental evidence that PAD4 targets multiple arginine sites in histone H3 and H4, including those sites methylated by CARM1 (H3/Arg17) and PRMT1 (H4/Arg3), has attracted considerable attention to characterize the role of histone modifications in regulating gene transcription [1, 2].

On the other hand, a recent single-nucleotide polymorphism (SNP) analysis of the PAD4 (*PADI4*) gene has identified a specific haplotype linked to an increased susceptibility for rheumatoid arthritis in Japanese people [3].

Here we present the crystal structures of Ca^{2+}-free, Ca^{2+}-bound, and Ca^{2+}-substrates bound PAD4 [4]. PAD4 has five non-EF-hand Ca^{2+} binding sites and adopts an elongated shape, consist of N- and C-terminal domain. These structural data indicate that Ca^{2+} binding in C-terminal domain induces conformational changes that generate the active site cleft. Our findings identify a novel mechanism for enzyme activation by Ca^{2+} ions.

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