CryoEM SPA for Structural Understanding of A-to-I RNA Editing: Human Adenosine Deaminase Acting on RNA 2 (ADAR2) Complexed with dsRNA

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Adenosine deaminases acting on RNA (ADARs) are enzymes which convert adenosine to inosine in the double-stranded RNA of humans and other animals. Double-stranded RNA- binding domains (dsRBDs) are present in all ADARs and are the main determinants of how many bases on a given RNA are edited. A healthy level of A-to-I RNA editing is necessary to produce mature RNA, but under- or over-editing leads to autoimmune and neurological diseases.
The goal of this work is to give insight into the structural basis of differential editing of RNAs by elucidating the binding sites of each dsRBD in human ADAR2:dsRNA complexes. To overcome preferential orientation of this small, flexible complex, a tilted data collection strategy was employed, resulting in a 5Å-resolution 3D reconstruction of ADAR2 bound to a perfectly complementary 61bp dsRNA substrate. Lessons learned from the ADAR2:61bp- dsRNA structure are now being applied to the characterization of ADAR2 in complex with an 89-base RNA which contains both double-stranded and internal loop regions.