Cancer, Diabetes, Malaria and Tuberculosis: new strategies for drug development

by Michael Groll

Center for Integrated Protein Science, Department of Chemistry, Technische Universität München

Abstract:

The proteasome, a large protein complex, plays a key role by breaking down used proteins for recycling. New hope was spawned several years ago with the discovery that inhibiting proteasomes can be used as a means to put the brakes on cell growth. Tripeptide aldehydes such as calpain inhibitor I (Ac-Leu-Leu-Nle-H) and leupeptin from actinomycete (Ac-Leu-Leu-Arg-H) were the first identified class of proteasome inhibitors. Meanwhile, analysis of diverse other functional electrophiles such as boronates, vinyl sulfones, and natural product-based α',β'-epoxyketones provide further insights into their various binding modes to the proteasomal active sites [1]. Interestingly, peptide boronates were found to be much more potent inhibitors than aldehydes and vinyl sulfones. Low concentrations of boronate compounds are sufficient for significant inhibition of proteasome activity, and due to their high selectivity and low dissociation rates, this class of compounds has been used in various medical research programs and clinical experiments. The successful dipeptide boronate candidate bortezomib has now been approved as prescriptive drug for treatment of relapsed and/or refracted multiple myeloma. However, bortezomib's boronic acid pharmacophore has been shown to produce substantial off-target activity by reacting with additional enzymes which translates to severe side effects. Not surprisingly, competitive products have been developed with increased in vivo specificity such as the natural compound salinosporamide A and carfilzomib, a synthetic tetrapeptide α',β'-epoxyketone, which is currently being evaluated for the treatment of multiple myeloma, non-Hodgkin's lymphoma, and solid tumors.

In this representation, I will focus on our recently identified mode of action of peptidyl α-ketoaldehydes as promising novel lead structure for drug design [2]. Although these compounds have been well established as proteasome inhibitors long time ago, elucidation of their molecular binding mode was necessary to explain the high selectivity and specificity for the protease. The crystal structure of the proteasome:ketoaldehyde complex revealed a cyclization mechanism that proceeds through hemiketal and Schiffbase formation of the ligand with the nucleophilic N-terminal threonine resulting in a reversible 5,6-dihydro-2H-1,4-oxazine ring. Interestingly, peptidyl glyoxal and the natural α',β'-epoxyketon peptide epoxomicin follow a similar bivalent mode of action via a six-membered ring formation, however, there exist a profound difference in the reversibility of the keto-aldehyde peptide: epoxomicin and carfilzomib form a irreversible secondary amine by morpholine-ring cyclization, thus, demonstrating high cellular cytotoxicity, which is in contrast to the oxazin-ring formation of the bound α-keto-aldehyde peptide. Furthermore, peptidyl glyoxals are hydrated in aqueous solution and therefore carry a much weaker functional reactive group compared to α',β'-epoxyketone and aldehyde-peptides. Based on the novel and specific mode of action of α-keto-aldehyde peptides, we expect that this agent might serve as a novel lead for the development of anticancer and immunosuppressive drugs.

Friday, May 27th, 2011, 13:00
Room PH 127

Contact: Prof. Matthias Rief, mrief@ph.tum.de , phone: 089 289-12471