GENOME-TARGETED DRUG DESIGN: UNDERSTANDING THE BLEOMYCIN-DNA INTERACTION

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Abstract: Knowledge of the sequence of the human genome has provided significant opportunities to exploit DNA as a target in the rational design of therapeutical agents. Bleomycins are glycopeptide antibiotics produced by the bacterium Streptomyces verticillus. These substances bind and cleave DNA which is also believed to be the basis of their anticancer properties. In general, the BLM structure consists of a positively charged bithiazole C-terminal tail, a methylvalerate-thr linker, a metal-binding domain, and a disaccharide moiety. The methylvalerate-thr linker connects the bithiazole tail to the metal-binding domain and the metal-binding domain is attached to the disaccharide moiety, which completes the bleomycin (BLM) structure. BLM A2 and B2 are the primary therapeutic forms used in cancer treatment. X-ray crystal studies have shown that both BLM A2 and B2 bind to DNA in two different binding modes. In the fully bound mode, all structural moieties of BLM interact with DNA. In the partially bound mode, BLM appears to partially bind to the DNA such that only the C-terminal bithiazole tails are observed to interact with nucleic acid. Structural modeling studies revealed that the conformation of BLM in the fully bound mode is determined by intramolecular H-bonds between the methylvalerate-thr linker, the metal-binding domain, and the disaccharide moiety. This conformation interacts with the DNA minor groove via intermolecular H-bonds, allowing the linker, metal-binding domain, and the disaccharide moiety to sit in the minor groove. The bithiazole tail protrudes from the minor groove through the GC/TA base-pair wall into the larger major groove, where it exhibits a high level of solution flexibility. In order to better understand the interactions between DNA and BLM and the two BLM binding modes, molecular dynamics simulations were carried out on the following DNA/BLM A2 complex: BLM A2/d(CTTAGTTAGC)2. The starting structure for the simulation consisted of BLM A2 bound to the DNA sequence such that all moieties were interacting with DNA. Understanding the details of the BLM/DNA interaction is a necessary first step in developing strategies for its modification into more specific DNA binding agents.

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