Electrostatic potential and binding of drugs to the minor groove of DNA

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The use of solid constructive geometry and color coding of electrostatic potential provides a clear distinction between the minor grooves of DNA with distinct sequences. The predicted differential binding of oxidized and reduced forms of ligands to the DNA grooves is proposed as a means of introducing tumor selectivity.

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The discovery of oncogenes has opened up a logical avenue to cancer chemotherapy. In principle it should be possible to design drugs that will recognize the oncogene DNA sequence and then switch off the gene by methylation or by preventing transcription. Encouragement to follow this logic is provided by the existence of naturally occurring molecules, the "lexitropsins," which bind in a highly specific way to the minor groove of A–T rich sequences of B–DNA.[1–5] To design a molecule to recognize a specific DNA sequence, an ideal starting point is the electrostatic potential in the groove of the DNA, so that complementary molecules can be constructed. Although it is relatively easy to calculate the electrostatic potential, it is less simple to display it in a manner that can be assimilated easily. Here we provide a display that encodes the computed potential on the molecular surface in a way simple enough for molecular features to be recognizable, yet subtle enough for the chemical properties of the molecules to be highlighted. The differential binding of oxidized and reduced forms of ligands to the DNA grooves, suggested by inspection of these displays, is proposed as a means of introducing tumor selectivity.

METHODS

The DNA structure was generated in the physiologically preferred B–DNA form using idealized coordinates;[6] counter ions (Na^+) were situated at the bisection of the phosphate groups. The electrostatic potential indicates the interaction energy between a molecule and a unit positive charge, assuming that the molecule is not perturbed by the unit charge; it is therefore a reasonable indicator of the reactivity of the molecule with electrophilic reagents. The electrostatic potential was generated on the surface of the DNA using the point-charge approximation. The individual atomic point charges were generated from *ab initio* molecular orbital calculations and were derived so as to reproduce the *ab initio* electrostatic potential of DNA at distances between 1.2 and 1.8 times the van der Waals radii.[7,8] The potential values were mapped on to the molecular surfaces formed by taking atoms with radii 20% and 80% larger than the van der Waals radii. These distances represent a reasonable compromise between the need for accuracy from the point-charge approximation and the desire to produce an image that leaves the chemical structure discernible at the atomic level. Color Plates 1–4 show views of poly(dA)–poly(dT) and of poly(dG)–poly(dC) for the two choices of atomic radii, looking at the minor groove of a nine base-pair sequence. (The major groove is also visible at the top left of each display.)

The graphic images were created using the Constructive Solid Geometry method.[9,10] Electrostatic potential values were calculated at points on a three-dimensional rectangular grid enclosing the DNA molecule, with grid spacing corresponding to intervals of approximately 0.5Å. Values outside this area were assumed to be zero. For each point on the molecular surface, the potential value was derived by linear interpolation from the neighboring grid points. Values were mapped on to seven colors ranging in spectral order from red (negative), through orange, yellow, green (neutral), cyan, blue and violet (positive) and covering a range of -0.2 to +0.2 atomic units.

RESULTS AND DISCUSSION

From the color figures a number of features of DNA chemistry are clearly highlighted. Most obviously, the minor groove of the model poly(dA)–poly(dT) has a much more negative electrostatic potential than the minor groove of poly(dG)–poly(dC), due particularly

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to the NH2 group on C–2 of guanine. This observation is in conformity with the preference of lexitropsins such as netropsin or distamycin (which carry positive charges, or partial positive charges, in the form of hydrogen bond donating groups) for the minor groove of A–T rich regions of DNA.

The chemistry of certain N-nitroso alkylating agents is also explained. Although the exact nature of the alkylating agent is not known,[11] it is electrophilic in nature, and a preference is shown for sites in the minor groove on adenine or thymine over those on cytosine or guanine.[12] For the major groove the affinity for adenine–thymine is reversed. Although cytosine is not alkylated, guanine is the major alkylation site, with N–7 preferred over O^6. This is clearly explained from the displays where cytosine has a neutral potential, with the potential becoming more negative through O^6 to N–7.

Some of the lexitropsins, however, do not appear to bind primarily electrostatically, and more complex potentials may be required. It is possible to use this display procedure for interaction potentials such as those generated by GRID,[13] which includes repulsion, dispersion and hydrogen bonding potentials for specific probes. For comparative purposes, however, the present figures already provide sufficiently clear detail to enable the design of molecules that mirror the DNA potential; these highly sequence-specific probes might be the first step toward switching off oncogenes as a form of cancer chemotherapy.

While this may be a long-term goal, a new possibility for targeting cancer cells is apparent from the displays. The ability of the minor groove to bind hydrogen bond donating groups, such as -OH, has already been noted. It is implicit in this observation that hydrogen bond acceptors, such as carbonyl groups, will have a repulsive interaction. Thus, for groove binding ligands containing quinone-type structures, a reduction of the quinone moiety to a hydroquinone could create an active ligand, whereas the quinone form would not be active. Such ligands could bind to the groove in the reducing conditions of solid tumors, which are frequently oxygen deficient,[14] but would be inactive in normal cells. This strategy has already been proposed for designing tumor-selective dihydrofolate reductase inhibitors[15] — its extension to DNA, as suggested by the displays, is another way of introducing selectivity into anti-cancer drugs.

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