DNA mismatch-specific targeting and hypersensitivity of mismatch-repair-deficient cells to bulky rhodium(III) intercalators

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Mismatch repair (MMR) is critical to maintaining the integrity of the genome, and deficiencies in MMR are correlated with cancerous transformations. Bulky rhodium intercalators target DNA base mismatches with high specificity. Here we describe the application of bulky rhodium intercalators to inhibit cellular proliferation differentially in MMR-deficient cells compared with cells that are MMR-proficient. Preferential inhibition by the rhodium complexes associated with MMR deficiency is seen both in a human colon cancer cell line and in normal mouse fibroblast cells; the inhibition of cellular proliferation depends strictly on the MMR deficiency of the cell. Furthermore, our assay of cellular proliferation is found to correlate with DNA mismatch targeting by the bulky metallointercalators. It is the Δ-isomer that is active both in targeting base mismatches and in inhibiting DNA synthesis. Additionally, the rhodium intercalators promote strand cleavage at the mismatch site with photoactivation, and we observe that the cellular response is enhanced with photoactivation. Targeting DNA mismatches may therefore provide a cell-selective strategy for chemotherapeutic design.