Angiotensin-converting enzyme: a structural study

Jean Watermeyer, E.D. Sturrock, B.T. Sewell

University of Cape Town/University of the Western Cape

Human angiotensin-converting enzyme (ACE) is involved in the regulation of blood pressure via the renin-angiotensin and kallikrein-kinin systems. A number of drugs have been developed that target somatic ACE, for the treatment of cardiac disease [1]. Structural information about ACE is an important key to understanding its mechanism and substrate-specificity. This information has only recently begun to be elucidated, with the solution of a crystal structure of human testis ACE (tACE)[2]. tACE is identical to the C-terminal domain of somatic ACE.

We have purified, crystallised and determined the structure of a glycosylation-deficient mutant of tACE, to 2.9Å. The structure is a predominantly alpha-helical with the active site deep in the cavity that separates two sub-domains. This is in agreement with the structure of a native form of tACE.

We have also carried out a normal mode analysis, revealing intrinsic flexibility of tACE about its active site cleft. The active site is "closed off" from the external medium, so that it is unclear how a large substrate molecule could gain access. This modelling study suggests a mechanism whereby this could be achieved.

The information obtained here will be used to inform the design of new inhibitors of the C-domain of somatic ACE. These domain-specific inhibitors are helpful in clarifying the function of ACE in vivo, and may provide lead compounds for a new generation of ACE inhibitors for clinical use.

1. K. R. Acharya, E. D. Sturrock, J. F. Riordan, and M. R. Ehlers. Ace revisited: a new target for structure-based drug design. Nat.Rev.Drug Discov. 2 (11):891-902, 2003.

2. R. Natesh, S. L. Schwager, E. D. Sturrock, and K. R. Acharya. Crystal structure of the human angiotensin-converting enzyme-lisinopril complex. Nature 421 (6922):551-554, 2003.