Induced fit in the specific recognition of transition metal ions by a gene-regulatory RNA

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Monovalent and divalent metal ions are essential for the folding and stabilization of RNAs. In the intracellular milieu, Mg^{2+} serves a primary role in RNA structure stabilization through diffuse electrostatic interactions as well as by inner-sphere chelation. The structural basis of specific cation recognition by RNA is not well understood. Recently, the yybP-ykoY family of riboswitches (bacterial RNAs that control gene expression) have been proposed to respond specifically to Mn^{2+} by Dambach et al. (Mol Cell 57:1099, 2015) and Price et al. (Mol Cell 57:1110, 2015). The latter group reported a 2.8 Å-resolution structure of the RNA in complex with Mn^{2+}. These authors found a number of cations bound to the RNA, but one site appeared to have strong preference for Mn^{2+} over Mg^{2+}, and they proposed that specificity for the soft cation arose from the participation of a soft ligand (the N7 imine of an adenine) in its hexacoordinate binding site. We have biochemically examined further the cation selectivity of this RNA, and found that several transition metal ions in addition to Mn^{2+} can bind and activate the RNA. In this study, we present a crystallographic analysis of alternative metal ion recognition by yybP-ykoY riboswitches. We obtained twinned and untwinned crystals, some of them diffracting beyond 1.8 Å-resolution, of the RNA in various metal ion-bound states. In our refined crystal structures, we observe a flexible binding site that adopts variable coordination schemes with different metal ions. Under near-physiological conditions, the bound transition metal ion is trapped in a high-spin state through atypical pseudo-heptacoordinate chelation, and its binding promotes extensive structural rearrangement of the RNA. Notably, a similar mechanism of discrimination through formation of a pseudo-heptacoordinate chelate has been observed previously in crystallographic studies of gene-regulatory proteins that function in the same pathway as the yybP-ykoY riboswitches (Kliegman et al. Biochemistry 45:3493, 2006).