Insight into somatic angiotensin-I converting enzyme structure and dynamics revealed by cryo-electron microscopy

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Hypertension, a major risk factor for cardiovascular disease and stroke, is commonly treated using drugs which acton the renin-angiotensin aldosterone system. The somatic isoform of angiotensin I-converting enzyme (sACE) is comprised of two catalytically active domains and plays a critical role in this system to increase blood pressure. Consequently, ACE inhibitors are widely used to treat hypertension, but this is associated with the development of life-threatening swelling in some patients. The sACE domains differ in physiological function and inhibitor binding affinity despite their 90% active site similarity. To develop improved ACE inhibitors, a clear understanding of sACE structure and function is required. As the interdomain linker flexibility and high degree of sACE glycosylation (~30%)is not amenable to crystallization, truncated minimally glycosylated forms of sACE are routinely used for X-ray crystallography and molecular dynamics simulations. Structural studies to date have thus provided limited insight into the structure, dynamics, function, and inhibition of full-length sACE as both intra- and interdomain cooperativity can affect ligand binding or hydrolysis. The mechanism of sACE homodimerization and intracellular signalling is also unclear and important to uncover as it could explain a receptor-like function of sACE. Here, we report the first structures of full-length, glycosylated, soluble sACE obtained through single-particle cryo-electron microscopy. Both monomeric (~138kDa) and dimeric forms of apo sACE were reconstructed from a single dataset of >7000 micrographs. The N- and C-terminal domains of monomeric sACE were resolved to 3.7 Å and 4.1 Å resolution, respectively, while the interacting dimer domains were resolved to 3.6-3.7 Å resolution. We propose mechanisms for sACE homodimerization, interdomain cooperativity, and intradomain hinging. This study advanced our understanding of sACE structure and has implications for the design of ACE inhibitors as the C-terminal domain is observed in an open conformation for the first time.

Keywords: Cryo-electron microscopy, Zinc metalloprotease, Glycoprotein, Dimerization