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Engineering a "metal switch" into molecular motors to control their activity

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Kinesins and myosins are molecular motors that use the energy from nucleotide hydrolysis to carry out cellular tasks. In addition to the P-loop, these proteins use similar structural motifs called switch-1 and switch-2, to sense and respond to the gamma-phosphate of the nucleotides and coordinate nucleotide hydrolysis. We have developed a strategy to probe metal interactions within kinesins and myosins by taking advantage of the differential affinities of Mg(II) and Mn(II) for serine (-OH) and cysteine (-SH) amino acids. We present the crystal structure of a recombinant kinesin motor domain bound to MnADP and report on a serine-to-cysteine substitution in the switch-1 motif of kinesin that allows its ATP hydrolysis activity to be controlled by adjusting the ratio of Mn(II) to Mg(II). This mutant kinesin binds ATP similarly in the presence of either metal ion but its ATP hydrolysis activity is greatly diminished in the presence of Mg(II). In multiple kinesin members, this defect is rescued by Mn(II), providing a way to control both the enzymatic activity and force-generating ability of these nanomachines. We also present results for an analogous substitution in non-muscle myosin-2. This mutant myosin shows aberrant actin interaction whereby dissociation becomes rate-limiting in the presence of Mg(II), yet is rescued by Mn(II). There are several relevant and important applications to this metal switch technology that will allow further biophysical characterization of molecular motors and molecular switch proteins.

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Protein fibrillation inhibition by polycyclic planner small molecules

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Neurodegenerative disease such as Alzheimer, Parkinson, Huntington and so many related diseases are linked with a form of protein conformational aggregation known as amyloid fibrils products. It was vastly documented that fibrils and protofibrils intermediates are the most cytotoxic species and numerous reports have been attempt to inhibit fibrillation process as a therapeutic methods. Peptides, surfactants and aromatic small molecules have been used as fibrillation inhibitors. In this report, we examined the interaction of the four natural small molecules (daidzein, resveratrol, fisetin and quercetin dihydrate) with hen egg white lysozyme (HEWL) for inhibiting the fibril formation products with different kinds of methods such as fluorescence, dynamic light scattering, transmission electron microscopy, circular dichroism and isothermal calorimetry. The aim of this study was based on bringing new information into possible association/dissociation constant of natural small molecules with amyloid formation products.

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