Proton Transfer Assisted Disulfide Bond Isomerization in Bacterial Oxidoreductase

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nDsbD (N-terminal Disulfide Bond Oxidoreductase-D) is a disulfide bond redox enzyme essential in disulfide bond isomerization and hence the repair of the mispaired disulfide bond in bacteria. A widespread excepted mechanism for the functioning of the nDsbD is by the proton motive force (PMF) method.

Recently, the proton transfer reactions are found to play a crucial role in enzyme catalysis. These reactions are also capable in generating nucleophiles by means of proton transfer and are thus functional in catalysing the disulfide bond redox chemistry in proteins. [1,2] Thus, the possibility of an internal nucleophile, $Tyr_{42}O^-$ (by the proton transfer between Tyr_{42} and Asp_{68}), assisting disulfide bond rearrangement between the reduced nDsbD (nDsbDRed , Cys103/109 SH state) and its substrate DsbC could be a huge possibility.

Our recent studies [2,3] establish that together with $Tyr_{42}O^-$, a secondary internal nucleophile ($Tyr_{40}O^-$) is also conceivable via proton transfer between Tyr_{40} and Asp_{68}. It is also identified that the solvent plays a huge role in achieving the proton transfer and thereby facilitating the internal necleophile formation. It is also highlighted that stand alone DsbC can also be activated (disulfide cleavage) by nDsbDRed. [3] It is thus to be expected that an effective inhibition of bacterial growth cannot be achieved unless all possible routes for the disulfide bond cleavage in nDsbD are targetted.

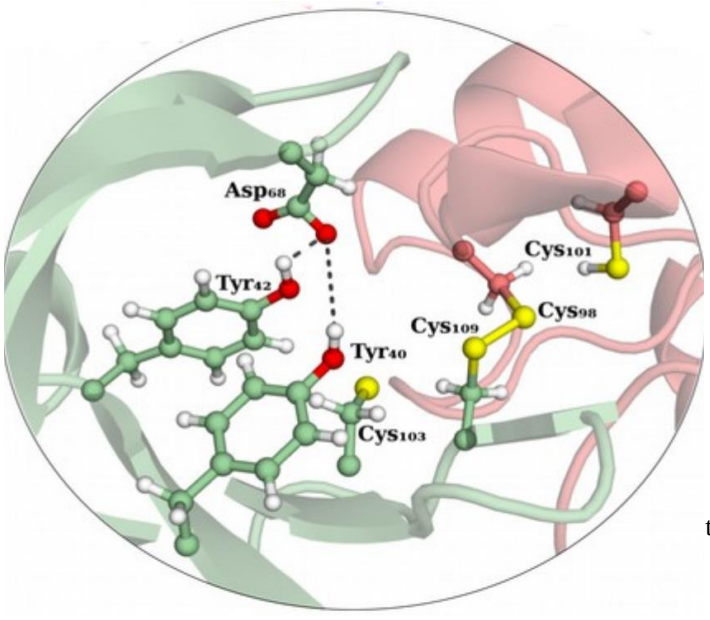

Figure 1. A schematic figure of Disulfide bond in nDsbD and the adjoining residues that could be a potential nucleophile for the Disulfide bond cleavage.

References

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3. A. G. Nair, D. S. Perumalla, P. Anjukandi, ChemPhysChem., e202200320 (2022).