Structural basis of OLA1 activation by BARD1 BRCT

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Centrosomes, the major microtubule organizing center in mammalian cells, play a critical role in cell division and spindle formation. The breast cancer associated gene 1 (BRCA1) is a tumor suppressor of breast and ovarian cancers. It forms a heterodimer with BRCA1-associated RING domain protein (BARD1), and acts as an E3 ubiquitin ligase in DNA repair, transcription, ubiquitination and centrosome regulation. Importantly, BRCA1 silencing and mutations result in abnormal centrosome amplification. In addition, an Obg-like ATPase OLA1 binds to the N-terminal region of BRCA1 and C-terminal region of BARD1. These interactions are critical for correct centrosome number. Here, we determined the molecular interplay between BARD1 and OLA1 by a series of biophysical and biochemical analyses. Based on the NMR and enzymatic studies, ATP-bound OLA1 binds to the BARD1 BRCT domain better than the nucleotide-free OLA1, and this interaction enhances the ATPase activity of OLA1, whose turnover number (k_{cat}) is increased in the presence of BARD1 BRCT. Structural analyses in combination with the mutagenesis study indicated that a highly conserved region on the BARD1 BRCT domain contribute to the binding of OLA1. Moreover, a cancer associated mutation on the BRCT significantly reduces its to activate OLA1. Altogether, these data identify a functional surface on the BARD1 BRCT domains that contribute to centrosome regulation by modulating the activity of OLA1.