Protamine-Controlled Reversible DNA Packaging: A Molecular Glue

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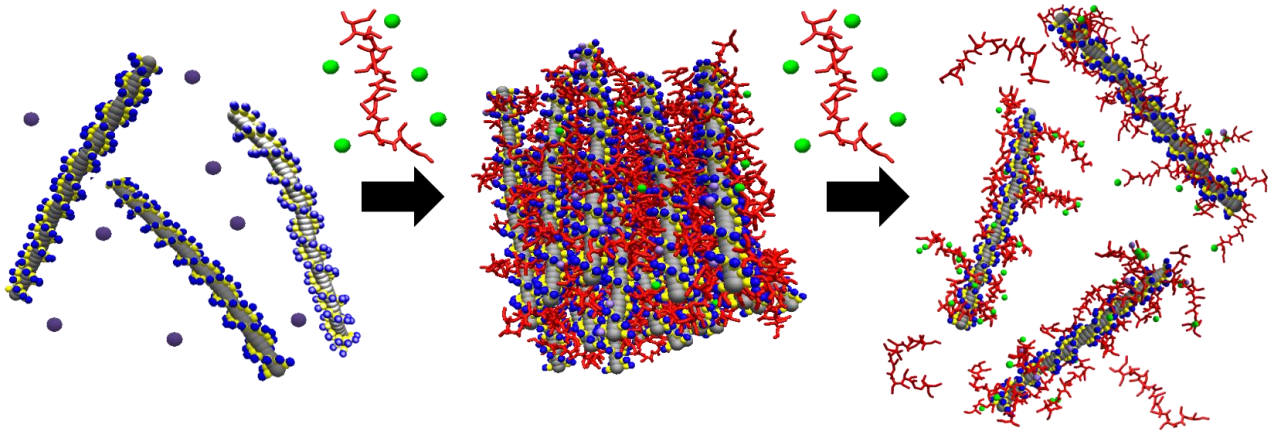
While DNA is one of the longest and the stiffest molecules in nature and is negatively charged, they are strongly condensed in a tiny space of cell nuclei. DNA undergo precise cycles of even stronger condensation and de-condensation during cell division or in sperm cells. Packaging paternal genome into tiny sperm nuclei during spermatogenesis requires 10^6-fold compaction of DNA, corresponding to a 10-20 times higher compaction than in somatic cells. Understanding and simulating the molecular-level principles underlying such fascinating and dynamic processes would not only bring us one step closer to the origin of life but also have applications in various other fields such as medicine, materials, and energy. However, while protamine, a small arginine-rich basic protein, is known to participate in such a high level of compaction, the precise mechanism at play is still unclear. In a series of our work,[1-2] effective pair potential calculation and large-scale molecular dynamics simulation using a simple idealized model incorporating solely electrostatic and steric interactions clearly demonstrate a reversible control on DNA condensates formation by varying the protamine-to-DNA ratio. Microscopic states and condensate structures occurring in semi-dilute solutions of short DNA fragments are in good agreement with experimental phase diagram and cryoTEM observations. The reversible microscopic mechanisms induced by protamination modulation should bring valuable information to improve a mechanistic understanding of early and intermediate stages of spermatogenesis where an interplay between condensation and liquid-liquid phase separation triggered by protamine expression and post-translational regulation might occur. Moreover, recent vaccines to prevent virus infections and cancers using protamine as a packaging and de-packaging agent might be fine-tuned for improved efficiency using protamination control.



1. Mukherjee, A.; de Izarra, A.; Degrouard, J.; Olive, E.; Maiti, P. K.; Jang, Y. H.; Lansac, Y. Protamine-Controlled Reversible DNA Packaging: A Molecular Glue. *ACS Nano* 15**,** 13094–13104 (2021).
2. Lansac, Y.; Degrouard, J.; Renouard, M.; Toma, A. C.; Livolant, F.; Raspaud, E. A Route to Self-Assemble Suspended DNA Nano-Complexes. *Sci. Rep.* 6, 21995 (2016)