Sequence-Specific DNA Alkylation by a Chlorambucil-Conjugated Cyclic Pyrrole–Imidazole Polyamide

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DNA alkylating agents, such as nitrogen mustard analogs and duocarmycin derivatives, form covalent bonds with DNA and inhibit DNA replication and cell proliferation. While some DNA alkylating agents have been used as anticancer agents taking advantage of their high cytotoxicity, side effects due to non-specific alkylation have been a problem. In order to solve this problem, sequence-specific DNA alkylating agents have been developed by conjugating DNA alkylating agents to pyrrole–imidazole polyamides (PIPs), which bind to DNA in a sequence-specific manner.

In this study, we conjugated DNA alkylator chlorambucil (Chb) to a cyclic PIP (cPIP)[1], which is known to have a higher DNA-binding affinity than a well-studied hairpin PIP (hPIP), and we evaluated its alkylating property. Capillary electrophoresis using long DNA strands and HPLC product analysis using short DNA fragments indicated that a cPIP–Chb selectively alkylated the N3 position of purine bases around the target sequences with higher DNA alkylation activity than hPIP–Chbs. Besides, cytotoxicity assays using LNCaP prostate cancer cells showed that cPIP–Chb exhibited cytotoxicity comparable to that of hPIP–Chb.[2] While some issues, such as side effects and working mechanisms, need to be clarified, these results indicated the potential of cPIP–Chbs for anticancer drug applications.

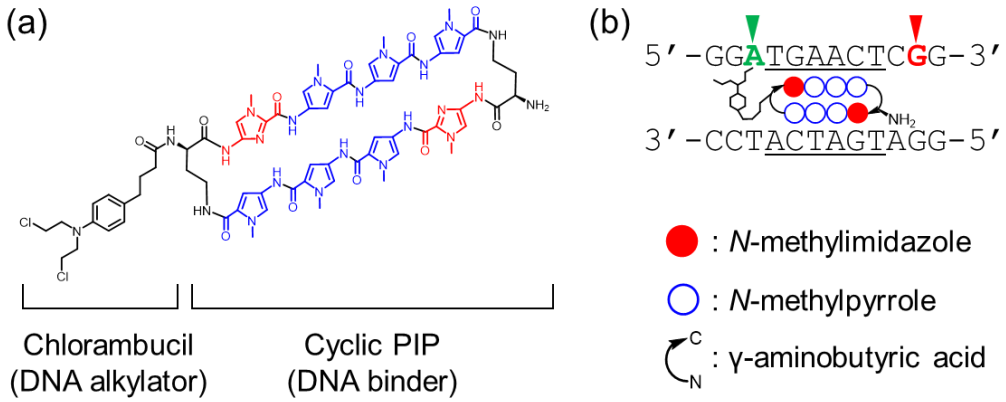

Figure 1. (a) The chemical structure of cPIP–Chb. (b) One of the alkylation sites of cPIP–Chb.

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2) Y. Hirose, K. Hashiya, T. Bando, H. Sugiyama, *Chem. Eur. J. in press.*