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Physical principles of phase-separation action on chromatin looping associated to pathogenic gene activation

Phase separation of chimeric proteins resulting from genetic mutations has been shown to trigger aberrant chromatin looping, contributing to disease development, including cancer [1]. However, the physical mechanisms regulating these processes remain unclear. In this study, we employ polymer physics models of chromatin to investigate the relationship between protein self-aggregation and chromatin structure [2]. We show that a simple model, including only protein-protein and protein-chromatin interactions, effectively explains the aberrant looping around certain oncogenes in cells expressing the NUP98-HOXA9 chimera [1], commonly found in leukemia. Moreover, when incorporating the presence of cohesin in a more complex model [3], similar results are observed, suggesting a weak dependence of this looping mechanisms from loop-extrusion. Finally, leveraging on our numerical simulations, we compare our findings with experimental data [1] and show that the phase-separation property of chimera can be harnessed to prevent enhancer-gene contacts, thereby offering a potential strategy for cancer prevention.

[1] J. H. Ahn et al., “Phase separation drives aberrant chromatin looping and cancer development”. Nature 595, 591-595 (2021).

[2] A. M. Chiariello et al., “Polymer physics of chromosome large-scale 3D organisation”. Sci. Rep. 6, 29775 (2016).

[3] M. Conte et al., “Loop-extrusion and polymer phase-separation can co-exist at the single-molecule level to shape chromatin folding”. Nat. Comm. 13, 4070 (2022).

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