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Recognition of DNA abasic site nanocavity by fluorophore-switched probe: Suitable for all sequence environments

Ying Wang, Yuehua Hu, Tao Wu, Lihua Zhang, Hua Liu, Xiaoshun Zhou, Yong Shao *

Institute of Physical Chemistry, Zhejiang Normal University, Jinhua 321004, Zhejiang, People's Republic of China

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ABSTRACT

Removal of a damaged base in DNA produces an abasic site (AP site) nanocavity. If left un-repaired in vivo by the specific enzyme, this nanocavity will result in nucleotide mutation in the following DNA replication. Therefore, selective recognition of AP site nanocavity by small molecules is important for identification of such DNA damage and development of genetic drugs. In this work, we investigate the fluorescence behavior of isoquinoline alkaloids including palmatine (PAL), berberine (BER), epiberberine (EPI), jatrorrhizine (JAT), coptisine (COP), coralyne (COR), worenine (WOR), berberrubine (BEU), sanguinarine (SAN), chelerythrine (CHE), and nitidine (NIT) upon binding with the AP nanocavity. PAL is screened out as the most efficient fluorophore-switched probe to recognize the AP nanocavity over the fully matched DNA. Its fluorescence enhancement occurs for all of the AP nanocavity sequence environments, which has not been achieved by the previously used probes. The bridged π conjugation effect should partially contribute to the AP nanocavity-specific fluorescence, as opposed to the solvent effect. Due to the strong binding with the AP nanocavity, PAL will find wide applications in the DNA damage recognition and sensor development.

1. Introduction

In living cells, the removal of a damaged base in DNA by specific enzymes produces an abasic site (AP site) nanocavity [1–7]. This site is a vacant site that is surrounded by the nearby nucleotides with its size in the range of about 1 nm. Thus, a nanocavity leaves for the subsequent biological process. DNA mutation can occur because of the nanocavity being un-repaired by the functional enzymes [6,8–11]. The level of this AP nanocavity can thus serve as one of general biomarkers for quantifying DNA damages [12]. Therefore, developing a selective recognition method for the AP nanocavity is critical to identify such the DNA damage level and to further explore the AP-targeted therapeutic drugs [13,14] and sensors [15–20].

Although some methods use fluorescent surrogates that have been covalently incorporated into the opposite position to sense the presence of the AP nanocavity [21–25], tedious synthesis procedures must be needed for such the DNA invasive modification and the case-dependent modification applied for a specific sequence limits its wide applications. Fluorescent materials that can perfectly fit the size and binding property of the AP nanocavity provide a more straightforward means to selectively target such site by a non-covalent manner and have promising applications in cell imaging. Recently, a novel detection method for single-nucleotide polymorphism (SNP) in the target strand has been established by introducing an AP nanocavity in the complementary probe strand. Some organic [26–33] and inorganic [34,35] fluorophores can enter into the AP nanocavity with a SNP-dependent fluorescence response. On the other hand, these probes would be otherwise directly used in the AP nanocavity recognition. However, some nonradiative processes within the excitation state of the AP nanocavity-bound fluorophores, such as collision with the nearby nucleotide environment and electron transfer with the nearby nucleotide, severely quench the fluorescence [26,27]. This usually suffers from a turn-off fluorescence response and there is still an open challenge in finding an ideal probe with a turn-on fluorescence response upon the AP nanocavity binding, namely the fluorophore-switched probe (FSP), especially which can operate for all of the sequence environments.

Thus, special efforts have been made in finding efficient fluorophores that have the AP nanocavity binding-favored fluorescence properties in competition with the nonradiative processes and give a switch-on fluorescence recognition. In this aspect, solvatochromicity [28], isomerity [29,30], excited-state intramolecular proton transfer (ESIPT) [32], and molecular rotor [33] have been found as the main mechanisms in achieving the lighting-up fluorescence responses for the AP nanocavity binding. However, the FSP that has a high selectivity and significant fluorescence enhancement in response to the AP nanocavity binding is still a challenge. In particular, for the case with guanine flanking the AP nanocavity, electron transfer-induced fluorescence quenching is usually resulted since guanine is the most easily oxidizable base in DNA. In order to overcome this drawback, recently, we found that silver nanoclusters can be in situ grown at the AP nanocavity, but serve as an emitter only for the case with guanine as the flanking

* Corresponding author.
E-mail address: yshao@zjnu.cn (Y. Shao).

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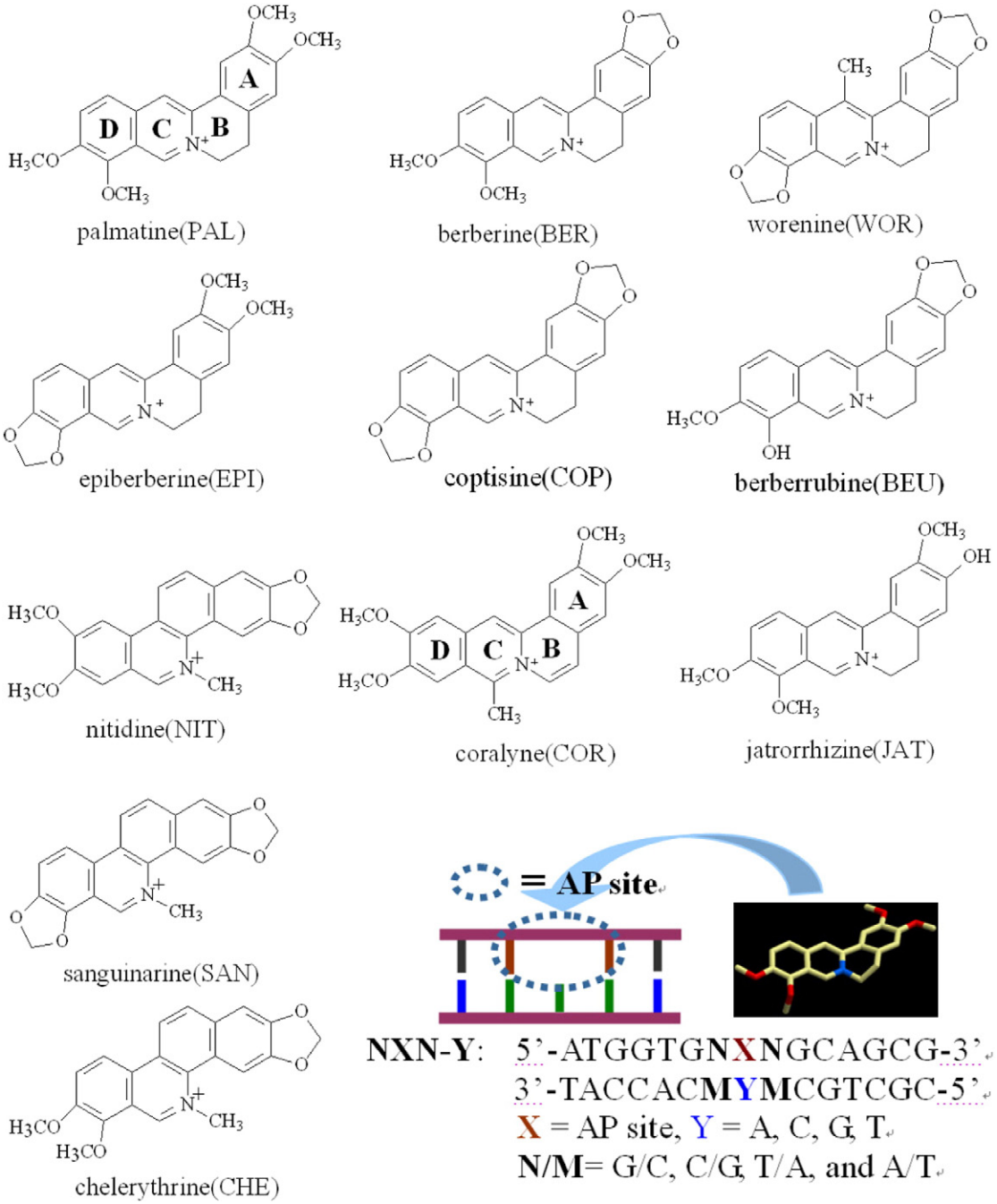
base [34,35]. Moreover, we also found that matching of the excited state energy level with that of guanine is also likely the other rationalization in favoring the bound organic ligand as the emitter [36]. In this work, we attempted to screen out a fluorophore ligand from the group of isoquinoline alkaloids (Scheme 1) that can sense the AP nanocavity by a switch-on fluorescence response. The ligand has a high binding selectivity that is independent on the types of the sequences nearby the AP site on the basis of our previously primary understanding in the binding of some isoquinoline alkaloids with the AP nanocavity [29,30]. Various biological and therapeutic activities have been found for isoquinoline alkaloids and their binding with nucleic acids is believed to be the main contributor in exerting their bio-activity [29,30,37,38]. Herein, palmatine (PAL) was identified as the most efficient FSP in selectively targeting the AP nanocavity. We rationalize that the activated fluorescence of PAL most likely results from the bridged π conjugation of the alkaloid macro-cycle.

2. Experimental

2.1. Materials and reagents

DNA species (Scheme 1) were synthesized by TaKaRa Biotechnology Co., Ltd (Dalian, China) and purified by HPLC. A tetrahydrofuran residue was used as the chemically stable abasic site (AP site) for replacement of the naturally-occurred unstable deoxyribose structure. The DNA concentrations were measured by UV absorbance at 260 nm using extinction coefficients calculated by the nearest neighbor analysis. BER, SAN, PAL, CHE, COR (Sigma Chemical Co., St. Louis, USA), COP, NIT, JAT



Scheme 1. Structures of investigated isoquinoline alkaloids (IAs) and the used DNA sequences containing the AP nanocavity (dotted circle).