Stimuli-responsive DNA-Based Nanodevices programmed by Purely Entropic Linker Domains

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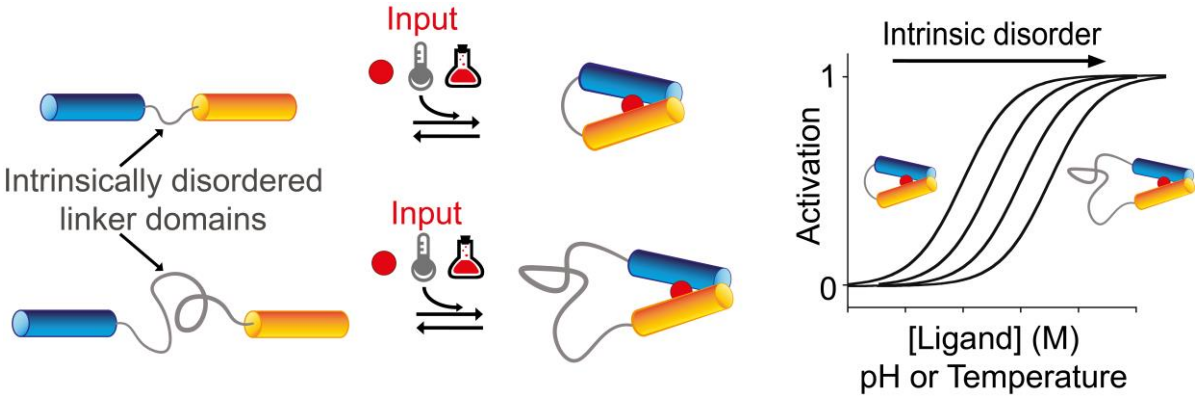
Herein, we present a generalizable and versatile strategy to program stimuli-responsive properties of synthetic DNA nanodevices in which the capacity of the receptor to respond to a specific ligand or an environmental input (e.g., pH or temperature) can be finely modulated by controlling the entropy associated with the linker connecting the ligand-binding or pH-responsive domains.[1,2] To do so, we have re-engineered two model DNA-based receptors and a set of pH-responsive nanodevices. Specifically, as receptors we used a triplex clamp DNA-based receptor that recognizes a specific DNA sequence and an ATP-binding aptamer; and as pH-responsive nanodevices we used the formation of an intramolecular triplex structure through hydrogen bonds (Hoogsteen interactions) between a hairpin duplex domain and a single-strand triplex-forming domain. We show that, by varying the length of the linker domain that connects the two ligand-binding or pH-responsive domains of these receptors, it is possible to: 1) finely control their affinity for their specific ligand;[1] 2) modulate their observed acidic constant (pK_a), therefore, their pH-dependence;[2] 3) program their thermos-responsive properties in order to release a specific molecular ligand at a defined temperature. Through mathematical modelling, thermodynamic and kinetic characterization, we demonstrate that the modulation of stimuli-responsive properties of the receptors results dependent on the total entropy associated with changes in linker length. Furthermore, the length of the linker does not affect the efficiency of the receptors during their loading/release process or binding. The possibility to rationally design stimuli-responsive DNA nanodevices using purely entropic domains can be of utility in applications such as biosensing, drug delivery, and production of smart materials in which the modulation of these systems could be obtained through a versatile, precise, predictable, and tunable approach.

References

[1] Mariottini D., Idili A., Nijenhuis M. A., de Greef T. F., Ricci F. *J. Am. Chem. Soc.*, 140 (**2018**), 14725-14734.
[2] Mariottini D., Idili A., Nijenhuis M. A., Ercolani G., Ricci F. *J. Am. Chem. Soc.*, 141 (2019), 11367-11371.

Figure



Stimuli-responsive properties of biomolecular receptors toward a specific input is strictly related to the presence of intrinsically disordered regions. With a higher entropic cost associated with the intrinsically disordered linker that connects two responsive domains, for example, a lower activation of the receptor for the same input will be observed. This mechanism is employed by Nature to dynamically control proteins function through the modulation of the entropy.