

CATALYTIC METALLODRUGS AS INORGANIC INHIBITORS OF VIRUS REPLICATION

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Our laboratory has developed the conceptual framework for, and sought experimental validation of, the use of catalytic metallodrugs as a novel antiviral strategy. Irreversible inactivation of structured target RNAs or proteins has been demonstrated for aminoglycoside and peptide molecules that include both a metal binding domain (to catalyze oxidative degradation of RNA or protein) and a target recognition domain. While such molecules may retain classical inhibitory properties, they can also mediate catalytic degradation of the drug target. Multiple turnover affords the potential for sub-stoichiometric administration of a drug, with the promise of a significant lowering of dosage and a commensurate decrease or elimination of side effects or toxicity. Improved selectivity is a consequence of a double-filter mechanism that reflects a need for not only target recognition, but also an appropriate orientation of the catalytic metal center to promote chemical inactivation. The implications of this novel mode of action for the emergence of drug resistance will also be discussed as these concepts are illustrated through studies of metallopeptide-promoted oxidation of HIV RRE RNA and protease, as well as HCV IRES RNA and protease. Studies with scavengers of reactive oxygen species and product characterization implicate hydrogen peroxide as a reaction intermediate, prior to formation of a copper-bound hydroxyl radical that promotes oxidation of ribose rings for RNA, and amino acid sidechains in the case of protein targets, respectively. Observation and determination of Michaelis-Menten kinetic profiles and parameters have established the “enzyme-like” nature of such catalysts, while a robust kinetic/thermodynamic understanding of the structural basis for recognition and reactivity has provided insights on how to improve catalyst performance. Results from solution studies are supported by cellular luminescence reporter assays, and studies with HCV replicons suggest at least an additive effect of one antiviral candidate with interferon alpha.