Cryo-EM structure of CLCA1 identifies CLCA1 as a founding member of a novel metzincin family

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Calcium-activated chloride channel regulator 1 (CLCA1) is implicated in several diseases, especially mucus-associated airway diseases, but its molecular function and regulation have remained unclear. By determining the structure of CLCA1 by negative stain electron microscopy and cryo-EM, we could confirm that CLCA1 forms large oligomeric complexes which adopts a compact domain organization comprising a metallohydrolase (MH), von Willebrand type A (VWA), β-sheet-rich (BSR), inhibitory (ID), and fibronectin type III-like (FnIII-l) domains. The unusually large MH domain bears hallmarks of metzincins but is distinguished by several unique features including an atypical active site zinc-coordination environment and a second Zn2+ -coordination site. Unlike classical metzincins, CLCA1 lacks a pro-domain; instead, a C-terminal inhibitory loop occludes the MH active site, providing an alternative mechanism of autoinhibition. The adjacent VWA domain, resolved in its closed state, is poised for conformational change upon ligand binding, suggesting a route for allosteric regulation of protease activity. Structural and functional assays support a role for CLCA1 in cleaving glycosylated substrates, leading to alterations in mucin architecture consistent with a regulated function in mucus remodelling. Together, these data establish CLCA1 as the founding member of a new eukaryotic metzincin family, here termed CLCAsins, with unique regulatory mechanisms.