Name:	**C1s Proenzyme**
Catalog Number:	**A103**
Sizes Available:	250 µg/vial
Concentration:	1.0 mg/mL (see Certificate of Analysis for actual concentration)
Form:	Frozen liquid
Activity:	>80 % C1s binds 1:1 with excess C1-INH after activation.
Purity:	>90 % by SDS PAGE
Buffer:	50 mM sodium phosphate, 130 mM NaCl, pH 7.2
Extinction Coeff.	$A_{280\ nm}$ = 0.96 at 1.0 mg/mL for pure C1s
Molecular Weight:	86,000 Da (1 chain)
Preservative:	None, 0.22 µm filtered.
Storage:	-70^{o}C or below. Avoid freeze/thaw.
Source:	Normal human serum (shown by certified tests to be negative for HBsAg, HTLV-I/II, STS, and for antibodies to HCV, HIV-1 and HIV-II).
Precautions:	Use normal precautions for handling human blood products.
Origin:	Manufactured in the USA.

General Description

C1s proenzyme is a single chain 86,000 dalton protein that is the native form of C1s enzyme. C1s is a subunit of the C1 complex which is the first complement component in the cascade referred to as the classical pathway of complement. C1s proenzyme is an inactive zymogen until C1 is activated. C1 complex binds to and is activated by antigen-antibody complexes (immune complexes) yielding C1r enzyme. C1r enzyme in the C1 complex activates C1s proenzyme generating C1s enzyme. C1 complex is a non-covalent calcium-dependent complex of one C1q, two C1r and two C1s molecules. C1q binds through two or more of its six arms to the Fc domains of IgG or IgM. The binding of multiple arms to immune complexes causes the two C1r proteins in the complex (protease zymogens) to activate producing two proteases that cleave and activate the two C1s proenzymes in the complex (Morikis, D. and Lambris, J.D. (2005)). This activation of C1s proenzyme is caused by cleavage into the two chain C1s enzyme with 58,000 and 28,000 dalton fragments.

Activated C1s enzyme cleaves complement component C4 releasing C4a and initiating covalent attachment of C4b to the activating surface. Activated C1s also cleaves C2 and the larger fragment of C2 binds to the surface-attached C4b forming C4b,C2a, the C3/C5 convertase of the classical pathway.

Physical Characteristics & Structure

C1s proenzyme is a high molecular weight (86,000 daltons), single chain, zymogen of a trypsin-like protease. C1s is present in plasma at 31 ug/mL. C1s proenzyme is activated by C1r enzyme (Dodds, A.W. and Sim, R.B. editors (1997)). Two C1r molecules form a C1r-C1r complex in the presence of calcium. C1r-C1r subequently forms a stable complex with two C1s molecules in the presence of calcium. This tetramer can exist in solution, but in the presence of C1q it binds forming the C1 complex which is stable in the presence of calcium. C1s proenzyme circulates in blood

in this 766,000 dalton C1 complex. C1r self-activation, and subsequent C1s activation, is controlled by a weak association of C1r with C1 esterase inhibitor (C1-INH) when it is in the C1 complex and similar stabilization occurs with purified C1r. C1s and C1r enzymes, however, are irreversibly inactivated by binding to C1-INH (Ziccardi, R.J. (1982)).

Function

C1s proenzyme can be used in the presence of calcium to form the C1 complex with C1q and C1r proenzyme. C1s proenzyme has no proteolytic activity and must be converted to C1s enzyme by incubation with C1r enzyme to be active. C1s enzyme can be used to activate C4 or C2 in the fluid phase. In the presence of Mg++ activated C4b and C2a can form fluid phase C4b,C2a which is the C3/C5 convertase of the classical pathway. The C1 complex made from C1s proenzyme will, after activation to C1s enzyme, activate C4 and C2. This occurs after binding of C1 to a cell bearing antibodies such as EA (Dodds, A.W. and Sim, R.B. editors (1997); Morgan, B.P. ed. (2000)). EA are sheep erythrocytes with rabbit IgM anti-sheep erythrocytes antibodies bound to their surface (CompTech #B200) (Morgan, B.P. ed. (2000)).

Assays

The activity of C1s proenzyme is checked by first activating it with C1r enzyme and subsequently measuring its ability to bind to the protease inhibitor C1 inhibitor (C1-INH, CompTech #A140). It may also be used to form the C1 complex composed of one C1q, two C1r and two C1s molecules and this may be assayed as described for C1 complex (CompTech #A098).

Applications

See section titled Function above.

Regulation

Activation of C1s proenzyme in the C1 complex is regulated indirectly by C1-INH. C1r self-activation, and subsequent C1s activation, is controlled by a weak association of C1r with C1 esterase inhibitor (C1-INH) when it is in the C1 complex (Ziccardi, R.J. (1982)). Once activated, C1s enzyme is rapidly inactivated by C1-INH.

Genetics

The EMBL/Genbank cDNA accession number for C1s proenzyme is J04080. The genes for C1r and C1s are closely linked and located on chromosome 12p13.

Deficiencies

Deficiencies of each of the three components of C1 have been found (Ross, G.D. (1986)). C1r and C1s deficient patients are prone to systemic lupus erythematosus (SLE) and recurrent pyogenic infections (Rother, K., et al. (1998)). They lack classical pathway function and may or may not exhibit antigen in blood.

Diseases

See section titled Deficiencies above.

References

Dodds, A.W. and Sim, R.B. editors (1997) Complement. A Practical Approach (ISBN 019963539) Oxford University Press, Oxford.

Morikis, D. and Lambris, J.D. editors. (2005) Structural Biology of the Complement System. (ISBN 0-8247-2540-9) Taylor & Francis Group, Florida.

Morgan, B.P. ed. (2000) Complement Methods and Protocols. (ISBN 0-89603-654-5) Humana Press, Inc., Totowa, New Jersey.

Ross, G.D. (1986) Immunobiology of the Complement System. (ISBN 0-12-5976402) Academic Press, Orlando.

Rother, K., Till, G.O., and Hänsch, G.M. (1998) The Complement System. (ISBN 3-540-61894-5) Springer-Verlag, Heidelberg.

Ziccardi, R.J. (1981) Activation of the early components of the classical complement pathway under physiologic conditions. J. Immunol. 126:1769-1773.

Ziccardi, R.J. (1982) Spontaneous activation of the first component of human complement (C1) by an intramolecular autocatalytic mechanism. J. Immunol. 128:2500-2504.

Ziccardi, RJ. (1982) A new role for C-1-inhibitor in homeostasis: control of activation of the first component of human complement. J. Immunol. 128:2505-2508.

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