

P035 A tiny mutation and its enormous consequences:
R42Q causes domain miscommunication in p47^{phox} of
NADPH oxidase

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We report biochemical, molecular dynamics and crystallographic studies for p47^{phox}, a subunit of NADPH oxidase.

The O₂⁻-production through the multi-protein enzyme NADPH oxidase plays a crucial role in fighting invading pathogens. Its activity is dependent on regulated assembly of six subunits, one of them being the p47^{phox} protein. p47^{phox} comprises a PX domain, two adjacent SH3 domains, a polybasic and a proline rich region. A single point mutation (R42Q) in the N-terminal PX domain causes hereditary Chronic Granulomatous Disease, an inability to kill certain ingested pathogens. Comparing wild-type and mutant biochemically we first discovered different behaviour towards proteases.

We carried out 5.0 ns molecular dynamics of wild-type p47^{phox} PX domain and the R42Q mutant. The mutant trajectory shows a strong tendency of the membrane insertion loop to be very mobile. This rearrangement supports the theory of the mutant leading to a miscommunication between the PX domain and the C-terminal end of the protein. Further molecular dynamics and mutational studies revealed more insights about specificity and consequences of the pathologic mutation.