Metallobleomycins: Oxidative Cleavage of Nucleic Acids

Marjorie Ang Literature Seminar March 4, 1997

Because cancer remains as the leading cause of death in America, there is a growing need for the discovery and development of potent anticancer drugs. One example is bleomycin (BLM, Figure 1), which was isolated from the fungus *Streptomyces verticillus* in 1966,[1] and is used in combination chemotherapy as metalloBLM's, despite its toxic side-effects on tested animals.[2] Currently, iron- and cobalt-BLM's are most widely understood.

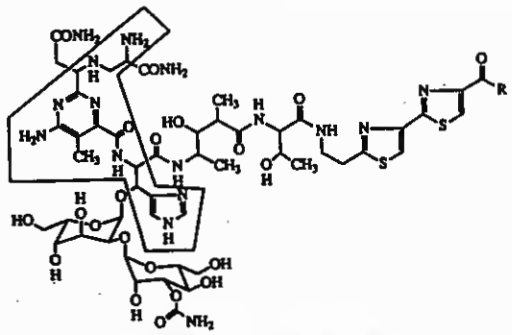

Figure 1. BLM

Initial chemical degradation studies have indicated that BLM consists of three domains,[3] DNA-binding, tumor cell localization, and metal-binding (boxed region in Figure 1); inorganic chemists have placed an emphasis on studying this latter domain. By comparing Fe(II)BLM to synthetic analogs,[4] various spectroscopic techniques such as UV-Vis,[5] low-temperature MCD,5 Resonance Raman,[5] EPR,[4,6] and XAS[5] have been used to characterize the metal oxidation and spin states, ligand-field environment, coordination number, and geometry. In this complex, Fe(II) is high-spin with a square-pyramidal geometry, containing an open-coordination site for dioxygen activation. Backbonding occurs as a result of a Fe(II) d Æ π^* (pyrimidine) charge transfer band, and accounts for its reactivity. The N-donor ligands consist of the pyrimidine, imidazole, and b-aminoalanine (A) moieties. Combining these results has led to the proposed structure for Fe(II)BLM, which coincides with the single known x-ray crystal structure of a BLM-biosynthetic precursor, Cu(II)(P-3A) (Figure 2).[3,7]

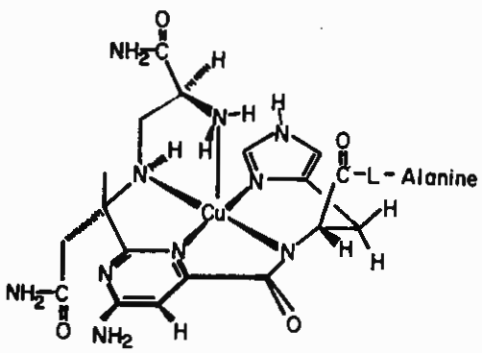

Figure 2. Cu(II)(P-3A)

Disagreement exists, however, on the identity of the axial ligand. While the Cu(II)(P-3A) structure and supporting spectroscopic evidence point toward the A moiety's primary amine group as the ligand, NOESY spectra and comparison of proton-solvent exchange rates between Co(III)-pepleomycin(PEP) with Co(III)deglycoPEP as diamagnetic structural probes by Wang and coworkers[8] conclude that the axial ligand is the carbamoyl nitrogen of a-D-mannose.

Activation of iron-bleomycin can occur by two pathways (Figure 3),[9] which are identical to the proposed catalytic cycle for cytochrome P-450 (Figure 4).[10] Although, both systems are able to catalyze various organic oxidation reactions,[11] there is a lack of evidence to support the presence of a ferryl-oxo species in FeBLM by Mössbauer,[12] XAS,[13] EPR,[6,14] and ESI-MS[15] studies; instead a low-spin ferric hydroperoxo BLM has been determined to be the active intermediate. Further NMR studies showing cleavage products[16] and intercalation into the DNA minor groove via the bithiazole moiety[17] have led to a proposed mechanism for DNA degradation. Finally, strand scission is enhanced with the 2'-amino group of guanine as a recognition element; cleavage preferentially occurs between 5'-guanine-purine-3' sites on the double helix.[18]

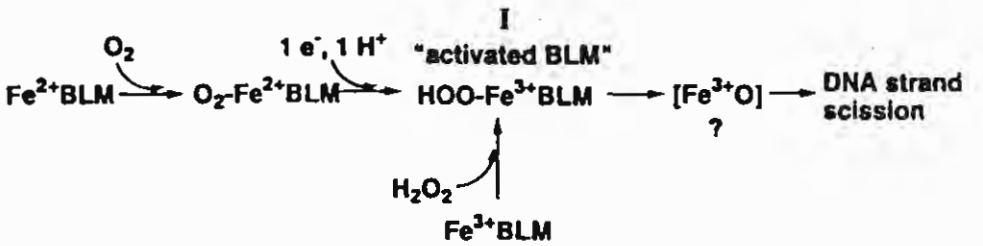

Figure 3. Fe(II)- and Fe(III)-BLM activation

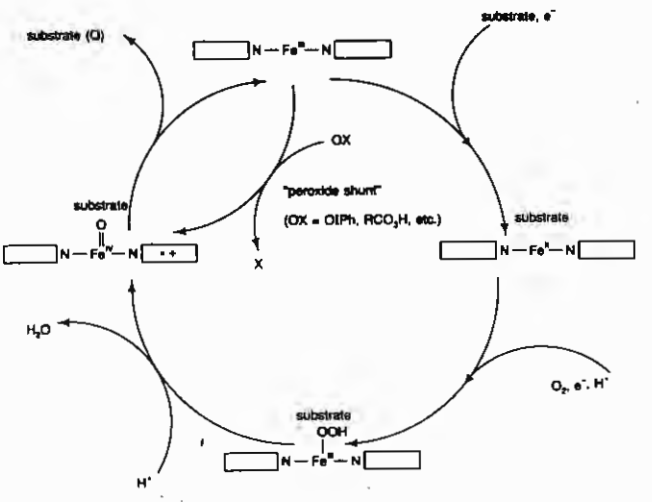

Figure 4. Catalytic Cycle of Cytochrome P-450

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