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Data Article

Structural basis of specific inhibition of tissue-type plasminogen activator by plasminogen activators inhibitor-1

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ABSTRACT

Thrombosis is a leading cause of death worldwide [1]. Recombinant tissue-type plasminogen activator (tPA) is the FDA-approved thrombolytic drug for ischemic strokes, myocardial infarction and pulmonary embolism. tPA is a multi-domain serine protease of the trypsin-family [2] and catalyses the critical step in fibrinolysis [3], converting the zymogen plasminogen to the active serine protease plasmin, which degrades the fibrin network of thrombi and blood clots. tPA is rapidly inactivated by endogenous plasminogen activators inhibitor-1 (PAI-1) [4] (Fig. 1). Engineering on tPA to reduce its inhibition by PAI-1 without compromising its thrombolytic effect is a continuous effort [5]. Tenecteplase (TNK-tPA) is a newer generation of tPA variant showing slower inhibition by PAI-1 [6]. Extensive studies to understand the molecular interactions between tPA and PAI-1 have been carried out [7–18], however, the precise details at atomic resolution remain unknown. We report the crystal structure of tPA · PAI-1 complex here. The methods required to achieve these data include: (1) recombinant expression and purification of a PAI-1 variant (14-1B) containing four mutations (N150H, K154T, Q319L, and M354I), and a tPA serine protease domain (tPA-SPD) variant with three mutations (C122A, N173Q, and S195A, in the chymotrypsin numbering) [19]; (2) formation of a tPA-SPD · PAI-1 Michaëlis

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complex in vitro [19]; and (3) solving the three-dimensional structure for this complex by X-ray crystallography [deposited in the PDB database as 5BRR]. The data explain the specificity of PAI-1 for tPA and uPA [19,20], and provide structural basis to design newer generation of PAI-1-resistant tPA variants as thrombolytic agents [19].

Specifications table

Subject area	*Biology*
More specific subject area	*Protein structure and biochemistry*
Type of data	*X-ray crystal structure, Mass spectrometry*
How data was acquired	*X-ray diffraction data were collected at Shanghai Synchrotron Radiation Facility. Mass spectra of MALDI-TOF-MS were obtained on a Bruker REFLEX III MALDI-TOF-MS (Bruker-Franzen, Bremen, Germany).*
Data format	*Processed*
Experimental factors	*Recombinant proteins were purified to high homogeneity before use.*
Experimental features	*The structure of the tPA · PAI-1 complex was determined by X-ray crystallography.*
Data source location	*City, Country and/or Latitude & Longitude (& GPS coordinates) for collected samples/data if applicable*
Data accessibility	*The data is available from the related publication by Gong et al. (http://www.ncbi.nlm.nih.gov/pubmed/26324706), and the structure deposited in the Protein Data Bank (entry 5BRR).*

Value of the data

- Determines the crystal structure of the Michaëlis complex between tPA and PAI-1.
- Provides insight on the specificity of PAI-1 for tPA and uPA.
- Identifies key residues of tPA for binding to PAI-1.
- Explains the PAI-1-resisting property of Tenecteplase.
- Offers important clues to design newer generation of PAI-1-resistant tPA variants.

1. Data, experimental design, materials and methods

1.1. Data and experimental design

We have determined the structure of tPA · PAI-1 Michaëlis complex and identified key residues of tPA for binding to PAI-1 by X-ray crystallography, and the data are summarized in the original publication [19].

We expressed the recombinant PAI-1 variant 14-1B (N150H, K154T, Q319L, and M354I) [21], using the expression vector pT7-PL and BL21 cells as soluble protein [22]. The choice of this particular variant is to obtain PAI-1 in active form, advantageous for crystallization, because the wild type PAI-1