PAGE4 and Conformational Switching: Insights from Molecular Dynamics Simulations and Implications for Prostate Cancer

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1 Abstract

Prostate-Associated Gene 4 (PAGE4) is an intrinsically disordered protein (IDP) implicated in prostate cancer. The stress-response kinase Homeodomain-Interacting Protein Kinase 1 (HIPK1) phosphorylates two residues in PAGE4, serine 9 and threonine 51. Phosphorylation of these two residues facilitates the interaction of PAGE4 with Activator Protein-1 (AP-1) transcription factor complex to potentiate AP-1's activity. In contrast, hyperphosphorylation of PAGE4 by CDC-Like Kinase 2 (CLK2) attenuates this interaction with AP-1. Small-angle X-ray scattering (SAXS) and single molecule fluorescence resonance energy transfer (sm-FRET) measurements have shown that PAGE4 expands upon hyperphosphorylation and that this expansion is localized to its N-terminal half. To understand the interactions underlying this structural transition, we performed molecular dynamics simulations using Atomistic AWSEM, a multi-scale molecular model that combines atomistic and coarse-grained simulation approaches. Our simulations show that electrostatic interactions drive transient formation of an N-terminal loop, the destabilization of which accounts for the dramatic change in size upon hyperphosphorylation. Phosphorylation also changes the preference of secondary structure formation of the PAGE4 ensemble, which leads to a transition between states that display different degrees of disorder. Finally, we construct a mechanism-based mathematical model that allows us to capture the interactions of different phosphoforms of PAGE4 with AP-1 and its downstream target, the androgen receptor (AR) — a key therapeutic target in prostate cancer. Our model predicts intracellular oscillatory dynamics of HIPK1-PAGE4, CLK2-PAGE4, and AR activity, indicating phenotypic heterogeneity in an isogenic cell

population. Thus, conformational switching of PAGE4 may potentially affect the efficiency of therapeutically targeting AR activity[1].

References

[1] X. Lin, S. Roy, M. K. Jolly, F. Bocci, N. P. Schafer, M.-Y. Tsai, Y. Chen, Y. He, A. Grishaev, K. Weninger, J. Orban, P. Kulkarni, G. Rangarajan, H. Levine, and J. N. Onuchic. PAGE4 and Conformational Switching: Insights from Molecular Dynamics Simulations and Implications for Prostate Cancer. *Journal of Molecular Biology*, June 2018.