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Extended Abstract

Determination of the Binding Sites of Activators within the Proteasome Structure †

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The proteasome degrade most of the proteins in eukaryotic cells, thereby controlling the key cellular processes. Impaired degradation mechanisms can lead to accumulation of damaged proteins, resulting in the development of aging processes. Reduced activity of the proteasome also underlies the etiology of some neurodegenerative disorders, such as Alzheimer's or Parkinson's disease. It is believed that low-molecular mass proteasome activators could prevent progression of age-related neurodegenerative disorders.

Blm10 is an activator of the yeast 20S proteasome, which stimulates hydrolysis of peptides and some partially unstructured proteins. The crystal structure of the Blm10-yeast 20S complex revealed that C-terminal residues of Blm10 insert into the pocket between the α5 and α6 subunits of the 20S core particle, and their binding allows to partially open the gate that leads to the catalytic chamber of the proteasome [1].

Blm-pep is a 14-mer peptide, designed based on the sequence of the Blm10 protein, which efficiently stimulates chymotrypsin-like activity of human 20S proteasome. The crystal structure of the complex of Blm-pep and yeast 20S proteasome shows that Blm-pep docks into the same pocket as the C-terminus of Blm10 [2]. So far, we have obtained dozens of analogs of Blm-pep, which stimulate the proteasome peptidases at 10 μM concentration several times. Some of these compounds also are able to enhance the rate of protein substrates degradation in vitro. To determine the place of binding of obtained activators in the structure of human proteasome, we applied different techniques such as cross-linking in combination with mass spectrometry, X-ray crystallography, and molecular modelling. These studies have revealed that there are several sites that are able to bind modulators.

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