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Post-translational regulation of gene expression in the immune system by Roquin/RC3H1 and ribonucleases of the Regnase/ZC3H12/MCPIP family

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Roquin/RC3H1 and Regnase/ZC3H12/MCPIP family members control the lifetime and degradation of their target mRNAs by binding to characteristic stem-loop structures in their 3'-untranslated regions (3'UTRs). In earlier work [1] we have determined the crystal structure of the ROQ domain of human Roquin-1 and characterized its binding to constitutive decay elements (CDEs) present in the 3'UTRs of tumor necrosis factor-α (TNF-α) and the inducible T-cell co-stimulator (ICOS) mRNA. Roquin-1 was shown to post-transcriptionally regulate the A20 mRNA, thereby modulating the activity of the IKK/NF-κB pathway [2]. Roquin-1 mediates mRNA degradation by recruiting the CCR4-CAF1-NOT deadenylase complex to mRNAs after CDE binding. Closely similar stem-loop structures are recognized by the Regnase enzymes that mediate mRNA breakdown through their intrinsic ribonuclease activity. These enzymes share a PIN-type ribonuclease domain followed by a unique CCCH zinc-finger (ZnF) domain. In recent work, we have determined crystal structures of the Regnase-3 PIN domain and of a heptaribonucleotide bound to a Regnase-3 fragment containing both the PIN and the ZnF domain. These structures reveal binding modes of the RNA to both the PIN domain and the zinc finger of Regnase-3 and suggest a basis for RNA loop recognition by the unique zinc finger. In addition, we discovered - by serendipity - a novel form of double-stranded RNA incorporating a half-turn of A-like RNA based entirely on wobble-base pairing, which we termed W-RNA [3]. The W-RNA formed under acidic crystallization conditions from oligonucleotides expected to form CDE-like RNA stem-loops and is stabilized by C-A+ wobble-base pairing. We propose that RNA duplexes based on pH-switchable wobble-base pairing may find biotechnological applications in the future.

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