Near atomic cryo-electron microscopy structure of human BRISC deubiquitinase complex inhibited by SHMT2 suggests link to cancer cell growth in hypoxic environments

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The BRCC36 deubiquitinase cleaves K63-linked ubiquitin chains in metazoan cells and is implicated in human disease. Deubiquitinases (DUBs) are commonly regarded as constitutively active and promiscuous, with limited regulatory capacity. Therefore, insights into mechanisms for K63 DUB regulation will be very valuable for exploitation for therapeutic use. We determined the near atomic-resolution structure of the BRCC36-containing BRISC complex bound to SHMT2 by single-particle cryo electron microscopy at 4.2 Å. The 8 protein homo-dimeric human BRISC complex with subunits BRCC36, ABRO1, BRE and MERIT40 binds to dimeric SHMT2 via the ABRO1 subunit, forming a 445 kDa complex. The metabolic enzyme SHMT2 is frequently found overexpressed in cancer cells and adapts these cells to the hypoxic conditions inside tumours by increasing reliance on single-carbon metabolism. In the complex we find that SHMT2 sequesters BRCC36 in an inactive state, therefore inhibiting BRISC K63 deubiquitination. Our results suggest that an increase in SHMT2 expression will impact cellular K63 homeostasis with consequences for DNA repair, immune signalling and other BRISC targets in cancer cells.

We also solved the BRCC36 containing BRCA1-A complex structure by X-ray crystallography to 3.9 Å resolution. BRCA1-A shares a tripartite core comprised of BRCC36, MERIT40 and BRE with BRISC, replaces the ABRO1 scaffold protein with ABRAXAS and further includes RAP80 as constitutive subunit. Comparing the two complexes revealed them to be modular DUBs, with ABRAXAS and ABRO1 specifically integrating accessory factors and conferring targeting and regulation.

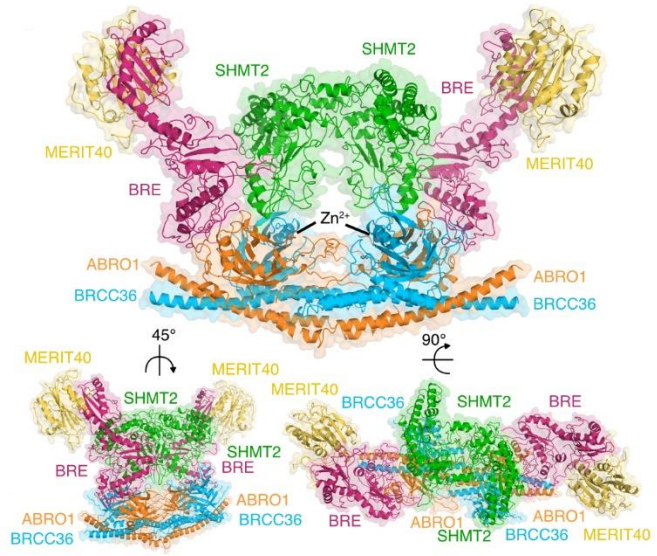

Figure 1: Structure of the human BRISC/SHMT2 complex solved by cryo-electron microscopy to 4.2 Å