

## Innate Immunity and Aging

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The innate immune system, that mediates the first line of defense against microbial pathogens, is essential for the activation of acquired immune system.

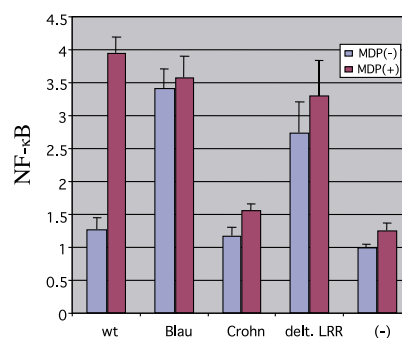
Mutations in Nod2, one of the innate immune factors, have been associated with Crohn's disease, the inflammatory bowel disease, and Blau syndrome, characterized by systemic granuloma. Our analysis revealed that the Nod2 variants carried by CD patients demonstrated impaired MDP-dependent response, and Nod2 alleles associated with Blau's syndrome promoted MDP-independent activation. We

also identified precise ligand recognition mechanism through the analysis of 500 Nod2 mutants.

Blau syndrome  
autosomal dominant  
systemic inflammatory disease  
constitutive active

Crohn's disease  
autosomal recessive  
bowel inflammatory disease  
loss of MDP response

LRR deletion mutant  
constitutive active  
analysis of Nod2 pathway



MDP response of Nod2 mutants

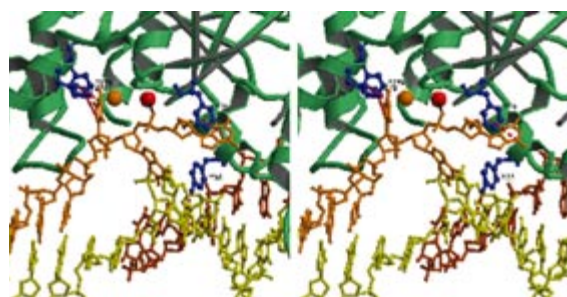
## Mechanism of FEN-1 with DNA Substrate to Form the Complex

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Flap endonuclease-1 (FEN-1) play important roles in DNA replication and repair. In this study, the kinetics parameters of mutants at highly conserved aromatic residues, Tyr<sup>33</sup>, Phe<sup>79</sup>, and Phe<sup>278</sup>Phe<sup>279</sup>, in the vicinity of the catalytic centers of the FEN-1's molecules were examined. According to the kinetic parameters of the mutants and other results, DNA binding model of the phFEN-1 with the nick substrate was proposed as shown in the figure. The stacking interactions of Tyr<sup>33</sup> and Phe<sup>79</sup> might play important roles to fix the template strand and the downstream strand, in close proximity to the active

center to form the productive transient state leading to the hydrolysis.



The proposed model showing the interactions between the aromatic residues of phFEN-1 and the nick substrate. The main chain structure of phFEN-1 is shown in green. Magnesium ions 1 and 2 are colored in red and orange, respectively. The template strand of nick substrate is colored yellow. The downstream and upstream strands are in orange and brown, respectively.