Elucidating the specificity of STAT proteins recognition by dual-specificity phosphatases

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Kinases and phosphatases play complementary roles in maintaining an equilibrated balance between phosphorylated and unphosphorylated proteins within the cell. This equilibrium is of critical importance, and aberrations generally lead to the pathogenesis of numerous diseases, including cancer, diabetes, and immune deficiencies.
Negative regulation of the classical JAK/STAT signalling pathway can be exerted, e.g. via dephosphorylation of a C-terminal phosphotyrosine residue of activated (i.e. phosphorylated) STAT proteins by protein tyrosine phosphatases (PTPs).
In the recent years, it has been shown that members of the dual-specificity phosphatases (DSPs), a subfamily of the PTPs, exhibit enzymatic activity towards specific STAT protein partners: VHR specifically dephosphorylates STAT5 [1], whereas VH1 dephosphorylates both STAT1 and STAT2 but neither STAT3 nor STAT5 [2].
Mutational and kinetic experiments have provided first information about the existence of multiple interaction sites between these atypical DSPs and STAT factors [1]. However, there is up-to-date no structural explanation for the specific recognition of STAT proteins by these phosphatases.

Therefore, a combined approach of docking and MD simulations was developed, which allows to investigate the individual relevance of the different interaction sites formed between the phosphatases VHR and VH1 and their respective substrates STAT5 and STAT1. This approach did not only allow us to characterize these interactions, but it also provided us the basis for the specific recognition of STAT proteins by the dual specificity phosphatases. Briefly, these simulations reveal that the primary interactions formed at the active site of the phosphatase are highly similar for different ligands suggesting that they play only a minor role for binding specificity. In contrary, numerous specific interactions are formed within a second interface involving the SH2-domain of the STAT factors.

[1] R. Hoyt, W. Zhu, F. Cerignoli, A. Alonso, T. Mustelin and M. David. *J. Immunolog.*, **2007**, 179, 3402–3406.
[2] B.A. Mann, J.H. Huang, P. Li, H.C. Chang, R.B. Slee, A. O'Sullivan, M. Anita, N. Yeh, M.J. Klemsz, R.R. Brutkiewicz, J.S. Blum and M.H. Kaplan. *J. Interferon Cytokine Res.*, **2008**, 28, 367–380.