A fortuitous insight into a common mode of RNA recognition by the dsRNA-specific zinc fingers

Insight into tRNA recognition by dimethylallyltransferase [isopentenyltransferase (IPTase)] was an expected gain from the first structures of the enzyme's complexes, reported by Zhou and Huang (1). There is also an unexpected bonus overlooked in the original report. The C-terminal zinc-finger domain of eukaryotic enzyme is not a new RNA-binding motif, as the authors suggested, but actually displays sequence and structural similarity to a family of zinc finger proteins that bind specifically to double-stranded RNA (Fig. 1) (2, 3). Like IPTase, these proteins comprise variant C₂H₂ zinc fin-

gers with an atypical kinked helix (3). The characteristic kink results from the incompatibility of their zinc-coordinating H-X₅-H motif with a regular α -helix. The helix-kink-helix (HkH) motif was implicated in interaction with dsRNA, but hitherto its recognition mode remained unknown (3). The IPTase domain's interaction with the anticodon stem of tRNA offers the first glimpse of this mode. The N-terminal helix packs against the minor groove, whereas the C-terminal helix runs across the major groove. The zinc-coordinating histidine residue in the former, the positive N-end of the latter, and the basic residues at the kink recognize specifically 3 consecutive phosphates in a single strand. Other basic residues in the C-terminal helix interact with phosphates in the opposite strand. These recognition determinants are conserved in the dsRNA-specific zinc fingers and related proteins (3–5), which are predicted here to share the same interaction mode. Individual fingers could have been tuned to recognize different local shapes of RNA duplexes and their junctions by varying the angle between the helices.

Fig. 1. Comparison of the C-terminal domain of IPTase with the HkH motif-containing C₂H₂ zinc fingers of known structure. (A) Structure-guided sequence alignment; residue numbering is as in the corresponding Protein Data Bank (PDB) entries or UniProt entries (second column). Zinc-coordinating cysteine and histidine residues are shown in orange and blue, respectively; the kink site residues are in green, and the conserved basic residues are in magenta. (B) Stereo view of C α superposition of the HkH zinc finger structures, colored as their PDB codes in A (colored gray is a 6-residue insertion, specific to the IPTase from yeast species). Zinc ion is depicted as a sphere, the zinc-coordinating residues of IPTase are shown as sticks, and those of the other proteins are shown as wires. Note that in the more deviant structures, 1zr9 and 2vrd, the second histidine ligand coordinates zinc ion with N ϵ 2 atom, whereas in all other structures, including IPTase, it employs N δ 1 atom. (C) Superposition of the first zinc finger from the dsRNA-binding protein ZFa onto the IPTase domain bound to tRNA. The coaxial stack of the anticodon stem and the D stem is shown as a space-filled model; the protein-interacting phosphate groups are highlighted in purple. The zinc-coordinating and RNA-interacting residues of IPTase are shown as sticks (see also figure 4C in ref. 1), and the equivalent ZFa residues are shown as wires.

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