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Mapping the topographic epitope landscape on the urokinase plasminogen activator receptor (uPAR) by surface plasmon resonance and X-ray crystallography

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ARTICLE INFO

Article history:

Received 14 July 2015

Received in revised form

14 August 2015

Accepted 25 August 2015

Available online 4 September 2015

Keywords:

uPAR

CD87

Epitope mapped antibodies

SPR

Allostery

Hot spots

Vitronectin

Cancer invasion

ABSTRACT

The urokinase-type plasminogen activator receptor (uPAR or CD87) is a glycolipid-anchored membrane protein often expressed in the microenvironment of invasive solid cancers and high levels are generally associated with poor patient prognosis (Kriegbaum et al., 2011 [1]). uPAR is organized as a dynamic modular protein structure composed of three homologous Ly6/uPAR domains (LU). This internally flexible protein structure of uPAR enables an allosteric regulation of the interactions with its two principal ligands: the serine protease urokinase-type plasminogen activator (uPA) and the provisional matrix protein vitronectin (Vn) (Mertens et al., 2012; Gårdsvoll et al., 2011; Madsen et al., 2007 [2–4]). The data presented here relates to the non-covalent trapping of one of these biologically relevant uPAR-conformations by a novel class of monoclonal antibodies (Zhao et al., 2015 [5]) and to the general mapping of the topographic epitope landscape on uPAR. The

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methods required to achieve these data include: (1) recombinant expression and purification of a uPAR-hybrid protein trapped in the desired conformation [patent; WO 2013/020898 A12013]; (2) developing monoclonal antibodies with unique specificities using this protein as antigen; (3) mapping the functional epitope on uPAR for these mAbs by surface plasmon resonance with a complete library of purified single-site uPAR mutants (Zhao et al., 2015; Gårdsvoll et al., 2006 [5,6]); and finally (4) solving the three-dimensional structures for one of these mAbs by X-ray crystallography alone and in complex with uPAR [deposited in the PDB database as 4QTH and 4QTI, respectively].

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Specifications table

Subject area	Protein structure and biochemistry
More specific subject area	Trapping a flexible protein structure in a defined conformation by mAbs
Type of data	X-ray crystal structures, surface plasmon resonance studies (SPR), and generation of mAbs with defined reactivity
How data was acquired	X-ray diffraction data were collected at Shanghai Synchrotron Radiation Facility SPR data was recorded on a CM5 chip with a Biacore3000™ (GE Healthcare Life Sciences)
Data format	Processed
Experimental factors	Recombinant proteins and monoclonal antibodies were affinity purified to high homogeneity before use.
Experimental features	Kinetic rate constants for the interaction between immobilized anti-uPAR mAbs and recombinant uPAR mutants were determined by SPR, the structure of the mAb · uPAR complex was determined by X-ray crystallography
Data source location	Not applicable
Data accessibility	The data is available from the related publication by Zhao et al. (http://www.ncbi.nlm.nih.gov/pubmed/25659907), from the patent (WO 2013/020898 A12013) and the structures deposited in the Protein Data Bank (entries 4QTH and 4QTI).

Value of the data

- Defines the structure of a closed, active conformation of native uPAR^{WT} without covalent modifications;
- defines a topographic epitope landscape on uPAR for 6 different bins of anti-uPAR mAbs;
- establish that occupancy of the Vn-binding site by mAbs drives uPAR into to its closed conformation;
- data defining this interdomain flexibility are important for functional studies on uPAR biology;
- and for the future design of uPAR-targeted intervention studies in human disease [1,7–9].

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