Regulation of Gene Expression by Inhibition of B-Z Transition

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DNA is generally stored in the nucleus as canonical right-handed B-DNA conformation. Due to flexibility, B-DNA can flip into left-handed Z-DNA confirmation depending on the surrounding environment. The Z-DNA formation in some gene was proposed to involve in the regulation of gene expression.[1] Hence gene expression can be controlled by inhibition of B-Z transition and such studies have not been reported yet. Here, we used DNA binding pyrrole–imidazole polyamide (PIP) as a regulatory molecule for controlling B-Z transition.

PIPs are a class of synthetic molecules composed of *N*-methylpyrrole unit and *N*-methylimidazole unit that can bind to the minor groove of the B-DNA in a sequence selective manner. Due to its high binding affinity and sequence selectivity, we considered that the formation of the B-DNA–PIP complex can inhibit the B-Z transition. Based on this hypothesis, we designed PIP1 and PIP1-R_3 targeting the (TG) repeat sequence where B-Z transition is known to occur (Figure 1). The PIPs were synthesized by Fmoc solid-phase synthesis and to improve the cellular uptake, we conjugated PIP1 with three arginine residues (PIP1-R_3).[2] To confirm the inhibition of Z-DNA formation RT-qPCR was performed and the results showed the suppression of the target gene by PIP1-R_3.

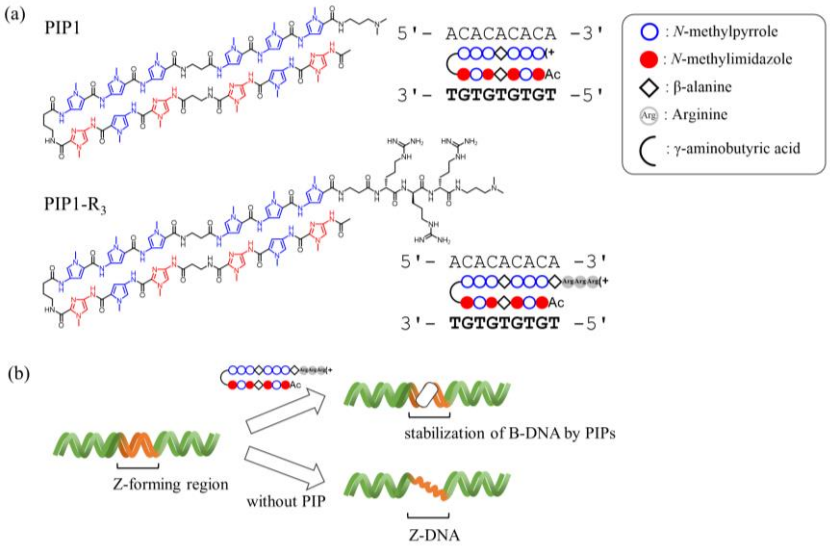

Figure 1. (a) Chemical structures of PIPs. (b) Mechanism of inhibition of B-Z transition by using PIP.

1) J. Zhang, *et. al.*, *Mol. Cell. Biol.*, **2006**, *26*, 7942.
2) T. Hidaka, *et. al.*, *Chem. Commun.*, **2020**, *56*, 12371.