Targeting DNA Mismatches with Rhodium Intercalators Functionalized with a Cell-Penetrating Peptide†

Jens Brunner and Jacqueline K. Barton*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received June 15, 2006

Revised Manuscript Received August 10, 2006

Abstract:

Cell-penetrating peptides are widely used to deliver cargo molecules into cells. Here we describe the synthesis, characterization, DNA binding, and cellular uptake studies of a series of metal-peptide conjugates containing oligoarginine as a cell-penetrating peptide. D-Octaarginine units are appended onto a rhodium intercalator containing the sterically expansive chrysenequinone diimine (chrysi) ligand to form $Rh(chrysi)(phen)(bpy)^{3+}$-tethered oligoarginine conjugates, where the peptide is attached to the ancillary bpy ligand; some conjugates also include a fluorescein or thiazole orange tag. These complexes bind and with photoactivation selectively cleave DNA neighboring single-base mismatches. The presence of the oligoarginines is found to increase the nonspecific binding affinity of the complexes for both matched and mismatched DNA, but for these conjugates, photocleavage remains selective for the mismatched site, as assayed using both gel electrophoresis and mass spectrometry experiments. Significantly, the rhodium complex does not interfere with the delivery properties of the cell-penetrating peptide. Confocal microscopy experiments show rapid nuclear localization of the metal-peptide conjugates containing the tethered fluorescein. Mass spectrometry experiments confirm the association of the rhodium with the HeLa cells. These results provide a strategy for targeting mismatch-selective metal complexes inside cell nuclei.